SUSTAINED RELEASE FLOATING *IN SITU* GELLING SUSPENSION OF ACYCLOVIR

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(Received 11 May 2022) (Accepted 22 November 2023)

ABSTRACT

Acyclovir has a 10-30 % oral bioavailability with a half-life of 2-3 h. Acyclovir mainly gets solubilized in acidic conditions, and its absorption is found in the upper GIT. The primary aim of this research work was to formulate gastroretentive dosage form of acyclovir that can float on gastric content. The polymer used was sodium alginate, while the floating agent was calcium carbonate. The dependent variables of drug release, floating lag time and viscosity were significantly impacted by sodium alginate and $CaCO_3$ concentrations. To assess the desired release pattern, a dissolution was performed in 0.1 N HCl at 50 rpm. Shear-thinning behaviour, instant gelation, 99.2 % drug release at 12 h, and instant floating ability greater than 12 h in 0.1 N HCl were all observed in the suspension. Consequently, a sustained-release floating dosage form for acyclovir, with a duration of 12 h, was successfully developed.

Keywords: Acyclovir, floating *in situ* gel, oral drug delivery, sodium alginate, suspension, sustained drug release

INTRODUCTION

In the pharmaceutical industry, the utilization of oral controlled release drug delivery has been steadily increasing due to its ability to provide several advantages in terms of therapeutic benefits. These advantages include convenient dosage administration, improved patient compliance, and enhanced formulation flexibility. When drugs have short half-lives and are easily absorbed through the GIT, they are rapidly eliminated from the bloodstream[1]. To obtain the desired therapeutic action, these medicines must be administered again. To address this issue, the objective is to gradually release the drug within the GI tract, ensuring a sustained and effective drug concentration in the bloodstream over an extended duration[2]. A gastroretentive drug delivery system can enhance the controlled release of pharmaceuticals with an absorption window in the gastrointestinal area by slow release of the medication for extended periods. This system ensures sufficient bioavailability of the drug by prolonging its retention in the stomach, leading to reduced wastage and improved solubility for medications that exhibit low solubility at high pH levels[3].

The oral route is commonly utilised to deliver drug molecules because it has the lowest cost of therapy and is easy to give, resulting in high patient compliance. Oral medication delivery techniques account for more than half of all available drug delivery systems[1]. Oral sustained drug delivery systems (SDDS) are modified release systems that release drugs in a predictable, regulated, and predefined way. The SDDS has several advantages, including maintaining the optimal concentration of medications in the blood and releasing the drug in a consistent and long-lasting way. It also enhances patient care by increasing the action of short-half-life medications, reducing adverse effects, dosing frequency, drug waste, and optimising therapy[4]. SDDS, on the other hand, are ineffective for drugs with an upper gastrointestinal absorption window. Most of the drawbacks of the SDDS are known to be addressed by gastroretentive drug delivery systems (GRDDS)[5]. These technologies are supposed to extend stomach retention duration, while also releasing contents in a preset, predictable and regulated way. Gastroretentive approaches are suitable for drugs, whose action is locally required in GIT as well as when drugs are not stable in GI pH conditions. Additionally, drugs having narrow absorption window and low solubility at high pH levels can also benefit from gastroretentive approaches. GRDDS is a site-specific approach that works by extending the time between drug contact and absorption window for maximal site-specific absorption. As

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https://doi.org/10.53879/id.60.12.13503

a result, medication solubility improves thereby increasing oral bioavailability[6]. Several methods are employed to enhance the duration of stomach retention, which include utilization of bioadhesive systems, raft systems, swelling as well as expanding systems, high-density systems and floating systems[7].

Acyclovir is an antiviral drug that acts by inhibiting DNA synthesis. It is mainly prescribed in *Herpes simplex* and *Herpes zoster* infections[8, 9]. The oral bioavailability of acyclovir account 10-30% with shorter half life of 2-3 h. It is slightly water-soluble[10]. The pK_a values of acyclovir are 2.27 and 9.2 and the log P values is 1.22. Consequently, the drug exhibits solubility in an acidic pH environment and is efficiently absorbed in the upper section of the GI tract[11]. Considering all the above parameters, acyclovir was selected as a drug candidate to provide sustained drug release which can help in reducing the frequency of dosing. The suspension containing *in situ* gelling polymers effective at pH (1.2) can be used for sustained drug delivery. Acyclovir has good absorption in upper GIT, which remains un-ionized in the stomach for better absorption[12]. So it is an ideal drug for the GRDDS. The primary focus of this study was directed towards the formulation of acyclovir that enhances its absorption in the upper GI tract while providing extended release action. Literature survey revealed that acyclovir floating drug delivery systems in the form of tablets has been developed. But for pediatric and geriatric patients, tablets cannot be given and in such cases, solutions or suspensions are suitable. Consequently, our objective was to design a suspension-based gastroretentive drug delivery system that exhibits floating characteristics on the gastric content.

MATERIALS AND METHODS

Materials

Acyclovir was gifted by Ciron Pharmaceuticals, Mumbai. Sodium alginate, hydroxyl propyl methylcellulose (HPMC K100M), sodium citrate, calcium carbonate ($CaCO_3$), methylparaben, propylparaben and sucrose were obtained from Loba Chemie, Mumbai.

Methods

Drug release calculations and dose fixation[13]

Calculations were employed to determine the sustained drug release profile by considering pharmacokinetic parameters. The IR dose was calculated by the following formula (1):

$$IRD = \frac{C_{ss} \times V_d}{F}$$

where

V_d: Volume of distribution

F: bioavailability

C_{ss}: Steady-state concentration

Maintenance dose/total dose (MD) represents the drug fraction required to maintain sustained delivery of drug from formulation for the required time (t). The calculations were done by using the following formula:

$$MD = IRD \{1 + (0.693 * t/t_{1/2})\}$$

where

IRD: Immediate release dose,

t: A pre-defined time of sustained action is required, lasting for a period of 12 h

$t_{1/2}$: half-life.

Acyclovir and excipient compatibility study

The compatability study was performed using DSC. Initially, drug and excipient were properly mixed at a 1:1 ratio in a mortar. This mixture was filled in glass vials which were then kept at room temperature for 15 days and DSC analysis was performed. The pure acyclovir and the mixture were subjected to heating at 40 to 300°C at 10°C per minute, accompanied by a nitrogen flow of 40 mL per minute. The DSC thermogram obtained was used to determine the possible incompatability.

Formulation of *in situ* gelling suspension

3^2 factorial design was used to develop and optimise *in situ* gelling suspensions of the acyclovir. The independent variables in this study were Na alginate concentration (X1) and Ca carbonate concentration (X2), while the dependent

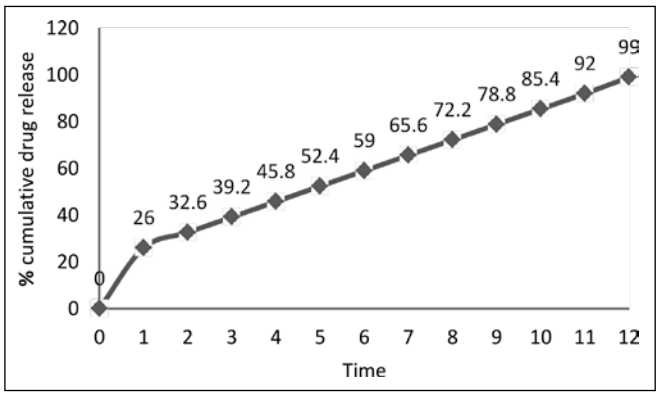

Fig. 1: Theoretically calculated drug release in 12 h

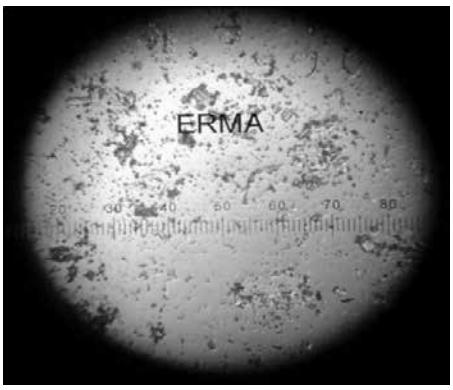

Fig. 2: Particle size analysis of the acyclovir suspension

variables were drug release at 12 h (Y1), floating lag time (Y2), and viscosity (Y3). The concentration of remaining excipients and process variables were kept constant throughout the studies. Table I summarises the actual values and coded values of independent and dependent variables.

Table II provides a summary of the experiment run designs in coded form. According to Table III, each element was assessed at three levels, resulting in nine different formulations being tested. The floating lag time (F) and viscosity were the dependent factors.

Table I: Actual values and coded values of independent variables

Coded value	Actual values	
	X_1 (Sodium alginate) % w/V	X_2 (Calcium carbonate) % w/V
-1 (Low)	1	0.5
0 (Medium)	2	1
+1 (High)	3	1.5

Table II: Composition of gel formulations in coded form as per design

Batch	Independent variable		Actual value	
	X_1	X_2	X_1 (%)	X_2(%)
F 1	-1	-1	1	0.5
F 2	-1	0	1	1
F 3	-1	1	1	1.5
F 4	0	-1	2	0.5
F 5	0	0	2	1
F 6	0	1	2	1.5
F 7	1	-1	3	0.5
F 8	1	0	3	1
F 9	1	1	3	1.5

All weighed ingredients mentioned in Table III were taken together and were triturated properly in mortar and pestle. They were mixed in geometric order to ensure homogenous mixing. The content was then transferred to and kept in a bottle. The required volume was made up with water and mixed thoroughly by shaking the bottle.

Characterisation of the *in situ* gelling suspension[5,10]

Clarity, appearance and pH

The clarity of the formulations was assessed through visual examination against white and black backgrounds. The appearance of the final formulation was checked

Table III: Formulation of *in situ* gelling solutions for optimization

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Acyclovir (mg 10mL^{-1})	250	250	250	250	250	250	250	250	250
Sodium alginate (% w/V)	1	1	1	2	2	2	3	3	3
Xanthan gum (% w/V)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium citrate (% w/V)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium lauryl sulphate (% w/V)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Calcium carbonate (% w/V)	0.5	1	1.5	0.5	1	1.5	0.5	1	1.5
Methyl paraben (% w/V)	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Propyl paraben (% w/V)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Sucrose (% w/V)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Water qs	100	100	100	100	100	100	100	100	100

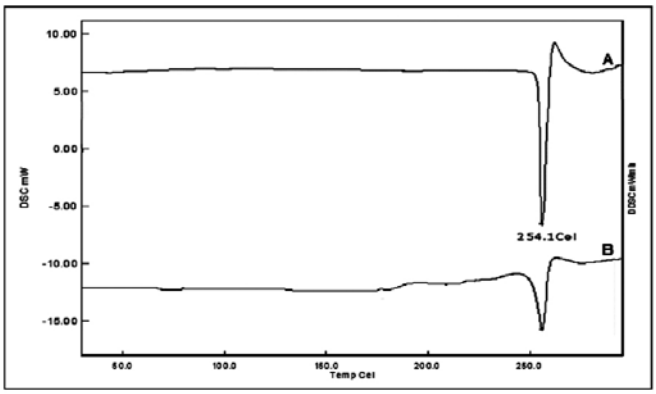

Fig. 3: DSC thermogram of (A) acyclovir (B) physical mixture

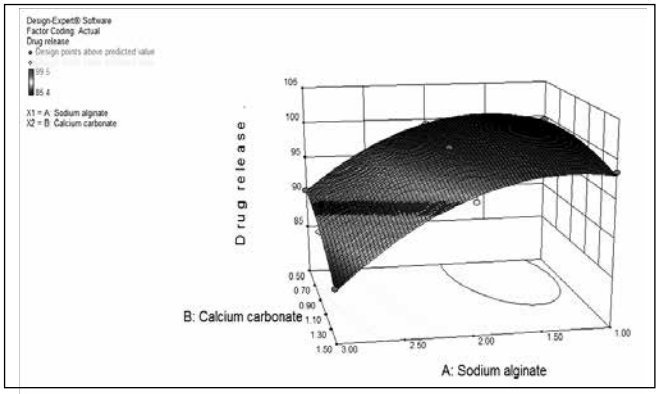

Fig. 4: Three response surface plots for Y_1 (drug release)

Table IV: Effect of independent variables on dependent variables

Batch	Variable level		Y_1 (% Drug release)	Y 2 (Floating lag time) (sec)	Y3 (Viscosity) (cps)
	X_1	X_2			
F1	-1	-1	99.5±0.2	78±1.1	108±1.9
F2	-1	0	99.3±0.8	54±1.5	112±1.6
F3	-1	+1	98.5±0.7	45 ±1.2	110±1.3
F4	0	-1	99.6±0.7	70±1.8	152±1.3
F5	0	0	99.2±0.1	42±1.3	156±0.4
F6	0	+1	99.4±0.7	39±1.1	167±1.3
F7	+1	-1	90.4±0.8	56±0.9	296.±0.9
F8	+1	0	89.12±0.5	45±0.5	298±1.2
F9	+1	+1	85.4±0.7	39±1.2	295±1.9

visually for its color and transparency. Using a pH meter, the formulation's pH was determined[14].

Particle size measurement

The suspension was spread evenly on a glass slide. The diameters of the particles on the slide were measured employing a calibrated micrometer eyepiece under 10 X magnification.

Gelation study

Gelation solution (5 mL) was dissolved in 500 mL of 0.1N HCl (pH 1.2) at 37±1°C. The gels were then placed on the surface of the fluid and slowly withdrawn using a pipette. Upon contact with the gelation solution, the formulations rapidly transformed into a rigid gel-like structure. The stiffness of the resulting gel and the duration for which it retained its rigid state were observed[15].

Viscosity

1 mL aliquot of the sample was used to test the viscosity of *in situ* gelling formulations using a rheometer (Anton Paar Rheometer, USA) with a probe at 25 ^{0}C. Rheoplus software was used to measure each value in triplicate at a predetermined shear rate of 50 (1/sec). The shear-thinning behaviour of *in situ* gelling suspensions was investigated. Shear-thinning behaviour is defined as a reduction in viscosity when the shear rate is increased continuously[16].

Measurement of gel strength

The rheometer was also used to evaluate the strength of the gel. At 37 ^{0}C, gels were produced in 0.1 N HCl. Gel strength was determined by piercing a gel sample with a needle or cone[17]. The energy used or work done for piercing the needle through the gel sample was measured using direct reading with a unit of dyne cm^{-2}.

Table V: ANOVA for Y_1

Source	Sum of squares	Df	Mean square	F value	p-value Prob > F	
Model	278.60	5	55.72	206.21	<0.0001	Significant
A-X1	181.5	1	181.50	671.70	<0.0001	
B-X2	16.50	1	16.5	61.50	0.0002	
AB	4	1	4	14.80	<0.0001	
Cor Total	280.22	11				

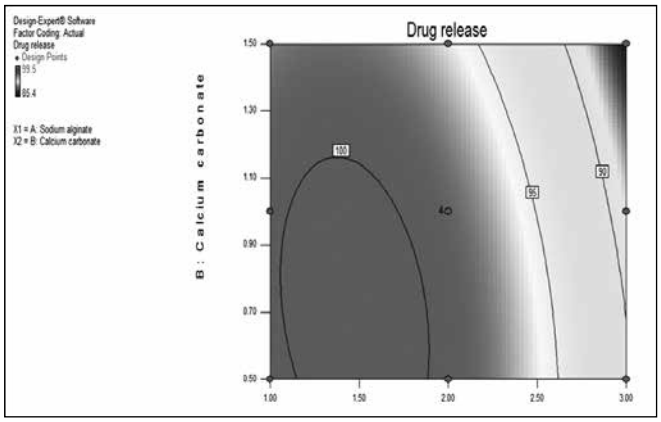

Fig. 5: Contour plots for Y_1 (drug release)

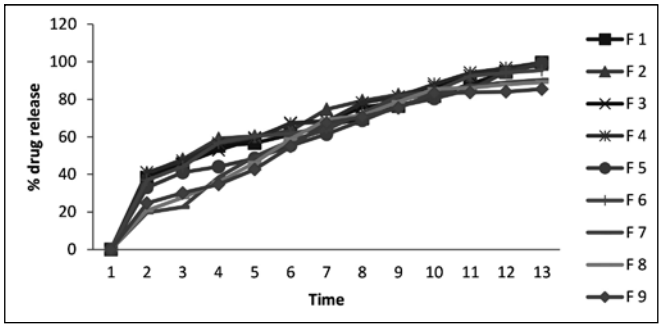

Fig. 6: The comparative DR profiling

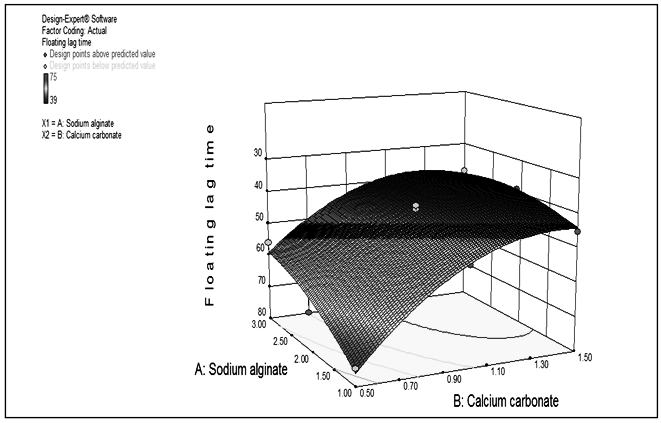

Fig. 7: 3D surface response plots for Y_2

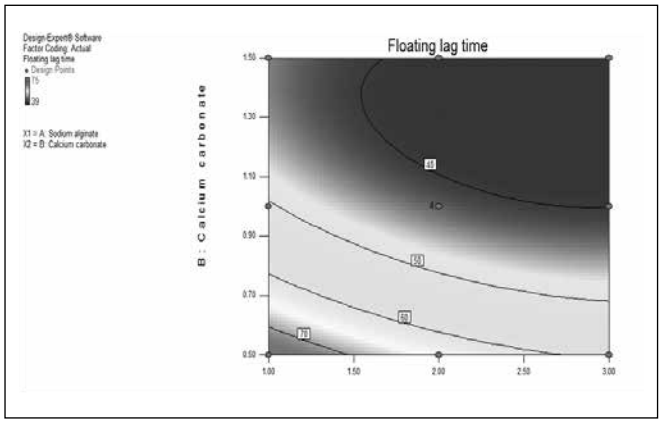

Fig. 8: Contour plots for Y_2

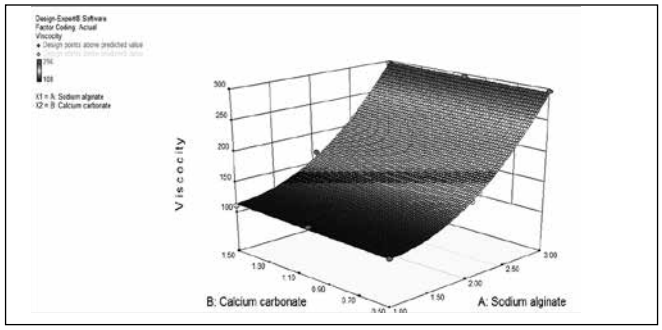

Fig. 9: 3D surface response plots for Y_3

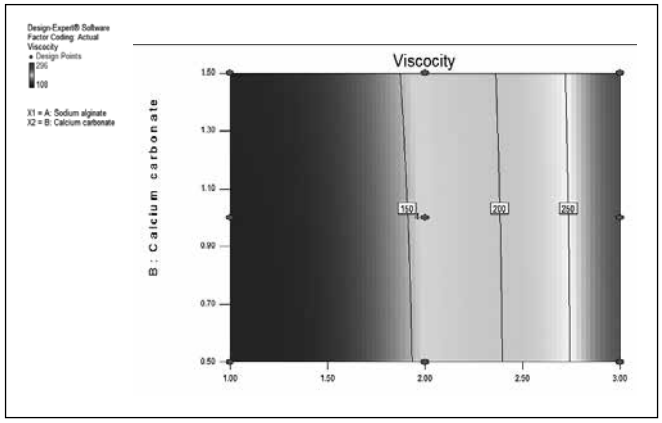

Fig. 10: Contour plots for Y_3

Acyclovir content

A measured quantity of 10 mL formulation was transferred into a 100 mL flask. Subsequently, 70 mL of 0.1N HCl was added to the flask and mixed for a duration of 30 minutes. The resulting mixture was then subjected to sonication for 15 minutes to ensure complete dispersion of the components. Visual inspection confirmed the homogeneity of the solution, and it was further diluted to a final volume of 100 mL using 0.1N HCl followed by filtration. The filtered solution was adequately diluted with 0.1N HCl, and spectrophotometric analysis was performed at a wavelength of 255 nm[18].

Drug release study

It was performed utilizing the USP 2 paddle technique with a total volume of 900 mL of 0.01N HCl

Table VI: Different r^2 values for Y_1(drug release)

Std. Dev.	**0.52**	**R^2**	**0.9942**
Mean	96.02	Adj R^2	0.9894
C.V. %	0.54	Pred R^2	0.9572
PRESS	12.01	Adeq Precision	39.710

Table VII: ANOVA for Y_2

Source	**Sum of Squares**	**Df**	**Mean Square**	**F Value**	**p-value Prob > F**	
Model	1555.83	5	311.17	35.17	0.0002	Significant
A-X_1	170.67	1	170.67	19.29	<0.0046	
B-X_2	988.17	1	988.17	111.69	0.0001	
AB	42.24	1	42.25	4.78	0.0715	
Cor Total	1608.92	11				

Table VIII: Different R^2 values for Y_2

Std. Dev.	**2.97**	**R^2**	**0.9670**
Mean	48.58	Adj R^2	0.9395
C.V. %	6.12	Pred R^2	0.7253
PRESS	442	Adeq precision	17.71

Table IX: ANOVA for Y_1

Source	**Sum of squares**	**Df**	**Mean square**	**F value**	**p-value Prob > F**	
Model	57410.88	5	11482.1	774.67	<0.0001	Significant
A-X_1	51245.04	1	51245.04	3457.36	<0.0001	
B-X_2	37	1	37	2.50	0.1652	
AB	06	1	3.06	0.21	0.6654	
Cor Total	57499.81	11				

Table X: Different r^2 values for Y_3 (viscosity)

Std. Dev.	**3.85**	**R^2**	**0.9985**
Mean	180.66	Adj R^2	0.9972
C.V. %	2.13	Pred R^2	0.9859
PRESS	810.58	Adeq precision	69.72

Table XI: Evaluation parameters of all the batches

Batch No.	Viscosity (cps)	Gel strength (dyne cm^{-2})	Drug content (%)	Drug release (%)	Floating lag time (sec)
F1	108±0.8	827.14±1.07	99.26±0.22	99.5±0.2	78±1.1
F2	112.4 ±0.2	1216.3±2.53	99.13±0.23	99.3±0.8	54±1.5
F3	110.5 ±0.7	2013.23±3.9	98.16±0.23	98.5±0.7	45 ±1.2
F4	152± 1.2	2104.16±2.3	96.03±0.38	99.6±0.7	70±1.8
F5	156 ±1.8	2545.21±1.3	99.2±0.36	99.2±0.1	42±1.3
F6	167.4± 1.1	2027.17±1.1	99.83±0.36	99.4±0.7	39±1.1
F7	296± 0.9	2096.69±1.1	97.13±0.86	90.4±0.8	56±0.9
F8	298± 1.2	2431.17±1.12	97.37±0.63	89.12±0.5	45±0.5
F9	295± 0.7	2798.78±0.8	99.23±0.162	85.4±0.7	39±1.2

at 37±0.5°C for a duration of 12 h. The paddle was set to rotate at a speed of 50 rpm during the study. The samples were analysed at 255 nm at predetermined time intervals[18].

Drug release kinetic studies

Zero order, first order, Matrix, Hixson-Crowell and Korsemeyer-Peppas models were applied considering the drug release and correlation coefficient (r2) was used as a criterion to determine the best fit among the studied models[19].

Determination of sedimentation volume

A 100 mL suspension was placed into a 100 mL graduated cylinder and left undisturbed for 14 days after being properly shaken. At appropriate time intervals, the volume of sediment was recorded[20]. Sedimentation volume (F) was determined using following equation.

$$F = \frac{V_u}{V_o}$$

where, V_u = volume of sediment, V_o = total volume

Floating behaviour

In a paddle-type dissolving test apparatus, 5 mL of developed formulations were dissolved in 0.1 N HCl (900 mL at 37 ^{0}C) and the floating behavior of all formulations was visually examined. The duration it takes for a formulation to start floating on medium is referred to as the buoyancy lag time. Complete floating time is defined as the calculated period during which the formulation remains buoyant on the surface[21].

Stability study

The optimized final formulation underwent stability studies under controlled conditions of 40 °C and 75% RH for 3 months.

RESULTS AND DISCUSSION

For developing the formulation, a variety of excipients were chosen. Sodium alginate was employed as the

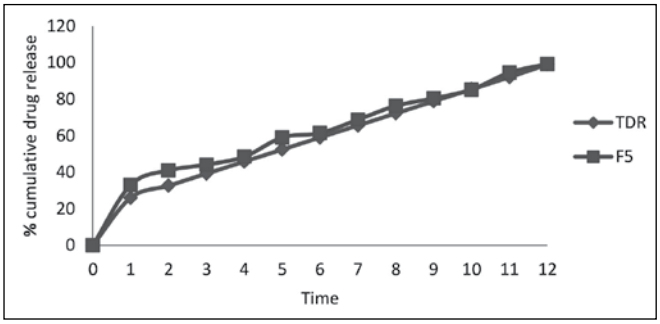

Fig. 11: Comparative analysis for dissolution profile of optimized formulation and theoretical drug release

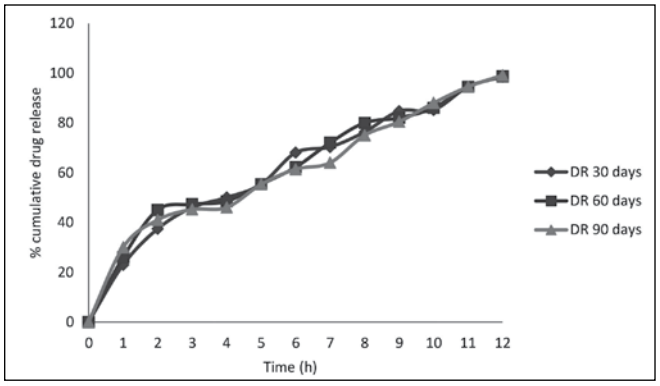

Fig. 12: Dissolution profile of formulation F 5 after 30, 60 and 90 days

Table XII: Evaluation results of optimized batch F5

Sr. No.	Parameter	Results
1	Appearance	Good
2	Taste	Sweet
3	Drug content	99.3% ±0.2
4	pH	6.4 ±0.67
5	Gel strength	2545.21±1.3dyn/cm^2
6	DR at 12 h	99.2 ±0.1
7	Viscosity	156 ±0.4 cps
8	Floating lag time	42 ±1.3sec
9	Sedimentation volume	0.7
10	Gelation time	10 sec
11	Particle size	45 ±0.5µ

Table XIII: Model fitting of the optimised batch F5

Sr. No	Model	R^2
1	Zero-order	0.9959
2	1st order	0.9737
3	Korsemeyer-Peppas	0.9967
4	Hixson-Crowell	0.9527

Table XIV: Drug content over the stability period

Sr. No.	Days	Drug content
1	0	98.52%±0.02
2	30	98.4%±0.19
3	60	98.2%±0.56
4	90	98.14%±0.9

gelling agent, while xanthan gum and HPMC K100M were utilized as suspending agents. Sodium citrate was used as the complexing agent and calcium carbonate was used as a floating agent. Sodium lauryl sulfate was used as the wetting agent. Sucrose was used as the sweetener. Methylparaben and propylparaben were used as preservatives. HPMC K100M was used as a suspending agent and the studies showed that it forms a viscous gel. For this reason less than 1.5 % concentration was useful for the preparation of suspension. Xanthan gum was also tried as a suspending agent and it showed good suspending properties as well as desirable viscosity (easily pourable). Sodium citrate was used as a complexing agent which forms a complex with calcium. Calcium carbonate, when used in a concentration of more than 1.5 %, forms an undesirable precipitate. These results were taken into consideration for further studies.

Drug release calculations and dose fixation

The immediate-release dose was calculated by formula mentioned below (1)

$$\frac{V_d \times C_{ss}}{F} = \frac{50 \times 39.47}{30} = 65.78 \text{ mg}$$

To calculate the total dose necessary for sustained drug delivery from a formulation over a 12 h period was calculated by following formula (2)

$$\text{Total Dose} = \text{IRD}\{1 + (0.693 * t/t_{1/2})\} = 248.12 \text{ mg} \sim 250 \text{ mg}$$

where $t_{1/2}$= 2 h and t = 12 h

Based on the given information, 250 mg of dose was established as the sustained release dose for the formulation. Of this dose, 26% was designated as the immediate release fraction, intended to be released within 1 h to achieve the desired therapeutic effect. The rest of the drug was allocated for release over the subsequent 11 h, with a rate of 6.6% per hour. Fig. 1 shows the drug release profile over 12 h.

Physicochemical characterisation of formulations

The formulated gel formulations were characterized for physicochemical parameters. It has been observed that all formulations were clear and transparent, while the pH of the formulation ranged between 6.2-7.4. The particle size of the suspension was found to be between 15 to 45 µ (Fig. 2).

Drug excipient compatibility study

The DSC thermogram of the formulation blend is shown in Fig. 3, which depicts the DSC thermogram of acyclovir (A) and physical mixture of drug and excipients (B). DSC observations indicate a pronounced endothermic peak at 254.1 ^{0}C, which corresponds to pure acyclovir's melting point. The endothermic peaks remained in their original positions, indicating that the drug did not interact with other excipients present in the formulation. Thus, the excipients and medication in the formulation do not interact with one another.

Optimization by factorial design

ANOVA was applied to identify the significant factors[22, 23]. The factorial design batches in coded form and their responses are presented in Table IV.

Statistical analysis of the drug release at 12 h (Y1)

Based on the data presented in Table V, Model F-value of 206.21 is indicated as a significant model.

Given the presence of noise, there is a mere 0.01 percent probability for a "Model F-value". In this scenario, model terms hold significance when the "Prob > F" value is less than 0.0500. Specifically, in this situation, terms A, B, and AB are considered important model terms. The quadratic equation for drug release can be given by

$$Y_1 = 98.82 - 5.50X_1 - 1.66X_2 - 1\ X_1X_2 - 4.66X_1^2 - 0.94X_2^2$$

Fig. 4 depicts three-dimensional response surface plots which indicate that when sodium alginate and calcium chloride concentrations rise, drug release at 12 h decreases. As a result, changing both independent factors had a considerable impact Y1. Fig. 5 exhibits contour plots illustrating the impact of independent variables on Y1. The influence of these variables is visually represented. In Table VI, the R2 values for Y1 are presented. The "Adeq Precision" metric measures the signal-to-noise ratio, with a ratio greater than 4 considered desirable. With a ratio of 39.710, the signal is deemed adequate.

Fig. 6 showcases the comparative drug release profiles of all the formulation batches. The release profiles of these batches exhibit variation, with drug release after 12 h ranging from 85% to 99.5%.

Statistical analysis of the floating lag time (Y2)

The Model F-value of 35.17 indicates the significant model. Considering the presence of noise, the occurrence of a "Model F-value" of this magnitude is only expected with a 0.02 % chance. Statistical analysis using ANOVA was conducted, and the results can be found in Table VII. The polynomial equation for Y2 can be given by

$$Y_2 = 42.33 - 5.33\ X_1 - 12.83\ X_2 + 3.25X_1\ X_2 + 3X_1^2 + 9.5X_2^2$$

Fig. 7 illustrates three-dimensional reaction surface plots that indicate that floating lag time reduces when calcium carbonate and sodium alginate concentrations rise. As a result, changing both independent variables had a considerable impact on response Y2. Fig. 8 shows contour plots depicting the influence of various proportions of independent factors on the response Y2. Table VIII displays the various R^2 values for Y2.

The "Adeq Precision" metric assesses the signal-to-noise ratio, with a ratio exceeding 4 considered desirable. In this case, the ratio of 17.71 indicates an adequate signal, indicating that the model is reliable for navigating the design space.

Statistical analysis of viscosity (Y3)

The statistical significance is supported by the Model F-value of 774.67. Considering the presence of noise, the probability of observing a "Model F-value" of this magnitude is only 0.01 %. In this scenario, model terms hold importance when the "Prob > F" value is below 0.0500. Specifically, in this situation, terms A and B are considered important model terms. The statistical analysis was conducted using ANOVA, and the results can be found in Table IX.

The quadratic equation for Y3 can be given by

$$Y_3 = 157.85 + 92.42\ X_1 - 2.48X_2 - .87X_1\ X_2 + 44.96X_1^2\ X_2 + 0.66X_2^2$$

Fig. 9 shows three-dimensional response surface graphs for Y3. These plots are useful for examining the impact of two variables on a response at the same time. Fig. 9 illustrates that viscosity rises as sodium alginate and calcium carbonate concentrations rise[24]. The Y3 response (viscosity) was significantly affected by variations in the proportion of independent variables. These changes had a substantial impact on the observed results.

Fig. 10 illustrates the contour plots depicting the influence of different proportions of independent variables on the floating lag time. The plots visually demonstrate the impact of these variable proportions on the observed floating lag time. The different R^2 values for Y_3 are shown in Table X.

The "Adeq Precision" metric is used to measure the signal-to-noise ratio, with a ratio exceeding four considered favorable. With a signal-to-noise ratio of 69.72, the signal is deemed sufficient. Therefore, the design space can be effectively explored and navigated using this concept. The viscosity of all batches ranges from 108 to 295 cps, and it was observed that as the concentration of the independent variable grew, so did the viscosity.

The varying proportions of sodium alginate and calcium chloride had significant effect on drug release, floating lag time and viscosity, according to ANOVA-based factorial analysis. The F5 batch, with a viscosity of 156 cps and superior gel strength, had the shortest floating lag time (42 sec) among F1 to F9 batches. According to the results of the investigation, F5 is the best batch, and hence it was further studied. Table XI shows an overview of all the assessment parameters for all batches.

Comparisons of release profiles, floating lag time and viscosity

For batch F5, the similarity factor (f2) values were higher than 50 when compared with the theoretical

release profile, indicating a favorable level of similarity in dissolution. The batch F5 shows a similarity value of f2 (72.20) with minimum viscosity, floating lag time and optimum gel strength. Optimized batch F5 shows 99.2 % drug release after 12 h and theoretical drug release is 99 %. Comparative drug release profile of F5 batch and calculated theoretical drug release are shown in Fig. 11.

Evaluation of optimized formulation

The evaluation results of optimized batch F5 are depicted in Table XII. The appearance was good, with a sweet taste. The results of assay, content uniformity and weight variation showed compliance of the formulation with the official compendia requirement. The natural anionic gelling polymer sodium alginate, which is biodegradable, demonstrates its effectiveness at pH 1.2 and good gelation properties in the stomach environment. It aided in delaying the drug's release for 12 h. The particle size distribution profile revealed little variance in particle size.

Drug release kinetic studies

To further elucidate the drug release pattern, optimised formulation was fitted to several mathematical models. The R^2 value indicates the best-fitting kinetic model. Table XIII provides the interpretation. Because the diffusion value of the exponent in this investigation is 0.4293, the formulations are released mostly via Fickian transport. It means that a diffusion process is in charge of medication release. The optimised formulation was determined to have the best fit with Korsemeyer-Peppas kinetics (R^2 = 0.9967). In this model, the value of 'n' characterizes the drug release mechanism. When $n \leq 0.5$, it indicates Fickian diffusion, where the release rate is independent of time (t). Anomalous (non-Fickian) transport is indicated when $0.5 < n < 1.0$, and a value of n=1 signifies zero-order release. By analyzing the data, the value of n for the optimized batch was found to be 0.4293, suggesting that its release pattern corresponds to Fickian diffusion.

Stability study

The color of the F5 formulation remained consistent before and after stability studies, indicating color stability. The drug content of formulation F5 was assessed after 30, 60 and 90 days. Table XIV reveals that the optimized batch did not show drastic change in drug content across different storage conditions and time periods. Additionally, Fig. 12 demonstrated no significant change in drug release values over 12 h during the stability studies. These findings suggest that the optimized batch maintained its stability throughout the study period.

CONCLUSION

Based on optimization research, independent variables were found to impact on drug release, floating lag time and viscosity. Specifically, increasing the sodium alginate and calcium carbonate resulted in a deceleration of acyclovir release from the gel. In addition, when the sodium alginate and calcium carbonate concentrations increased, the viscosity increased as well. Batch F5, showing optimum results in terms of release profile and viscosity, was considered an optimum formula. The optimal formulation consisted of 2% w/V of sodium alginate and 1% w/V of calcium carbonate. This formulation exhibited a floating lag time of 42±1.3 seconds, a floating duration of over 12 h, and a drug release of 99.2±0.36% after 12 h.

ACKNOWLEDGEMENT

The authors would like to thank AICTE, New Delhi, India for providing a scholarship to Pallavi Chiprikar.

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