CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Online at: www.iajps.com *Research Article*

FORMULATION, DEVELOPMENT AND EVALUATION OF INTRAGASTRIC FLOATING INSITU GEL OF BRIVARACETAM

Ms. Singh Garima S.[1*], Dr. Kantilal B. Narkhede[1], Dr. Anuradha P. Prajapati[2], Dr. Sachin B. Narkhede[3]

[1] * Department of Pharmaceutics, Smt. B.N.B. Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat, India.

[1] Associate Professor, Department of Pharmaceutics, Smt. B.N.B. Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat, India.

[2] Head of The Department of Pharmaceutics, Smt. B.N.B. Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat, India.

[3] Principal, Smt. B.N.B. Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat, India.

Article Received: March 2021 **Accepted:** March 2021 **Published:** April 2021

Abstract:

The aim of the present study was to establish and evaluate gastro retentive in situ gelling system of Brivaracetam using HPMC K100M, sodium alginate gelling polymer, calcium chloride and sodium citrate as a possible linking agent to treat bifocal epilepsy. In situ drug delivery systems that form polymeric formulations are in sol form before being administered to the body, but once administered, that under gelation in situ forms a gel. The composition of the gel depends on factors such as temperature fluctuations, pH changes and the presence of ions in which the drug is released continuously and in a controlled manner. In situ gelling floating systems were prepared by dissolving various concentrations of sodium alginate in distilled water, to which varying concentration of drug. The results show that formulas containing a combination of polymers (sodium alginate and HPMC K 100 M) show more delay in drug release than formulas based solely on sodium alginate by the same percentage. The F2 formulation was very well prepared for the ability to control long-term drug release with suitability in terms of pH and viscosity. The insitu-gel reflects expected, viscosity, drug content, pH, in vitro gelling capacity, in vitro floating capacity, water absorption capacity and continuous drug release. The gastro retentive Brivaracetam insitu gel can be prepared using a floating method to prolong the stay in the stomach and thus increase absorption.

Keywords: Insitu gel, Gelation, Gastro Retentive Drug Delivery System, Epilepsy, Brivaracetam

Corresponding author:
Ms. Singh Garima S.
E-301, Dhanlaxmi Society,
Koparli Road, Chharwada, Vapi, Gujarat, India.
Email ID:*ssinghgarima9@gmail.com*

QR code

Please cite this article in press Singh Garima Set al., ***Formulation, Development and Evaluation of Intragastric Floating In-situ Gel Of Brivaracetam****..,Indo Am. J. P. Sci, 2021; 08(04).*

INTRODUCTION: [1-6]

In more recent times, insitu-gel systems have been used as regulated drug delivery vehicles. There are many in-situgel polymeric delivery systems benefits' namely, easy management and reduced frequency of management, improved patient compatibility, and comfort. Normal gel formation occurs as a result of a single substance or combination of various factors such as pH changes, temperature fluctuations, and solvent exchanges. Therefore, in a situ gelling system with., A different line such as oral, nasal, and ophthalmic can be Prepared. Various natural and synthetic polymers were used for the formulation development of in situ forming drug delivery systems. In situ gelling system helps to increase the availability of the drug in comparison to the other liquid formulations. The gel produced by the in-situ gelling system, is lighter than abdominal fluid, floats above the contents of the stomach, or adheres to the abdominal mucosa due to the abundance of polymer and produces stomach retention in volume form and prolongs abdominal stay leading to longer delivery of gastrointestinal tract (GI). The system uses polymers that show the transformation of the sol-to-gel phase due to changes in certain physicochemical parameters. The formulation of the sol-gel system of the stomach involves the use of a gelling agent that can create a stable sol system containing the dispersed drug and other active ingredients. The implantation of this sol system will be found in the abdominal area, which is caused by ionic complex due to changes in pH. The formulation adopted is a solution of sodium alginate containing calcium chloride (as a source of Ca^{2+}) and sodium citrate, which makes Ca^{2+} ions free and releases them only to the acidic area of the stomach. Sodium alginate acts as a gelling agent and can produce texture in the final product ranging from hard, nonelastic, brittle gels to gel fluid. Free Ca^{2+} ions are bonded with polymeric chains of sodium alginate thus causing the bonding of the polymer chains to form a matrix structure. This gelation involves the formation of two helical cones followed by a re-assembling of the two helical components to form a three-dimensional network by mixing cations with hydrogen bonding and water.

In this way, the formation remains in a liquid form up to the stomach, where the gelation of sodium alginate occurs immediately.

Brivaracetam is a chemical analogue of levetiracetam with ten times more Potency. It is used for the treatment of bifocal epilepsy, mild, or complex partial seizures. It is absorbed throughout the GI tract. It belongs to BCS Class I. It has a half-life of 9h. The current study aims to develop a liquid solution containing Brivaracetam that will form gel when combine with the gastric juice, keeping the gel made to float in the stomach for longer to ensure better absorption of the drug.

MATERIALS AND METHODS:[7,8]

Materials

Brivaracetam was obtained as gift sample. Sodium alginate, sodium citrate, calcium chloride and hydroxypropyl methylcellulose (HPMC) K100M were taken from Vishal chemicals. Other Ingredients used are of analytical reagent grade.

Formulation of insitu gelling solutions

Solutions of sodium alginate in various components [Table 1] were prepared by the volume of selected water containing calcium chloride and sodium citrate. The solution was heated to 60 ° C by stirring. After cooling below 40 ° C; one-third of the selected water containing HPMC K100M is added by continuous stirring. In addition, Brivaracetam (120mg), Sodium Bicarbonate, Methylparaben, Propylparaben, and Sodium Saccharine were added to the above mixture, and the final volume was formed up to 10 ml of distilled water.

Evaluation of preliminary batches for selection of working concentration range of gelling polymers.

Different formulations were prepared using various concentration ranges of sodium alginate for selection of working concentration range of gelling polymers on the basis of invitro gelling capacity and pourability.

In vitro gelling capacity

the volume of in vitro gelling of the in situ gelling solution was determined by taking 500 mL of 0.1N hydrochloric acid (HCl, pH 1.2) into the beaker. Properly measured 10 mL of the prepared solution was added to HCl with aagitation (mild) to prevent breakage of the formed gel. Gelling was visually noticeable in quality measurements and reported according to the Strokesdepending on their gelation pattern

+ = gels after few minutes, dispersed rapidly
++ = gelation immediate remains for few hours
+++ = gelation immediate remains for an extended period.

Determination of viscosity

The viscosities of the prepared formulas are determined by the brook field viscometer. Samples (100 ml) were sheared at a rate of 50 rpm / min using a suitable spinning rod at 37 ° C or at room

temperature. The viscosity measurement of each sample was made in threes, each measurement taking approximately 30 s.

Table 1 : Preliminary Trial Batch

Batches	Sodium Alginate	Viscosity (cps)	In vitro Gelling Capacity	Gel Strength (dyne/cm	Pourability
S1	0.6	178.3±1.2	---		Easy to Pour
S2	0.8	212.6±2.4	++-		Easy to Pour
S3	1.0	230.6±0.9	+++	836.2±0.05	Easy to Pour
S4	1.2	260.3±1.2	+++	2412.3±2.7	Easy to Pour
S5	1.4	280.3±1.2	+++	2746.2±3.2	Pourable
S6	1.6	328±1.6	+++		Difficult to Pour
SD : Standard Deviation					

Preliminary Trial Batches forSelection of Working Range of Complexing Agent (Calcium Chloride), Hydroxypropyl methylcellulose K100M and sodium bicarbonate concentration.

On basis of pourability and invitro gelling capacity 1.2% w/v concentration of sodium alginate was fixed. Further formulations was prepared using sodium alginate 1.2% w/v with the varying concentration of calcium chloride from 0.05 % w/v to 0.2 % w/v. working concentration of polymers were selected on the basis of its effect on release pattern. The rest of ingredient were not changed.

Table 2 :Preliminary Trial Batch

% W/V	T1	T2	T3	T4	T5	T6
Brivaracetam	1.2	1.2	1.2	1.2	1.2	1.2
Sodium Alginate	1.2	1.2	1.2	1.2	1.2	1.2
Calcium Chloride	0.05	0.075	0.1	0.125	0.15	0.2
HPMCK100M	-	-	-	0.5	1	1.5
Sodium Bicarbonate	0.4	0.8	1.2	0.4	0.8	1.2
Sodium Citrate	0.2	0.2	0.2	0.2	0.2	0.2
Sodium Sachharin	0.05	0.05	0.05	0.05	0.05	0.05
Propyl Paraben	0.008	0.008	0.008	0.008	0.008	0.008
Methyl Paraben	0.04	0.04	0.04	0.04	0.04	0.04

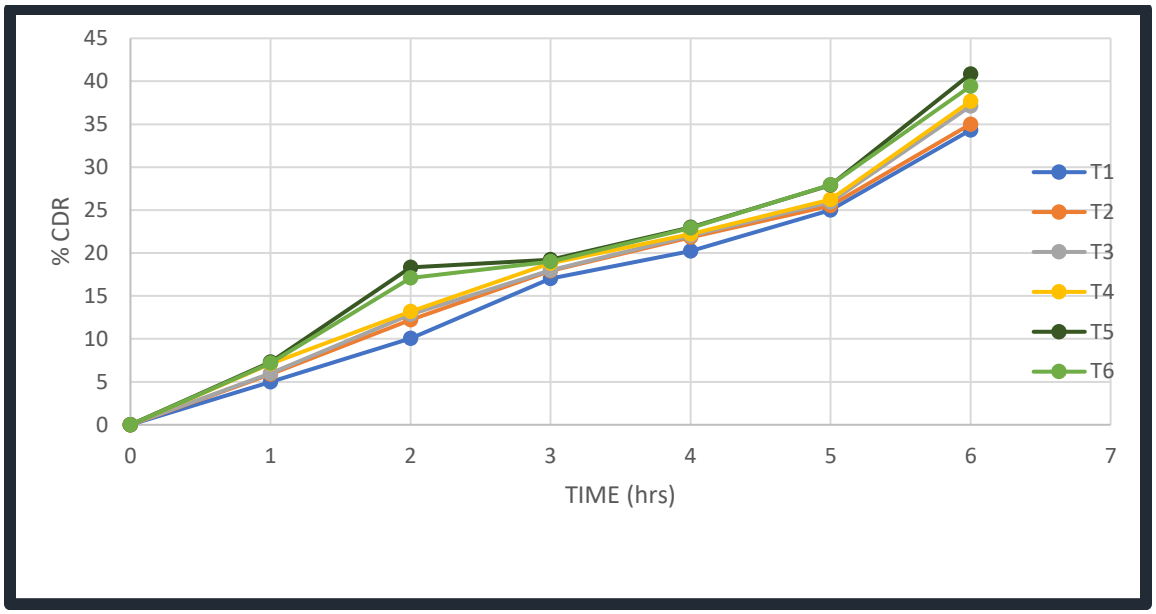

Figure 1 : %CDR Vs Time Graph

So from the above mentioned graph of %CDR vs Time the T5 having highest drug release was optimized and calcium chloride having 0.15% w/v , Sodium Bicarbonate 0.8%w/v, HPMCK100M 1% W/V was selected

Formulation Development

Preparation

- Sodium alginate solutions were prepared in half volume of distilled water containing Calcium Chloride and Sodium Citrate. This solution was heated to 60°C with stirring. After cooling below 40°C; another one-third quantity of distilled water containing HPMC K100M was added with continuous stirring. Further, Brivaracetam, Sodium bicarbonate, MethylParaben, PropylParaben, and Sodium Saccharine were added to above mixture, and final volume was made up to 10 ml with distilled water.

Experimental Design

- **Full Factorial Design:** A 3^2 randomized full factorial design was adopted to optimize the variables. In the design, 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The concentrations of,
  - Sodium Alginate (X_1)
  - Calcium Chloride (X_2)

➢ Were chosen as independent variables, as their marked effects were seen on drug release. And Floating Lag Time and % Drug Release at 1, 6, 18 hours were selected as dependent variables. The response (Y) is measured for each trial.

$Y= \beta_0+\beta_1X_1+\beta_2X_2+\beta_{12}X_1X_2+\beta_{11}X_1^2+\beta_{22}X_2^2$

➢ Where, Y is the dependent variable, β_0 is arithmetic mean response of the nine runs, β_1 is estimated coefficient for factor X_1, and β_2 is estimated coefficient forfactorX_2.

➢ 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 howresponse changes when two factors are simultaneously changed, the polynomial terms ($X_1^2$and X_2^2) are involved to investigate non linearity.

➢ The polynomial equation can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative).

➢ A 3^2 randomized full factorial design was utilized in the present study. The design layout and coded value of independent factor are shown. The factors were selected based on preliminary study.

Full Factorial Design Batches of oral Floating In Situ Gel

Table 3 : Coded Values of Factor and Level

Sr. No.	Formulation Code	Coded Factor Level	
		X1	X2
1.	F1	-1	-1
2.	F2	0	-1
3.	F3	+1	-1
4.	F4	-1	0
5.	F5	0	0
6.	F6	+1	0
7.	F7	-1	+1
8.	F8	0	+1
9.	F9	+1	+1

Variables for Factorial Design

Table 4 : List of Independent and Dependent Variables

Independent Variable		Dependent Variable			
X_1	X_2	Y_1	Y_2	Y_3	Y_4
Conc.of Sodium Alginate	Conc.Of Calcium Chloride	Floating Lag Time	% Drug Release at 1hr	% Drug Release at 6hr	% Drug Release at 18hr

Table 5: Design Layout

REAL VALUES			TRAMSFORMED VALUES		DEPENDENT VARIABLE			
BATCH CODE	SODIUM ALGINTE CONCENTRATION (% W/V)	CALCIUM CHLORIDE CONCENTRTION (% W/V)	X1	X2	Y1 FLOATING LAG TIME (seconds)	Y2 CDR(1HR) (%)	Y3 CDR (6HR) (%)	Y4 CDR (18HRS) (%)
F1	1	0.075	-1	-1	45.28	7.4	40.84	97.3
F2	1.2	0.075	0	-1	41	7.2	40.68	96.01
F3	1.4	0.075	1	-1	38.24	6.9	39.86	93.52
F4	1	0.10	-1	0	41	6.88	38.67	92.84
F5	1.2	0.10	0	0	37.5	6.4	38.21	91.64
F6	1.4	0.10	1	0	34.21	6.1	37.88	91.3
F7	1	0.15	-1	1	32.14	5.66	37.11	90.94
F8	1.2	0.15	0	1	30.21	4.3	36.97	90.7
F9	1.4	0.15	1	1	26	3.3	36.63	90.39

Data Analysis and Model Validation

- Statistical validation of the polynomial equations generated by Design Expert 12 was established on the basis of ANOVA in the software. A total 9 runs were generated. The models were evaluated in terms of statistically significant co-efficient and R^2 values. Various feasibility and grid searches were conducted to find the composition of optimized formulations.
- Various 3D response surface graphs were provided by the Design Expert 12 software. By intensive grid search performed over the whole

experimental region, one optimum checkpoint formulations was selected to validate the chosen experimental domain and polynomial equations.

- The checkpoint formulation was prepared and evaluated for various response properties. The resultant experimental values of the responses were quantitatively compared with the predicted values to validate the equation.

Statistical Analysis

- A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2$$

Contour Plot and Surface Plot of Design

- The optimization of formulation was carried out by plotting contour plots (2-D) and surface plots (3-D) for all observed dependent variables. Here, contour plots and surface plots were drawn using the Design Expert 12 software. These types of plots are useful in study of the effects of two factors on the response at one time.

EVALUATON F FLOATING ORAL INSITU GEL [9,10]

Clarity

The clarity of various formulations was determined by visual inspection under black and white background by using clarity test apparatus and it was graded as follows; Turbid +, Clear ++, Very clear (glassy) +++.

pH of the Solution and Gel

Each formulated batch pH was measured using pH meter which was previously calibrated using standard buffers of pH 4 & pH 7.

Gelation Study

In vitro gelling capacity of in situ gelling solution was determined by taking 500 mL of 0.1N hydrochloric acid (HCl, pH 1.2) in a beaker. Accurately measured 10 mL of prepared solution was added to HCl with mild agitation that avoids breaking of formed gel. Gelling was observed visually by qualitative measurement and reported in terms of strokes depending on their gelation pattern

Table 6 : Degree of Gelation

Sign	Grades of Gelation
-	No gelation
+	Weak gelation; dissolves rapidly
+ +	Immediate gelation remains for few hrs (less stiff gel)
+ + +	Immediate gelation remains for extended period (stiff gel)
+ + + +	Very stiff gel

Viscosity

The viscosities of the prepared formulations were determined by brook field viscometer. The samples (100 ml) were sheared at a rate of 50 rpm/min using suitable spindle at 37°C or at room temperature.

Viscosity measurement for each sample was done in triplicate, with each measurement taking approximately 30 s.

Determination of drug content

All preliminary batches were evaluated for drug content. Drug content for sodium alginate formulation varies from the range of 98.22% to 100.75%.

Floating lag time

The FLT is defined as the time taken by the gel to reach the top from the bottom of the dissolution flask. The FLT of gel was determined by visual inspection using a USP (Type II) dissolution test apparatus containing 900 ml of 0.1N HCl at 37°C ± 0.5°C.

Gel strength

The gel strength apparatus was fabricated in house using a measuring cylinder of 1.2 cm radius and a bore of 0.1 mm at its base. A needle 2 cm in length was used to which a nylon thread was tied. Test formulation (10 ml) was taken in the cylinder with

Floating duration

The duration of time for which the formulation floats constantly on the surface of the medium is known as the duration of floating. The duration of floating of gels was determined using a dissolution test apparatus USP (Type II) containing 900 ml of 0.1N HCl at 50 rpm at 37°C ± 0.5°C.

***In vitro* drug release studies**

The drug release study was carried out using USP Type II paddle type apparatus at 37°C ± 0.5°C and at 50 rpm using 900 ml of a dissolution medium having 0.1N HCl (pH 1.2). In situ gel equivalent to 120 mg of Brivaracetam was used for the test. 5 ml of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 µm membrane filter, dilute suitably, and analyzed by ultraviolet spectrophotometer at 210 nm. Same amount of fresh dissolution medium was replaced immediately after

withdrawal of the test sample. Each dissolution study was carried out for a period of 18h.

RESULT AND DISCUSSION:

Identification of Drug by FTIR

.

Identification study was performed using FTIR spectrophotometer. The characteristic absorption peaks of Brivaracetam were obtained at different wave numbers. The peaks obtained in the spectra of pure drug correlates with the peaks of official spectrum which confirms the purity of drug

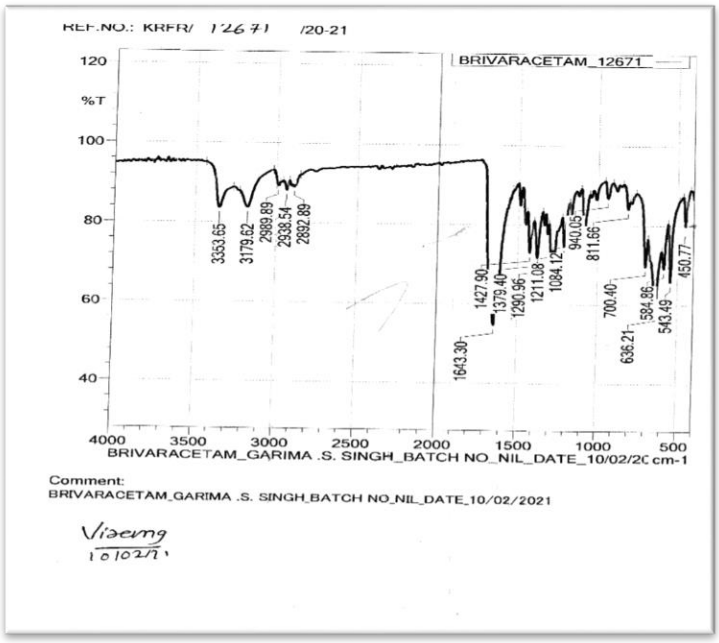

Fig 2 : Observed FTIR spectra of Brivaracetam

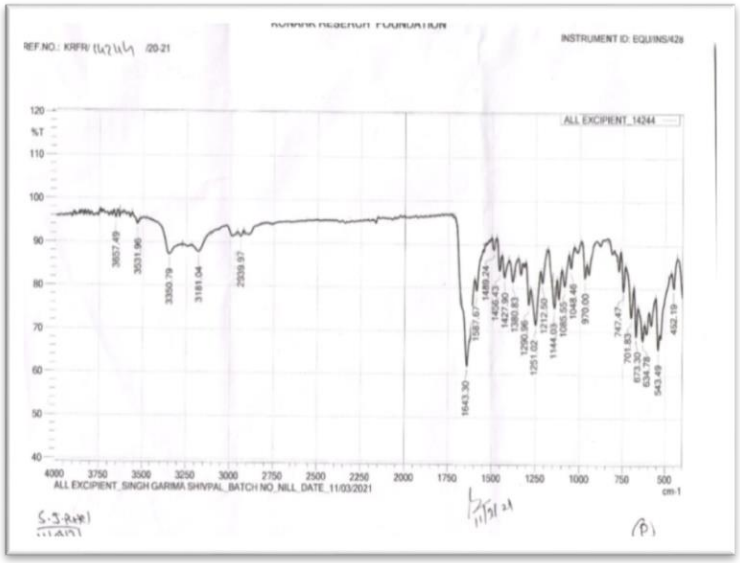

Fig 3 : Observed FTIR spectra of Brivaracetam with all Excipient

Evaluation of Factorial Batches

Table 7 : Evaluation of Factorial Batches

Batch	Clarity	pH	Gelation Study	Viscosity(cps) (Solution)	Drug Content (%)	Gel strength (dyne/cm^2)	Floating Duration(hrs)	Floating Lag Time (sec)
F1	++	6.59 ± 0.02	+	198.3 ± 4.10	100.05 ± 1.07	930.12 ± 1.03	> 18	45.28 ± 0.01
F2	**++**	**6.73 ± 0.01**	**++**	**210.2 ± 3.26**	**99.86 ± 0.31**	**3824.12 ±2.51**	**> 18**	**41 ± 0.02**
F3	++	6.65 ± 0.01	++	222.6 ± 5.73	100.22 ± 0.31	2512.23 ± 3.2	> 18	38.24 ± 0.06
F4	++	6.61 ± 0.01	++	274 ± 5.88	99.07 ± 0.25	2411.1 ± 2.1	> 18	41 ± 0.02
F5	++	6.78 ± 0.005	+++	280.3 ± 7.71	97.29 ± 0.36	3492.11 ± 1.2	> 18	37.5 ± 0.04
F6	++	6.82 ± 0.015	+++	287.3 ± 3.39	98.15 ± 0.31	4082.2 ± 1.02	> 18	34.21 ± 0.01
F7	++	6.85 ± 0.01	+++	302 ± 4.98	97.25 ± 0.20	3212.1 ± 1.01	> 18	32.14 ± 0.04
F8	++	6.88 ± 0.01	++++	322.2 ± 5.73	98.13 ± 0.30	3624.13 ± 2.01	> 18	30.21 ± 0.02
F9	++	6.56 ± 0.05	++++	348.6 ± 5.88	98.20 ± 0.20	2519.28 ± 3.1	> 18	26 ± 0.04

Table 8 : Dissolution Study of Factorial Batches

% Drug Release									
Time (min.)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	**0**	0	0	0	0	0	0	0
30	5.73 ± 0.14	**4.55 ± 0.08**	4.53 ± 0.08	4.29 ± 0.02	2.62 ± 0.03	2.38 ± 0.02	2.14 ± 0.01	1.91 ± 0.16	1.67 ± 0.01
60	7.4 ± 0.09	**7.21 ± 0.21**	6.90 ± 0.07	6.88 ± 0.10	6.45 ± 0.08	6.1 ± 0.03	5.66 ± 0.02	4.3 ± 0.15	3.3 ± 0.21
120	16.05 ± 0.23	**14.15 ± 0.09**	11.29 ± 0.02	11.26 ± 0.03	10.09 ± 0.07	8.90 ± 0.03	8.16 ± 0.01	7.449 ± 0.15	6.00 ± 0.02
180	20.92 ± 0.22	**16.130 ± 0.08**	19.48 ± 0.24	13.73 ± 0.16	13.94 ± 0.23	14.18 ± 0.07	12.02 ± 0.04	12.24 ± 0.02	11.58 ± 0.01
240	25.09 ± 0.26	**29.14 ± 0.23**	21.38 ± 0.21	21.90 ± 0.16	19.06 ± 0.08	19.56 ± 0.07	18.80 ± 0.08	18.54 ± 0.29	18.57 ± 0.23
300	34.32 ± 0.33	**31.68 ± 0.36**	29.90 ± 0.34	28.91 ± 0.18	28.74 ± 0.25	25.61 ± 0.11	22.01 ± 0.06	21.03 ± 0.69	19.63 ± 0.63
360	40.84 ± 0.33	**40.68 ± 0.02**	39.86 ± 0.16	38.67 ± 0.03	38.21 ± 0.02	37.88 ± 0.07	37.11 ± 0.02	36.97 ± 0.15	36.63 ± 0.07
1080	97.3 ± 0.02	**96.01 ± 0.09**	93.52 ± 0.16	92.84 ± 0.08	91.64 ± 0.23	91.3 ± 0.25	90.94 ± 0.11	90.7 ± 0.07	90.39 ± 0.63

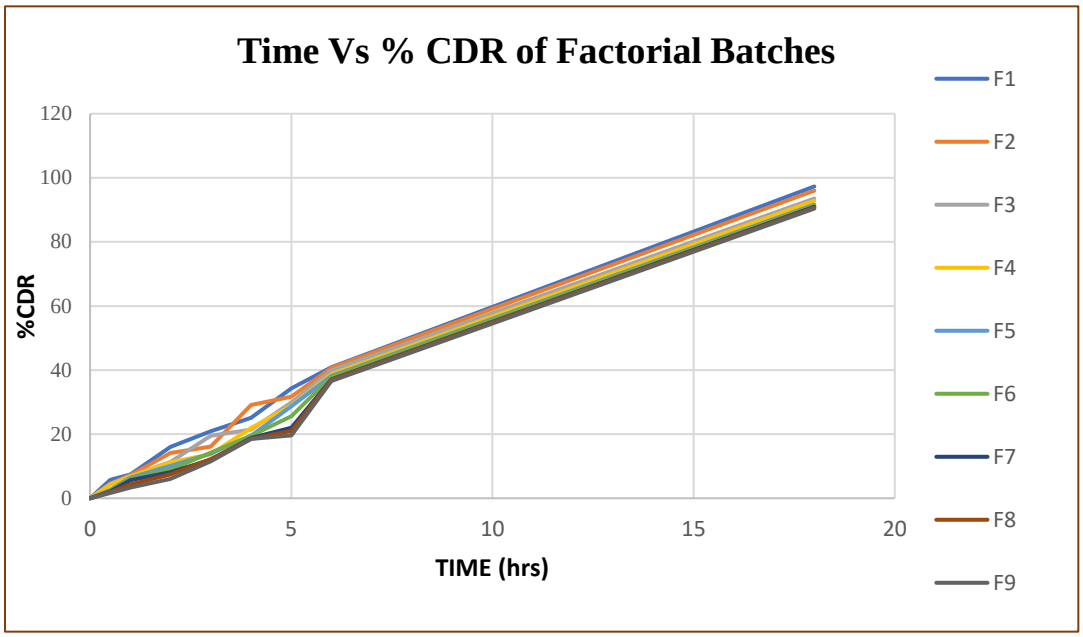

Figure 4 : %CDR Vs Time Graph

Statistical Analysis

Three level factorial was carried out using three different variable using design Expert software. In these concentration of Sodium Alginate and Concentration of Calcium Chloride was selected as independent Variable and % Drug Release at 1hr, 6hr, 18hr along with Floating Lag time was Selected as Dependent Variable

Table 9 : ANOVA Table for Y1(Floating Lag Time)

Transform | Fit Summary | Model | ANOVA | Diagnostics

Analysis of Variance

ANOVA for Quadratic model

Response 1: F.L.T

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	293.48	5	58.70	140.27	0.0009	significant
A-A	66.47	1	66.47	158.84	0.0011	
B-B	218.04	1	218.04	521.08	0.0002	
AB	0.2025	1	0.2025	0.4839	0.5367	
A^2	0.0168	1	0.0168	0.0402	0.8540	
B^2	8.75	1	8.75	20.91	0.0196	
Residual	1.26	3	0.4184			
Cor Total	294.74	8				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

Table 10 : Fit Statistics And Coefficient Table for Y1(Floating Lag Time)

Fit Statistics | Model Comparison Statistics

Fit Statistics

Std. Dev.	0.6469		R^2	0.9957
Mean	36.18		**Adjusted R^2**	0.9886
C.V. %	1.79		**Predicted R^2**	0.9487
			Adeq Precision	35.4304

The **Predicted R^2** of 0.9487 is in reasonable agreement with the **Adjusted R^2** of 0.9886; 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 35.430 indicates an adequate signal. This model can be used to navigate the design space.

Coefficients | Coded Equation | Actual Equation

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	37.63	1	0.4822	36.10	39.17	
A-A	-3.33	1	0.2641	-4.17	-2.49	1.0000
B-B	-6.03	1	0.2641	-6.87	-5.19	1.0000
AB	0.2250	1	0.3234	-0.8043	1.25	1.0000
A^2	-0.0917	1	0.4574	-1.55	1.36	1.0000
B^2	-2.09	1	0.4574	-3.55	-0.6360	1.0000

$$Y=37.63 - 3.33X_1 - 6.03x_2 - 0.0917X_1^2 - 2.09X_2^2 + 0.2250X_1X_2 + \varepsilon$$

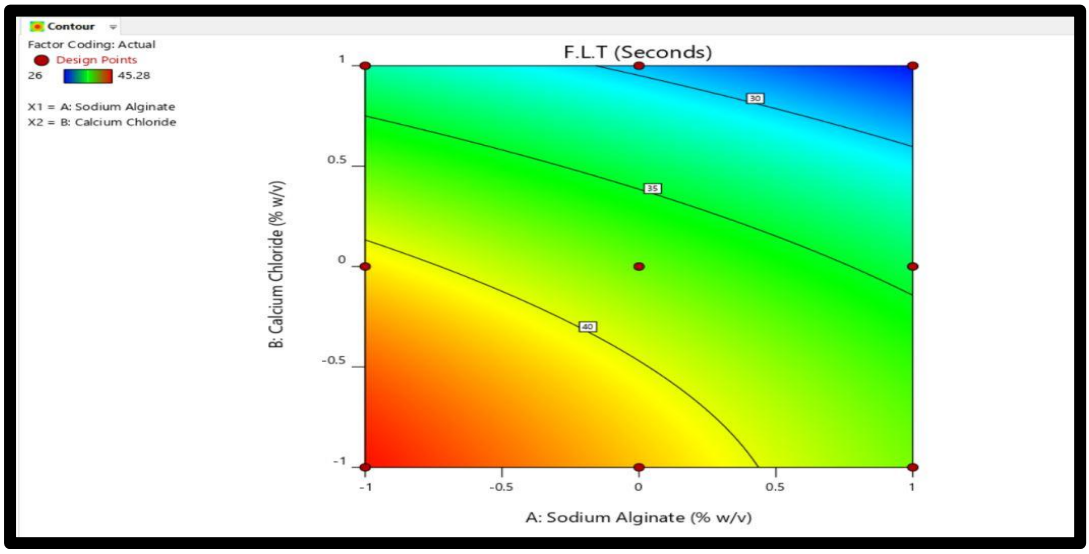

Figure 5: 2D Contour Plot for Y1

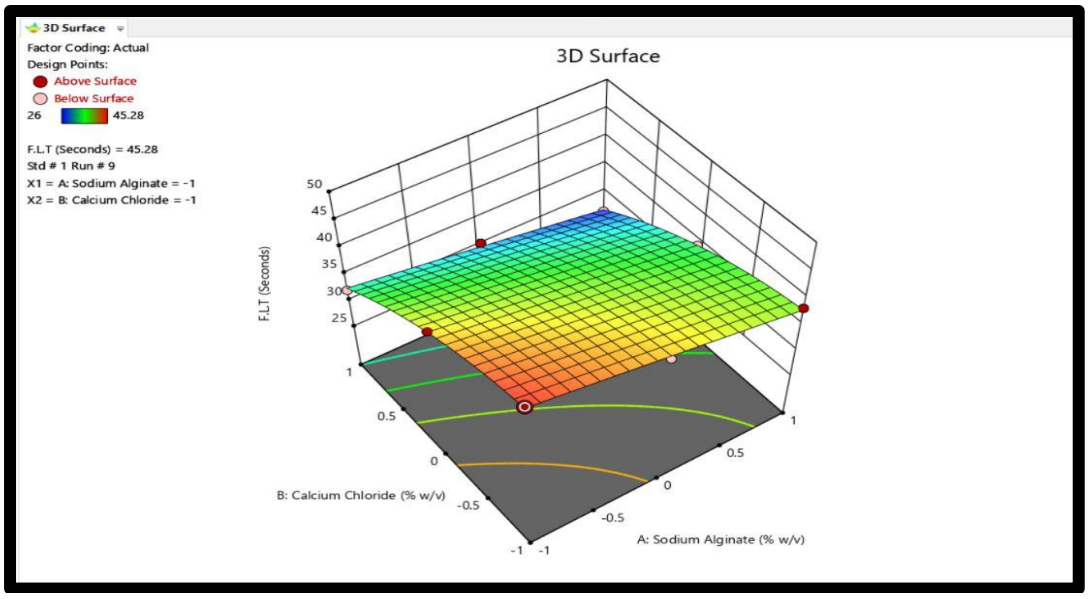

Figure 6 : 3DSurface Plot for Y1

Table 11 : ANOVA Table for Y2(% Drug Release at 1hr)

Analysis of Variance

ANOVA for Quadratic model

Response 2: CDR (1hr)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	15.29	5	3.06	57.79	0.0035	significant
A-A	2.21	1	2.21	41.73	0.0075	
B-B	11.32	1	11.32	213.86	0.0007	
AB	0.8649	1	0.8649	16.35	0.0272	
A^2	0.0108	1	0.0108	0.2033	0.6827	
B^2	0.8889	1	0.8889	16.80	0.0263	
Residual	0.1587	3	0.0529			
Cor Total	15.45	8				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

Table 12 : Fit Statistics And Coefficient Table for Y2(% Drug Release at 1hr)

Fit Statistics | Model Comparison Statistics

Fit Statistics

Std. Dev.	0.6469	R^2	0.9957
Mean	36.18	**Adjusted R^2**	0.9886
C.V. %	1.79	**Predicted R^2**	0.9487
		Adeq Precision	35.4304

The **Predicted R^2** of 0.9487 is in reasonable agreement with the **Adjusted R^2** of 0.9886; 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 35.430 indicates an adequate signal. This model can be used to navigate the design space.

Coefficients | Coded Equation | Actual Equation

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	37.63	1	0.4822	36.10	39.17	
A-A	-3.33	1	0.2641	-4.17	-2.49	1.0000
B-B	-6.03	1	0.2641	-6.87	-5.19	1.0000
AB	0.2250	1	0.3234	-0.8043	1.25	1.0000
A^2	-0.0917	1	0.4574	-1.55	1.36	1.0000
B^2	-2.09	1	0.4574	-3.55	-0.6360	1.0000

$$Y=37.63 - 3.33X_{.} - 6.03x_{.} - 0.0917X_{.}^{2} - 2.09X_{.}^{2} + 0.2250X_{.}X_{.} + \varepsilon$$

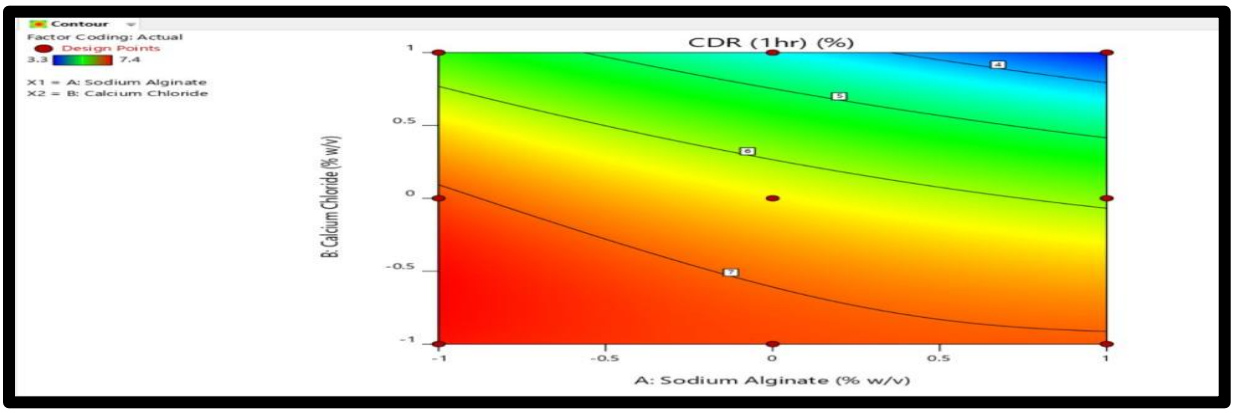

Figure 7 : 2D Contour Plot for Y2

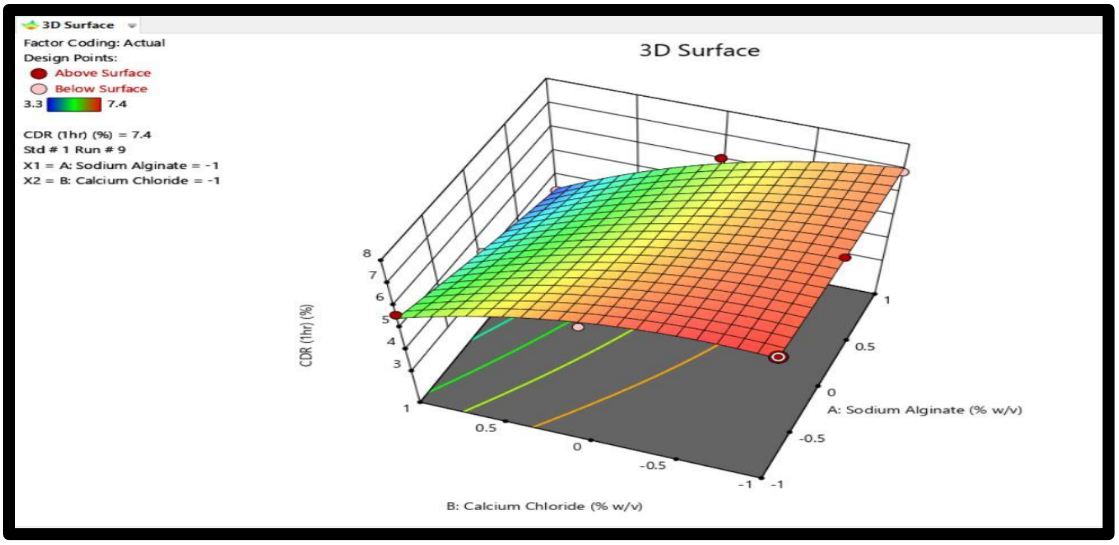

Figure 8 : 3D Surface Plot for Y2

Table 13 : ANOVA Table for Y3(% Drug Release at 6hr)

Analysis of Variance

ANOVA for Quadratic model

Response 3: CDR (6 hr)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	20.28	5	4.06	226.66	0.0005	significant
A-A	0.8438	1	0.8438	47.16	0.0063	
B-B	18.97	1	18.97	1060.48	< 0.0001	
AB	0.0625	1	0.0625	3.49	0.1584	
A^2	0.0296	1	0.0296	1.65	0.2886	
B^2	0.3669	1	0.3669	20.51	0.0201	
Residual	0.0537	3	0.0179			
Cor Total	20.33	8				

Factor coding is **Coded.**
Sum of squares is **Type III - Partial**

Table 14 : Fit Statistics And Coefficient Table for Y3(% Drug Release at 6hr)

Fit Statistics | Model Comparison Statistics

Fit Statistics

Std. Dev.	0.1338	R^2	0.9974
Mean	38.54	Adjusted R^2	0.9930
C.V. %	0.3471	Predicted R^2	0.9760
		Adeq Precision	39.4321

The **Predicted R^2** of 0.9760 is in reasonable agreement with the **Adjusted R^2** of 0.9930; 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 39.432 indicates an adequate signal. This model can be used to navigate the design

Coefficients | Coded Equation | Actual Equation

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	38.33	1	0.0997	38.02	38.65	
A-A	-0.3750	1	0.0546	-0.5488	-0.2012	1.0000
B-B	-1.78	1	0.0546	-1.95	-1.60	1.0000
AB	0.1250	1	0.0669	-0.0878	0.3378	1.0000
A^2	-0.1217	1	0.0946	-0.4227	0.1793	1.0000
B^2	0.4283	1	0.0946	0.1273	0.7293	1.0000

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design

$$Y = 38.33 - 0.3750X_1 - 1.78x_2 - 0.1217X_1^2 + 0.4283X_2^2 + 0.1250X_1X_2 + \varepsilon$$

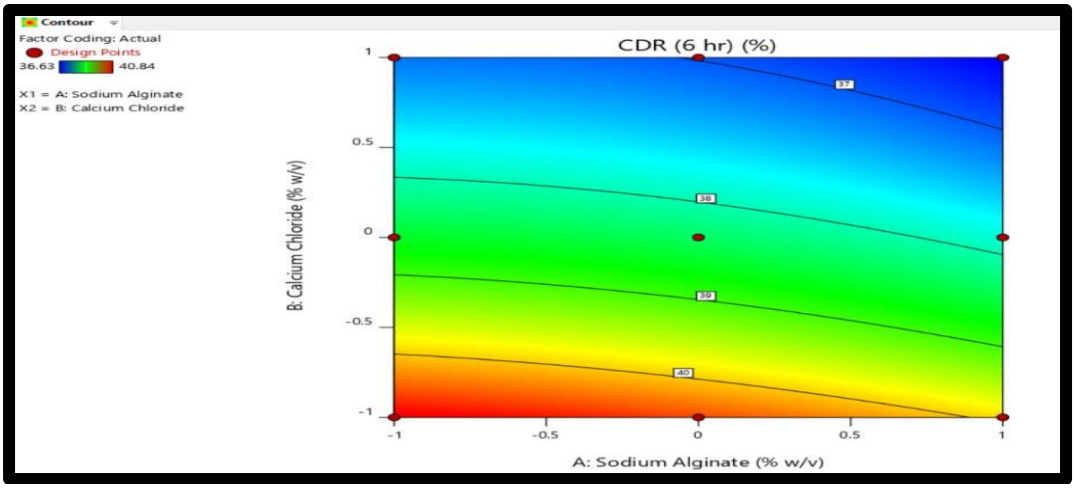

Figure 9 : 2D Contour Plot for Y3

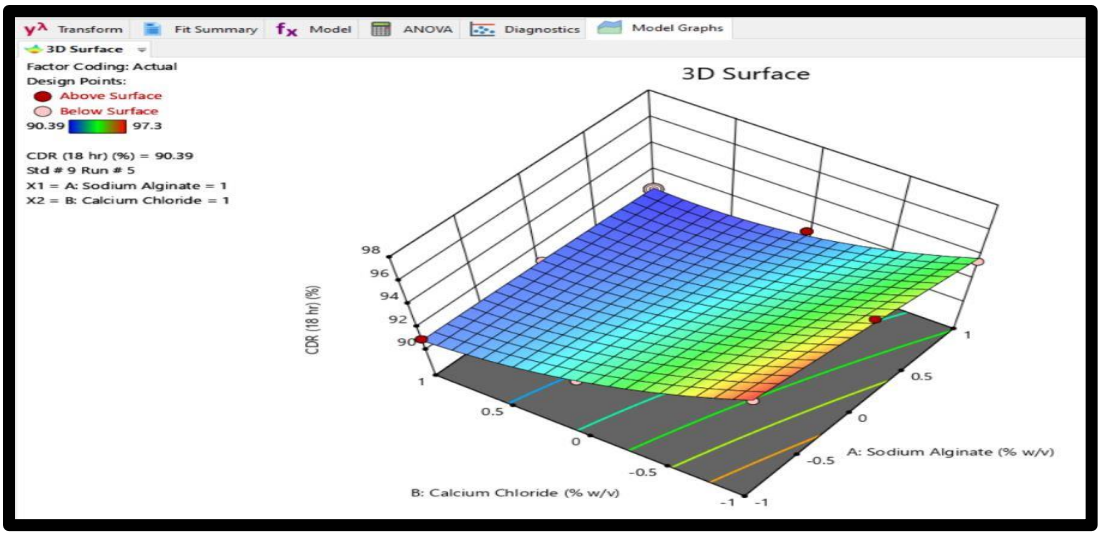

Figure 10 : 3D Surface Plot for Y3

Table 15 : ANOVA Table for Y4(% Drug Release at 18 hr)

Analysis of Variance

ANOVA for Quadratic model

Response 4: CDR (18 hr)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	47.83	5	9.57	59.17	0.0034	significant
A-A	5.74	1	5.74	35.53	0.0094	
B-B	36.51	1	36.51	225.84	0.0006	
AB	2.61	1	2.61	16.13	0.0277	
A^2	0.0093	1	0.0093	0.0578	0.8255	
B^2	2.96	1	2.96	18.31	0.0234	
Residual	0.4850	3	0.1617			
Cor Total	48.31	8				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

Table 16 : Fit Statistics And Coefficient Table for Y4(% Drug Release at 18hr)

Fit Statistics | Model Comparison Statistics

Fit Statistics

Std. Dev.	0.4021	R^2	0.9900
Mean	92.74	**Adjusted R^2**	0.9732
C.V. %	0.4335	**Predicted R^2**	0.9021
		Adeq Precision	20.9882

The **Predicted R^2** of 0.9021 is in reasonable agreement with the **Adjusted R^2** of 0.9732; 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 20.988 indicates an adequate signal. This model can be used to navigate the design space.

Coefficients | Coded Equation | Actual Equation

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	91.97	1	0.2997	91.02	92.93	
A-A	-0.9783	1	0.1641	-1.50	-0.4560	1.0000
B-B	-2.47	1	0.1641	-2.99	-1.94	1.0000
AB	0.8075	1	0.2010	0.1677	1.45	1.0000
A^2	-0.0683	1	0.2843	-0.9731	0.8364	1.0000
B^2	1.22	1	0.2843	0.3119	2.12	1.0000

$$Y = 91.97 - 0.9783X_1 - 2.47X_2 - 0.0683X_1^2 + 1.22X_2^2 + 0.8075X_1X_2 + \varepsilon$$

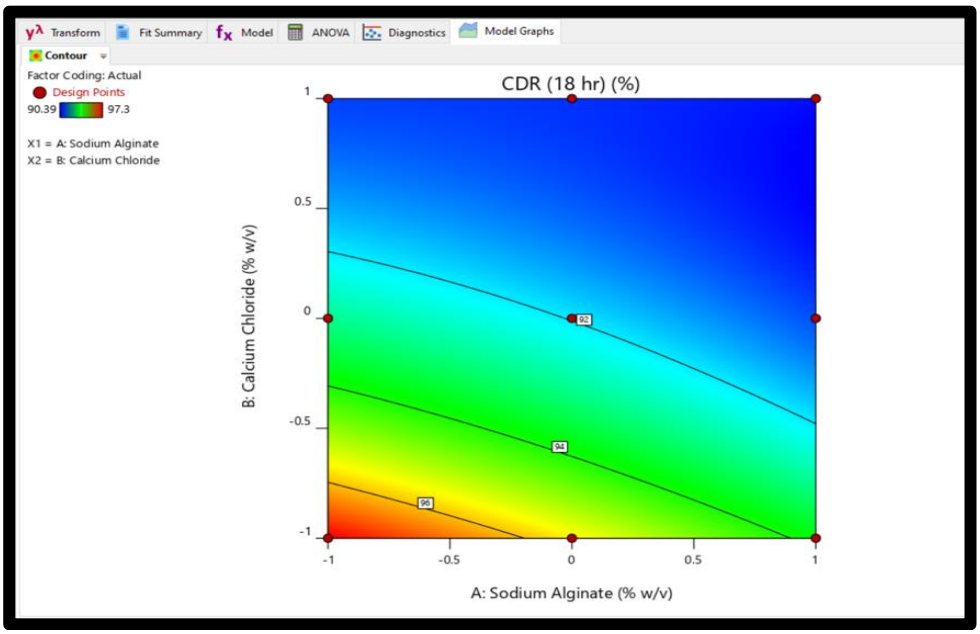

Figure 11: 2D Contour Plot for Y4

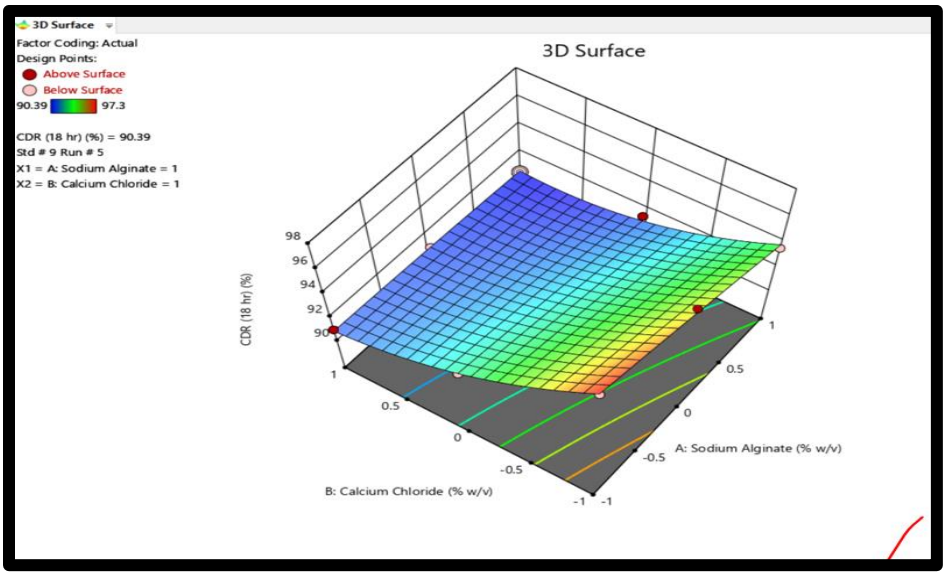

Figure12: 3D Surface Plot for Y4

- The result indicates that Y_1 is affected by the independent variables selected for the study. This negative value indicates that X_1 (Conc. Of Sodium Alginate) and X_2(Conc. of Calcium Chloride) has antagonist effect on % drug release.
- i.e as X_1 (Conc. Of Sodium Alginate) and X_2(Conc. of Calcium Chloride) decreases the % drug release increases. These two variables were found to be significant ($P < 0.05$) in affecting Y_1.
- The result indicates that Y_2 is affected by the independent variables selected for the study. This negative value indicates that X_1 (Conc. Of Sodium Alginate) and X_2(Conc. of Calcium Chloride) has antagonist effect on Floating Lag Time.
- i.e as X_1 (Conc. Of Sodium Alginate) and X_2(Conc. of Calcium Chloride) increases the Floating Lag Time Decreases. These two variables were found to be significant ($P < 0.05$) in affecting Y_2.

STABILITY STUDY [15]

During the stability studies product Exposure was

done with normal temperature and humidity conditions. However, study will take longer time so convenience will be observed through Accelerated Stability Study where the product is stored under Extreme Conditions. Study for assessment was done at 40 ± 2ºC Temperature and 75% RH. These studies were carried out as per the Q2R1 Guideline. After 30 days Sample was withdrawn and determination of physical Appearance, pH, Gelation Study, Gel Strength, Floating Lag Time, Viscosity, % Drug Content, % Drug Release (18hr) were done from the optimized Formulation.

Table 17: Accelerated Stability Study

Parameter	Accelerated Condition 40 ºC ± 2 ºC/ 75 ± 5 % RH		
	Initial	**After 15 days**	**After 30 days**
Physical Appearance	No Change	No Change	No Change
pH	6.73 ± 0.01	6.71 ± 0.03	6.69 ± 0.02
Gelation Study	+++	+++	+++
Floating Lag Time (sec)	41 ± 0.02	40 ± 0.02	40 ± 0.01
Gel Strength (dyne/cm^2)	3824.12 ± 2.51	3721.08 ± 1.21	3621.08 ± 2.32
Viscosity (cps)	210.2 ± 3.26	210.0 ± 2.01	209.1 ± 3.11
% Drug Content	99.86 ± 0.31	99.61 ± 0.18	99.03 ± 0.26
% Drug Release (18 hr)	96.01 ± 0.09	95.03 ± 0.04	95.01 ± 0.06

CONCLUSION:

In the present study, the liquid in situ gelling formulation was developed which transforms into a gel when it is entered into the gastric fluid (pH 1.2). It floats right away in the nature of the stomach and shows a controlled drug Release for 18h. The study found successful design, preparation and evaluation of intragastric floating in situ gelling system of Brivaracetam for the gastroprotective drug delivery for the treatment of epilepsy. In-situ gel was prepared using API Brivaracetam and all other excipients in distilled water. FTIR Study for API and API with all other excipients were done in order to assure that there doesn't arise any incompatibility between them. Nine formulation (F1- F9) were prepared by using Design Expert 12th version Software and all evaluation parameter was carried out for them. The F2 was found to be the Optimized Batch with 96.01% Drug Release in 18hrs , 99.86 ± 0.31 % Drug Content, 41 ± 0.02 secs of Floating Lag time and >18hrs Floating Duration. Also the Accelerated Stability Study Was Carried out as per Q2R1 Guideline At 40 ± 2ºC Temperature and 75% RH.

LIST OF SYMBOLS AND ABBREVIATIONS

% - Percentage
Cm – Centimeter
Mg- Milligram
Sec – Seconds
Hr – Hour
Ml – Milliliter
SD – Standard Deviation
ID – Internal Diameter
HPMC – Hydroxy Propoxy Methyl Cellulose
FTIR – Fourier Transform Infrared Spectroscopy
RH – Relative Humidity
ANOVA – Analysis Of Variance

ACKNOWLEDGEMENT

Author Would like to Express Special Thanks of Gratitude to Co-authors and Principal Of BNBSPC Vapi for Providing Suitable Environment to Carry out Research Project and also for Providing Support and Guidance throughout the Research Work

REFERENCES:

1. K.D.Tripathi Essentials of Medical Pharmacology;7thEdn; Jaypee Brothers, 411-424.
2. Sharma N, et al. A comprehensive review on floating drug delivery system. IJRPBS, 2011, 2(2), 428-441.
3. Dibyalochan Mohanty, et al. A Review on Insitu Gel; a Novel Drug Delivery System,International Journal of Pharma Sciences, 2018, 50(1) article no. 25, 125-181.
4. B. Srividya, R.M. Cardoza, P.D. Amin. Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system. J. Control Release., 73, 2001, 205–211
5. Drugbank—Brivaracetam-2020,https://go.drugbank.com/drugs/DB05541
6. Pubchem—Brivaracetam-2020, https://pubchem.ncbi.nlm.nih.gov/compound/Brivaracetam
7. Remya PN, Damodharan N, Venkata MA, Oral Sustained Delivery of Ranitidine From*In-Situ* Gelling Sodium-Alginate Formulation, Journal of Chemical and Pharmaceutical Research, 2011; 3(3): 814- 821.
8. Felice CHENG, Maggie J.M. LU, Yi-Ju Ko, min-Ying Lin, Shuen-Hsiang CHOU, Recipe for

in-situ gel, and implant, drug delivery system formed thereby, 2014.

9. Kalia Neha et al., " Insitu Gelling System : A Review", Journal of drug delivery and therapeutics.2014, 4(3), 93-103.

10. P.S.Dongre et al.- Review article on Floating Drug Delivery System; a better Approach review article pharmaceutical science International Journal of Pharmacy And Biological Sciences, 2013, 3(4),72-85.

11. Shelke Gajanan et al. Design and Optimization OfInsitu Floating Gel Containing Ondensetron Hydrochloride Dihydrate using 3^2 Factorial Design the Pharma Innovation journal 2017; 6(1): 83-88.

12. Lena Murad Thomas. Formulation and Evaluation Of Floating Oral Insitu Gel Of Metronidazole, International Journal Of Pharmacy And Pharmaceutical Science 6(10) 2014, 265-269.

13. Patel DM**,** Patel DK**,** Patel CN**,** Formulation and Evaluation of Floating Oral *In Situ* Gelling System of Amoxicillin**.** Journal of Chemical and Pharmaceutical Research**,** 2011**;** 1:102-108**.**

14. Sarrof R**,** Shaikh A**,** Pawar Y**,** Kumbhar S**,** Sodium Alginate Based Oral *in Situ* Floating Gel of Metformin Hydrochloride**,** Research Journal of Pharmaceutical and Biological and Chemical Sciences**,** 2012**;** 3 (1):890- 897**.**

15. International Conferences on Harmonization (ICH) Topic Q1A (R2) stability testing guideline: Stability testing of new drug substances and products.