Development and evaluation of *in situ* gel of pregabalin

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Abstract

Aim and Background: Pregabalin (PRG), an analog of gamma-aminobutyric acid, reduces the release of many neurotransmitters, including glutamate, and noradrenaline. It is used for the treatment of epilepsy; simple and complex partial convulsion. The present research work aims to ensure a high drug absorption by retarding the advancement of PRG formulation through the gastrointestinal tract. The work aims to design a controlled release PRG formulation which is administered as liquid and further gels in the stomach and floats in gastric juice. **Materials and Methods:** *In situ* gelling formulations were prepared using sodium alginate, calcium chloride, sodium citrate, hydroxypropyl methylcellulose (HPMC) K100M, and sodium bicarbonate. The prepared formulations were evaluated for solution viscosity, drug content, *in vitro* gelling studies, gel strength, and *in vitro* drug release. The final formulation was optimized using a 3^2 full factorial design. **Results:** The formulation containing 2.5% w/v sodium alginate and 0.2% w/v calcium chloride were considered optimum since it showed minimum floating lag time (18 s), optimum viscosity (287.3 cps), and gel strength (4087.17 dyne/cm^2). The optimized formulation follows Korsmeyer-Peppas kinetic model with *n* value 0.3767 representing Fickian diffusion mechanism of drug release. **Conclusion:** Floating *in situ* gelling system of PRG can be formulated using sodium alginate as a gelling polymer and calcium chloride as a complexing agent to control the drug release for about 12 h for the treatment of epilepsy.

Key words: Floating drug delivery, *in situ* gel, pregabalin

INTRODUCTION

In recent times, *in situ* gel forming systems have been used as vehicles for controlled drug delivery. There are many advantages of *in situ* forming polymeric delivery systems viz., ease of administration and reduced frequency of administration, improved patient compliance, and comfort. *In situ* gel formation occurs due to one or combination of different stimuli such as pH change, temperature modulation, and solvent exchange.[1] So, *in situ* gelling system via., different route such as oral, nasal, and ophthalmic can be formulated. Various natural and synthetic polymers such as alginic acid, gellan gum, xanthum gum, xyloglucan, pectin, chitosan, poly (DL lactic acid), poly

(DL-lactide-co-glycolide), and poly-caprolactone are used for formulation development of *in situ* forming drug delivery systems. *In situ* gelling system helps to increase bioavailability of drug compared to conventional liquid dosage form. The gel formed from *in situ* gelling system, being lighter than gastric fluids, floats over the stomach contents, or adhere to gastric mucosa due to presence of bioadhesive nature of polymer and produce gastric retention of dosage form and increase gastric residence time resulting in prolonged drug delivery in gastrointestinal (GI) tract.[2,3] The system utilizes polymers that exhibit sol-to-gel phase transition due to change in specific physicochemical parameters. Formulation of gastroretentive sol-gel system involves the use of gelling agent which can form a stable sol system to contain the dispersed drug and other excipients. The gelling of this sol system is to be achieved in gastric environment, triggered by ionic

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complexation due to the change in pH. The formulation adopted is a sodium alginate solution containing calcium chloride (as a source of Ca^{2+}) and sodium citrate, which complexes the free Ca^{2+} ions and releases them only in the acidic environment of the stomach.[3,4]

Sodium alginate acts as a gelling agent and can produce textures in the final product that vary from hard, nonelastic, brittle gels to fluid gels. The free Ca^{2+} ions get entrapped in polymeric chains of sodium alginate thereby causing cross-linking of polymer chains to form matrix structure. This gelation involves the formation of double helical junction zones followed by re-aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water.[5]

$$\text{Sodium citrate} + \text{Ca.chloride} \longrightarrow \text{Ca. citrate complex}$$

$$\xrightarrow[\text{Environment}]{\text{acidic}} Ca^{2+} + COO^{-}$$
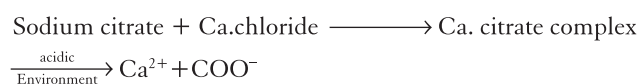
In this way, the formulation remains in liquid form until it reaches the stomach, where gelation of sodium alginate is instantaneous.

Pregabalin (PRG) is an analog of gamma-aminobutyric acid. It is used for the treatment of epilepsy, simple, or complex partial convulsion, either accompanied or not by secondary generalized convulsions, and of neuropathic pain. It is preferentially absorbed from the upper GI tract. Pregabalin undergoes rapid degradation at lower GI tract and colonic environment. It has a short half-life of 3-6 h.[4,5,26]

The present study aims to formulate a liquid solution containing PRG that shall gel on contact with gastric juice, further the formed gel shall float and remain in the stomach for a prolonged time period ensuring better absorption of the drug.

MATERIALS AND METHODS

Materials
PRG was obtained from Alkem Laboratories Mumbai, as a gift sample. Sodium alginate, sodium citrate, calcium chloride, and hydroxypropyl methylcellulose (HPMC) K100M were purchased from Research-lab Fine Chem Industries, Mumbai. Other ingredients used are of analytical reagent grade.

Formulation of *in situ* gelling solutions[6-8]
Sodium alginate solutions at different concentrations [Table 1] were prepared in half volume of deionized water containing calcium chloride (0.1% w/v) and sodium citrate (0.5% w/v). This solution was heated to 60°C with stirring. After cooling below 40°C; another one-third quantity of deionized water containing HPMC K100M (0.75% w/v) was added with continuous stirring. Further, PRG (300 mg), sodium bicarbonate (1% w/v), sodium methylparaben (0.1 mg), sodium propylparaben (0.02 mg), and sodium saccharine (0.05 mg) were added to above mixture, and final volume was made up to 20 ml with deionized water.

Evaluation of preliminary batches for selection of working concentration range of gelling polymers[9-11]
Various formulations were prepared using sodium alginate as described earlier and were used to select working concentration range of gelling polymers on the basis of *in vitro* gelling capacity and pourability (relative viscosity).

In vitro gelling capacity[12-14]
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 [Figure 1].

+ = gels after few minutes, dispersed rapidly

++ = gelation immediate remains for few hours

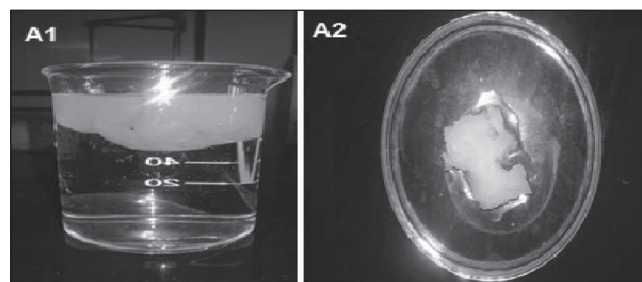+++ = gelation immediate remains for an extended period.

Figure 1: *In vitro* gelation study (A1): Initial gel in 0.1 N HCl at 0 h, (A2): Formulation after incubation for 24 h at 37°C

Table 1: Formulation and evaluation of sodium alginate trial batches

Batches	Sodium alginate (%w/v)	Viscosity (cps)	*In vitro* gelling capacity	Drug content (%) Mean ± SD, (n = 3)	Gel strength (dyne/cm²)	Pourability
S1	1	178.33±1.24	– – –	98.22±0.067		Easy to pour
S2	1.5	212.66±2.494	+ + –	99.20±0.0449		Easy to pour
S3	2	230.66±0.94	+ + +	100.75±0.542	836.23±0.578	Easy to pour
S4	2.5	260.3±3.68	+ + +	100.05±0.047	2412.36±2.76	Easy to pour
S5	3	280.3±1.24	+ + +	99.32±0.024	2746.27±3.21	Pourable
S6	3.5	328±1.63	+ + +	98.29±0.123		Difficult to pour

SD: Standard deviation

Determination of 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.

Selection of working range of complexing agent (calcium chloride) concentration

On the basis of *in vitro* gelling capacity and pourability [Table 1], sodium alginate concentration was fixed to 2.5% w/v and this was used for further study. Further formulations C1 to C6 were prepared using sodium alginate 2.5% w/v and varying the concentration of calcium chloride from 0.05%, 0.075%, 0.1%, 0.125%, 0.15%, and 0.2%, respectively and working concentration of calcium chloride was selected on the basis of its effect on release pattern [Figure 2]. The rest of the ingredients were not changed.

Selection of hydroxypropyl methylcellulose K100M and sodium bicarbonate concentration

Based on drug release of batch C5 (94.73% ± 0.38%), for the further study the value of calcium chloride was kept constant 0.15% w/v. Various formulations were prepared without HPMC and also using different concentrations of HPMC K100M (1%, 1.25%, and 1.5%) and based on viscosity and drug release the HPMC K100M concentration was fixed to 1.25% w/v. Further optimization of sodium bicarbonate was carried out by preparing batches B1, B2, B3 containing 0.5%, 1%, and 1.5% sodium bicarbonate, respectively. Based on drug release and floating time (97.65% ± 0.39% and 24.6 s) B2 batch was found to be suitable and concentration of sodium bicarbonate was fixed to 1%.

Optimization by using factorial design[15-18]

Further 3^2 full factorial design was constructed where the amounts of sodium alginate (X1) and calcium chloride (X2) were selected as the independent variables. The levels of the two variables were selected on the basis of the preliminary studies carried out before implementing the experimental design. The quantity of drug release at 1 h and 9 h, (Q_{1h}%, Q_{9h}%), time required to release 50% of drug ($t_{50\%}$), floating lag time (FLT) (sec) was selected as response (dependent) variables. All other formulation and processing variables were kept invariant throughout the study. Table 2 summarizes the experimental runs, their factor combinations and the translation of the coded levels to the experimental units used in the study.

Each factor was evaluated at three levels and experimental trials were performed for nine different formulations as given in Table 2.

All the nine formulations were subjected to evaluation for drug content, drug release, *in vitro* floating studies, gelling strength, pH determination, and viscosity.
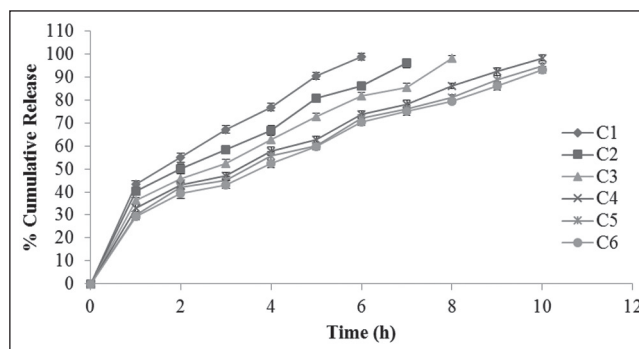

Figure 2: Effect of calcium chloride on drug release profile

Table 2: Evaluation of optimization batches, mean ± SD (*n* = 3)

Batch number	Viscosity (cps)	Gel strength (dyne/cm²)	Drug content (%)
F1	198.3±4.10	927.14±1.07	100.26±0.282
F2	210.2±3.26	1516.3±2.53	99.13±0.273
F3	222.6±5.73	2613.23±3.9	98.16±0.233
F4	274±5.88	2327.16±2.3	100.03±0.38
F5	280.3±7.71	3595.21±1.3	100.96±0.36
F6	287.3±3.39	4087.17±4.1	99.83±0.36
F7	302±4.98	3096.69±3.1	99.13±0.86
F8	322.2±5.73	3731.17±1.12	98.37±0.63
F9	348.6±5.88	4398.78±0.8	98.23±0.162

SD: Standard deviation

EVALUATION OF ORAL *IN SITU* GELS[19-23]

Physical appearance, clarity, and pH of the gels

The developed formulations were inspected visually for clarity in sol and gel form. The pH of the prepared formulation was determined by using calibrated digital pH meter at 25°C ± 2°C.

In vitro gelling capacity

In vitro gelling capacity and viscosity of *in situ* gelling solution were determined as per the method described in previous section.

Floating lag time[24]

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.

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 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

temporarily sealed bore followed by addition of 50 ml 0.1N HCl for gelation. After gelation, the HCl was drained off by opening bore seal leaving the gel mass formed. The needle was made to rest on to surface of the gel. At the free end of the thread a light weight pan was attached to which the weights were added. The gel strength was reported in terms of weight required to pass the needle probe through the formed gel mass. The gel strength is calculated using this formula:

$$Gel\ strength = Mg/a$$

Where,

M = Weight at which the pass the needle probe through formed gel mass

g = Gravitational force, and

a = Area of surfaces

In vitro drug release studies[25,26]

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 300 mg of PRG 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 460 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 9 h.

RESULT AND DISCUSSION

pH measurement

The pH of all the formulations was found to be in the range of 6.5-7.2, respectively.

In vitro gelling capacity

In the preliminary trial batches PRG *in situ* gelling formulations were prepared using sodium alginate polymers. The *in vitro* gelling capacity was graded in three categories on the basis of gelation time and time period for which formed gel floats. The observation in the formulation was noted as shown in Table 1.

Determination of viscosity

All preliminary batches were evaluated for viscosity. Viscosity for sodium alginate containing formulation varies from 178.33 cps to

328 cps. Flow properties of all formulations were also correlated with viscosity in relation to its ability to pour easily. Viscosities along with pourability for all batches were noted in Table 1.

Determination of drug content

All preliminary batches were evaluated for drug content [Table 1]. Drug content for sodium alginate formulation varies from the range of 98.22% to 100.75%.

Determination of gel strength

Based on gelling capacity, S3, S4, and S5 batches were found to be good and these batches were subjected to gel strength determination. All gel strength measurements were performed in triplicate with good reproducibility as shown in Table 1. All the gels showed good gelling strength.

Effect of complex forming agent (calcium chloride) on release pattern and selection of its working concentration range

Sodium alginate 2.5% w/v was selected for formulating further batches. Six batches (C-1 to C-6) were prepared with increasing concentration of calcium chloride. From the observation, it was concluded that increase in concentration of calcium chloride leads to increase in controlled release effect of drug. This could be explained by the fact that calcium chloride being present in the formulation which releases calcium ions in the acidic medium that cause gelation of sodium alginate. It was observed that only batches from C-3 to C-6 (containing 0.1–0.2% w/v of calcium chloride) have cumulative percent release for more than 8 h suggesting better stiffness of gel [Table 1]. Working concentration range of calcium chloride was fixed to 0.15% w/v. Further, increase in concentration to 0.2% w/v causes a decrease in cumulative percent release.

Effect of thickening agent (release retarding polymer) on release pattern to select its optimum concentration

Four batches (H-1 to H-4) were prepared to optimize amount of HPMC K100M as thickening agent [Table 3]. It was observed that trial batch H-1 without thickening agent was just able to control the drug release up to 5 h suggesting influence of HPMC K100M on drug release pattern of formulation. From the observation of cumulative percentage release at 12 h of prepared batches along with viscosity values as shown in Table 3, it was concluded that increasing concentration of HPMC K100M (1–1.5% w/v) increases release retarding effect as well as its viscosity (270.12 cps to 313.3 cps).

This could be explained by the fact that an increase in its concentration proportionally increased the number of particles

Table 3: Effect of HPMC K100M on drug release profile, mean ± SD (*n* = 3)				
Formulation	H1 (0%)	H2 (1%)	H3 (1.25%)	H4 (1.5%)
Percentage of cumulative release	98.99±0.61	97.94±0.475	96.96±0.594	88.81±2.41
Time (h)	5	11	12	12
Viscosity (cps)	—	270.12±4.10	282.6±3.339	313.3±4.71

SD: Standard deviation, HPMC: Hydroxypropyl methylcellulose

dispersed, thus contributing to increased viscosity. Batch H-3 (containing 1.25% w/v HPMC K100M) had optimum gel thickening effect which retard drug release from formulation and extends its cumulative percentage release up to 12 h (96.96%) also has less viscosity (282.6 cps) with easy pourability.

Effect of Sodium bicarbonate on release pattern to select its optimum concentration

From the observation of prepared batches (B1–B3), it was concluded that increase in concentration of sodium bicarbonate causes decrease in controlled release effect of drug as well as FLT [Table 4]. This could be explained by the fact that increase in concentration of sodium bicarbonate increases availability of generated carbon dioxide to get it entrapped in the formed gel matrix also instant effervescent reaction which accelerates drug release from the same. It was observed that batch B-2 (containing 1% w/v of sodium bicarbonate) has cumulative percentage release of about 12 h with minimum FLT (24.6 s) suggesting better controlled drug release with optimum FLT.

Evaluation of optimization batches

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 were performed for all 9 possible combinations. The concentration of sodium alginate (X1) and concentration of calcium chloride (X2) were chosen as independent variables in 3^2 full factorial designs, while FLT, Q_{1h}, Q_{9h} (% drug release after 1, 9 h, respectively), and $t_{50\%}$ (time required for 50% drug release) were taken as dependent variables. The concentrations of other ingredients were fixed based on preliminary trials. The formulation layout for the factorial design batches (F1–F9) is shown in Table 5.

The following statistical model incorporating interactive and polynomial terms were used to evaluate the responses:

$$Y = ß_0 + ß_1 X_1 + ß_2 X_2 + ß_3 X_1X_2 + ß_4 X_1^2 + ß_5 X_2^2 + ß_6 X_1 X_2^2 + ß_7 X_2 X_1^2 \quad (1)$$

Where, Y is the dependent variable, $ß_0$ is the arithmetic mean response of the 9 runs, and $ß_1$ is the estimated coefficient for the factor X_1. The main effects of the amounts of X_1 and X_2 represent the average result, when the factors were changed one at a time from their low to high values. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The release profile for 9 batches [Table 5] showed a variation, that is, initial 1 h release ranging from 20.33% to 42.16%, drug released after 9 h ranging from 75.19% to 98.62%, time required for 50% of the drug to release ranged from 120 to 316 min, and FLT ranging from 18 to 79 s. The data indicate that the release profile of the drug is strongly dependent on the selected independent variables [Figure 3].

The fitted equations relating the responses, FLT, Q_{1h}, Q_{9h}, and $t_{50\%}$, to the transformed factor are shown in the equation 2, 3, 4, and 5. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., negative or positive) so as to indicate either synergistic or an antagonistic effect. Analysis of variance was applied to identify insignificant factors. Data were analyzed using design expert 8.0.7.1 software. From the data obtained, it was evident that $P < 0.05$ for all formulations. The resulted equations for all five dependent variables in terms of coded factors are presented below.

Polynomial equation for response Y_2 (Q_{1h}%) surface quadratic model:

$$Y_1 = 31.48 + 7.98X_1 - 0.8X_1^2 + 5.16X_2 + 0.43X_2^2 - 1.60X_1X_2 + 3.02X_1^2X_2 + 1.55X_1X_2^2 - 2.29X_1^2X_2^2 \quad (2)$$

Polynomial equation for response Y_2 (Q_{9h}%) surface quadratic model:

$$Y_2 = 87.9 + 8.97X_1 - 1.69X_1^2 + 4.86X_2 + 0.4X_2^2 - 2.93X_1X_2 + 4.72X_1^2X_2 - 0.6X_1X_2^2 - 0.43X_1^2X_2^2 \quad (3)$$

Table 4: Effect of sodium bicarbonate on drug release profile

Formulation	B1 (0.5%)	B2 (1%)	B3 (1.5%)
Percentage of cumulative release	92.88±0.28	97.65±0.39	98.93±0.49
Time (h)	12	12	11
FLT (s)	63.6±4.6	24.6±0.94	11.6±1.24

FLT: Floating lag time

Table 5: Factorial design with corresponding 9 formulations, mean ± SD (*n* = 3)

Batch number	Variable levels in coded form		Y_1 (Q_{1h}%)	Y_2 (Q_{9h}%)	Y_3 ($t_{50\%}$) (min)	Y_4 (FLT) (s)
	X_1	X_2				
F1	−1	−1	42.16±1.73	98.62±1.14	120±0.18	79.6±1.69
F2	−1	0	40.68±1.91	96.48±1.63	138±0.95	63.21±2.16
F3	−1	+1	34.94±1.01	95.16±1.6	158±0.32	56.6±2.49
F4	0	−1	37.91±1.72	95.68±1.88	161±0.6	47±1.63
F5	0	0	28.95±1.4	85.15±1.39	222±0.20	28±0.94
F6	0	+1	25.12±1.16	77.80±1.11	300±0.66	18±1.63
F7	+1	−1	27.13±0.04	83.57±0.89	252±0.02	34.5±3.39
F8	+1	0	26.28±1.16	83.16±0.55	266±0.08	43.3±1.88
F9	+1	+1	20.33±1.30	75.19±1.32	316±1.41	48.3±1.69

For X_1: 2% (−1), 2.5% (0), 3% (+1); For X_2: 0.1% (−1), 0.15% (0), 0.2% (+1). FLT: Floating lag time, SD: Standard deviation

Polynomial equation for response Y_3 ($t_{50\%}$) surface quadratic model:

$$Y_3 = 214.83 - 75.0X_1 + 12.5X_1^2 - 35X_2 - 6.67X_2^2 + 19.17X_1X_2 - 29.83X_1^2 + 5.83X_1X_2^2 + 0.83X_1^2X_2^2 \quad (4)$$

Quadratic equation for Y_4 (FLT) in terms of actual factors:

$$Y_4 = 46.50 + 19.50X_1 - 15.33X_1^2 + 8.00X_2 - 1.67X_2^2 + 6.00X_1X_2 + 8.83X_1^2X_2 - 1.33X_1X_2^2 - 1.0X_1^2X_2^2 \quad (5)$$

All optimization batches were subjected to determination of viscosity (cps), gel strength (dyne/cm^2), pH, and drug content as shown in Table 2. Viscosity of all batches varies from 198.3 to 348.6 cps was found to increase with increase in concentration of both independent variables. The pH of all formulations was found to be in a range of 6.4-6.9. Gel strength of optimization batches varies from 927.14 to 4398.78 dyne/cm^2.

Response surface plots

Three-dimensional plots for the measured responses were presented to determine the change of the response surface. These types of plots are useful in the study of the effects of two factors on the response at 1-time. Figures 4 and 5 shows that cumulative percentage release at both 1 h and 9 h decreases with increase in concentrations of sodium alginate and calcium chloride. Therefore, it can be concluded that the change of both independent variables had significant effect on response Y_1 ($Q_{1h}\%$) and Y_2 ($Q_{9h}\%$)
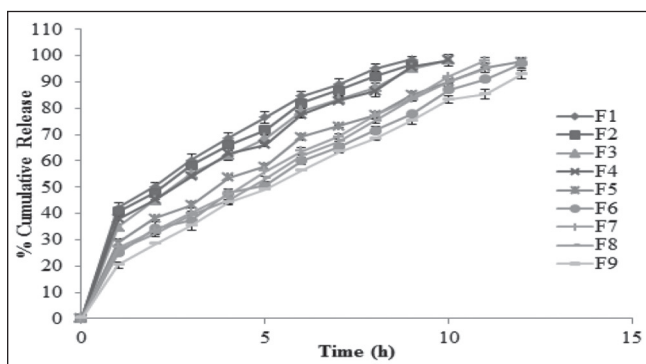
Figure 6 shows that time required to release 50% fraction of drug increases with increase in concentrations of sodium alginate and calcium chloride. Figure 7 shows that FLT decreases with increasing concentrations of sodium alginate and calcium chloride up to certain limit followed by an increase thereafter. Therefore, it can be derived that the change proportion of independent variables had significant effect on the response Y_4 (FLT).

The F6 batch (2.5% w/v sodium alginate and 0.2% w/v calcium chloride) was found to be the optimized formulation using the design software. The drug release rate was controlled up to 12 h from F6 batch. The FLT of F6 batch was found to be 18 s and floating duration was found to be more than 12 h [Figure 8]. Increasing the concentration of complexing agent (calcium chloride) and thickening agent (HPMC K100M) showed an increase in controlling drug release conversely increasing the concentration of gas forming agent (sodium bicarbonate), showed a decrease in controlling drug release from the formulation.

After the analysis of both independent variables and dependent variables, design expert software gives solutions as shown in Table 6 with desirability 0.946.

CONCLUSIONS

In the present study, floating *in situ* gelling formulation liquid was developed which converts into a gel form when added to
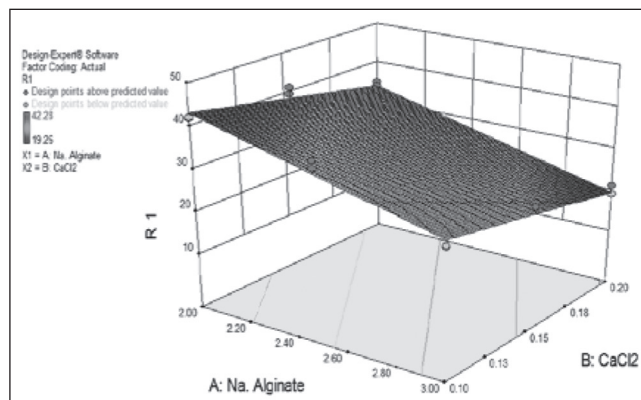

Figure 3: Dissolution profile of optimization batches F1–F9

Figure 4: Response surface plot for Y1 $Q_{1h}\%$

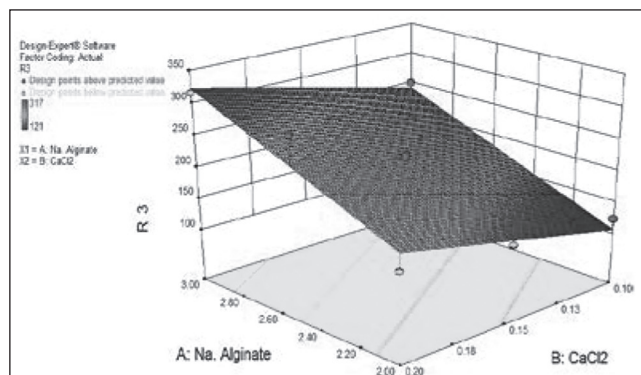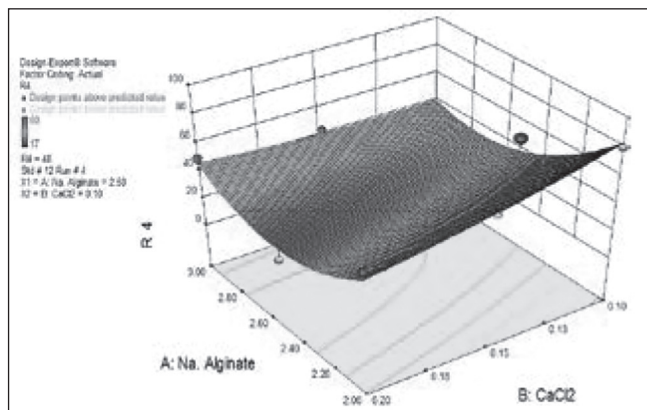**Figure 5:** Response surface plot for Y_2 ($Q_{9h}\%$)

Figure 6: Response surface plot for Y_3 ($t_{50\%}$)

Table 6: Solutions for optimized batch F6

Variable	Sodium alginate	Calcium chloride	Q_{1h}%	Q_{9h}%	$t_{50\%}$ (min)	FLT	Desirability
Observed	2.5	0.2	25.12	77.8	300	18	0.946
Predicted	2.64	0.2	24.25	80	279.69	24.13	

FLT: Floating lag time

Figure 7: Response surface plot for Y_4 (floating lag time)

Figure 8: Oral *in situ* gel of optimized formulation (batch F6)

simulated gastric fluid (pH 1.2). It instantaneously floats in the gastric environment and shows controlled drug release for 12 h. The study attained the successful design, preparation and evaluation of oral controlled release floatable *in situ* gelling system of PRG with stomach specific drug delivery which controlled the drug release for the treatment of epilepsy.

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Conflicts of interest
There are no conflicts of interest.

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