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. 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. 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

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 3² 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/cm²). 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

Abstract

Development and evaluation of in situ gel of pregabalin

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Original Research Article

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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.\(^{[5]}\)

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.

**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/cm\(^2\)) | Pourability |
|---------|------------------------|----------------|---------------------------|--------------------------------------|-----------------------------|-------------|
| S1      | 1                      | 178.33±1.24    | ☐ ☐ ☐                     | 98.22±0.067                          |                             | Easy to pour            |
| S2      | 1.5                    | 212.66±2.494   | ☐ ☐ ☉                     | 99.20±0.0499                         |                             | 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               | Pouroable               |
| S6      | 3.5                    | 328±1.63       | ☇ ☇ ☇                      | 98.29±0.123                          |                             | Difficult to pour       |

SD: Standard deviation

![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](A1)
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
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, (Q1h %, Q9h %), time required to release 50% of drug (t50%), 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.
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:

\[ \text{Gel strength} = \frac{Mg}{a} \]

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 \( \mu \)m 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
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 3² 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 3² full factorial designs, while FLT, Q₁h, Q₉h (% drug release after 1, 9 h, respectively), and t₅₀% (time required for 50% of the drug to 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:

\[ Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1 X_2^2 + \beta_7 X_1^2 X_2 + \beta_8 X_1 X_2 X_1^2 \]  

Where, Y is the dependent variable, \( \beta_0 \) is the arithmetic mean response of the 9 runs, and \( \beta_i \) is the estimated coefficient for the factor \( X_i \). 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 \( (X_1 X_2) \) 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, Q₉h, Q₁h, and t₅₀%, 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 \( Y_1 (Q_{1h} \%) \) surface quadratic model:**

\[ Y_1 = 31.48 + 7.98X_1 - 0.8X_2^2 + 5.16X_2 + 0.43X_1^2 - 1.60X_1X_2 + 3.02X_1^2X_2 + 1.55X_2^3 - 2.29X_2^2 \]  

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

\[ Y_2 = 87.9 + 8.97X_1 - 1.69X_2^2 + 4.86X_2 + 0.4X_2^2 - 2.93X_1X_2 + 4.72X_1^2X_2 - 0.6X_1^2X_2 - 0.43X_2^3 \]  

**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) |
|--------------|-------------------------------|----------------------|----------------------|----------------------|----------------------|
| F1           | \( X_1 \) = 0, \( X_2 \) = 0  | 42.16±1.73           | 98.62±1.14           | 120±0.18             | 79.6±1.69            |
| F2           | \( X_1 \) = 0, \( X_2 \) = 1  | 40.68±1.91           | 96.48±1.63           | 138±0.95             | 63.21±2.16           |
| F3           | \( X_1 \) = 1, \( X_2 \) = −1 | 34.94±1.01           | 95.16±1.66           | 158±0.32             | 56.6±2.49            |
| F4           | \( X_1 \) = 0, \( X_2 \) = 0  | 37.91±1.72           | 95.68±1.88           | 161±0.6             | 47±1.63             |
| F5           | \( X_1 \) = 0, \( X_2 \) = 0  | 28.95±1.4            | 85.15±1.39           | 222±0.20             | 28±0.94             |
| F6           | \( X_1 \) = 1, \( X_2 \) = +1 | 25.12±1.16           | 77.80±1.11           | 300±0.66             | 18±1.63             |
| F7           | \( X_1 \) = +1, \( X_2 \) = +1 | 27.13±0.04           | 83.57±0.89           | 252±0.02             | 34.5±3.39           |
| F8           | \( X_1 \) = +1, \( X_2 \) = 0  | 26.28±1.16           | 83.16±0.55           | 266±0.08             | 43.3±1.88           |
| F9           | \( X_1 \) = +1, \( X_2 \) = +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 \( X_2 \): 0.5% (-1), 0.75% (0), 1% (+1). FLT: Floating lag time, SD: Standard deviation
Polynomial equation for response $Y_1$ ($t_{50\%}$) surface quadratic model:

$$Y_1 = 214.83 - 75.0X_1 + 12.5X_1^2 - 35X_2 - 6.67X_1^2 + 19.17X_1X_2 - 29.83X_1^2 + 5.83X_1X_2 + 0.83X_1^2X_2^2$$  \hspace{1cm} (4)

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

$$Y_4 = 46.50 + 19.50X_1 - 15.33X_1^2 + 8.00X_2 - 1.67X_2^2 + 6.00X_1X_2 + 8.83X_1X_2^2 - 1.33X_2^2 - 1.00X_1^2X_2$$  \hspace{1cm} (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 $Y_1$ ($Q_{1\%}$) and $Y_2$ ($Q_{9\%}$)

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...
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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.

**REFERENCES**

1. Rowe RC, Sheskey PJ, Weller PJ. Handbook of Pharmaceutical Excipients. Washington, USA: American Pharmaceutical Association; 2003. p. 54, 55, 255, 1971.
2. Hoffman A, Stepensky D, Lavy E, Eyal S, Michael F. Review of expandable gastro retentive dosage forms. J Control Release 2003;90:143-62.
3. Benes L, Claustat B, Horriere F, Geoffriau M, Konsil J, Parrott KA, et al. Transmucosal, oral controlled-release, and transdermal drug administration in human subjects: A crossover study with melatonin. J Pharm Sci 1997;86:1115-9.
4. Strusi OL, Sonvico F, Bettini R, Santi P, Colombo G, Barata P, et al. Module assemblage technology for floating systems: *In vitro* flotation and *in vivo* gastro-retention. J Control Release 2008;129:88-92.
5. Singh BN, Kim KH. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Release 2000;63:235-59.
6. Shah S, Upadhyay P, Parikh D, Shah J. *In situ* gel: A novel approach of gastroretentive drug delivery. Asian J Biomed Pharm Sci 2012;2:01-8.
7. Kubo W, Miyazaki S, Dairaku M, Togashi M, Mikami R, Atwood D. Oral sustained delivery of ambroxol from *in situ*-gelling pectin formulations. Int J Pharm 2004;271:233-40.
8. Itoh K, Yahaba M, Takahashi A, Tsuruya R, Miyazaki S, Dairaku M, et al. *In situ* gelling xyloglucan/pectin formulations for oral sustained drug delivery. Int J Pharm 2008;356:95-101.
9. Deshpande A, Rhodes C, Shah N, Malick A. Controlled release drug delivery systems for prolonged gastric residence: An overview. Drug Dev Ind Pharm 1996;22:531-39.
10. Groning R, Heun G. Oral dosage forms with controlled gastrointestinal transit. Dev Ind Pharm 1984;10:527-39.
11. Rajinikanth PS, Mishra B. Floating *in situ* gelling system for stomach site-specific delivery of clarithromycin to eradicate *H. pylori*. J Control Release 2008;125:33-41.
12. Miyazaki S, Kubo W, Atwood D. Oral sustained delivery of theophylline using *in-situ* gelation of sodium alginate. J Control Release 2000;67:275-80.
13. Miyazaki S, Aoyama H, Kawasaki N, Kubo W, Atwood D. *In situ*-gelling gellan formulations as vehicles for oral drug delivery. J Control Release 1999;60:287-95.
14. Kadam VJ, Shidhaye SS. Sustained release floating drug delivery system of *in situ* gelation of sodium alginate. J Control Release 2008;125:33-41.
15. Debnath S, Niranjan M, Kusuma G, Saraswathi N, Sramika N, Reddy K. Formulation and evaluation of floatable *in situ* gel as carrier for stomach-specific drug delivery of metoclopramide HCl. Int J Pharm Front Res 2011;1:53-64.
16. Akhgari A, Aftasiabi Garekani H, Sadeghi F, Azimaei M. Statistical optimization of indomethacin pellets coated with pH-dependent methacrylic polymers for possible colonic drug delivery. Int J Pharm 2005;305:22-30.
17. Pal TK, Soloman S, Selvan S, Ghosh A, Gowda V, Mandal U. Formulation and optimisation of sustained release matrix tablet of metformin HCl using response surface methodology. Pharm Soc Jpn 2007;127:1281-90.
20. Pal TK, Solomon S, Selvan S, Ghosh A, Gowda V, Mandal U. Formulation and optimisation of sustained release matrix tablet of metformin HCl using response surface methodology. Pharm Soc Jpn 2007;127:1281-90.

21. Dey S, Pramanik S, Malgope A. Formulation and optimization of sustained release stavudine microspheres using response surface methodology. Cairo: International Scholarly Research Network; 2011. p. 1-7.

22. Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution testing as a prognostic tool for oral drug absorption: Immediate release dosage forms. Pharm Res 1998;15:11-22.

23. Patel DM, Patel DK, Patel CN. Formulation and evaluation of floating oral in situ gelling system of amoxicillin. Cairo: International Scholarly Research Network; 2011. p. 1-8.

24. Deshpande A, Rhodes C, Shah N, Malick A. Controlled release drug delivery systems for prolonged gastric residence: An overview. Drug Dev Ind Pharm 1996;22:531-9.

25. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001;13:123-33.

26. Tjandrawinata RR, Setiawati E, Putri RS, Gunawan VA, Ong F, Susanto LW, et al. Pharmacokinetic equivalence study of two formulations of the anticonvulsant pregabalin. Clin Pharmacol 2015;7:69-75.