# Formulation and optimization of tramadol loaded alginate beads using response surface methodology

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**Abstract**: Tramadol loaded alginate beads were formulated by ionic cross-linking technique employing calcium chloride as cross-linking agent. Several parameters like bead size, swelling index, incorporation efficiency, *in vitro* release and *in vivo* drug activity studies were investigated. Tramadol loading and concentration of calcium chloride were found to have a significant effect on the selected parameters. Tramadol release decreased with decreasing drug loading and increasing concentration of cross-linking agent. Kinetic modeling indicates the involvement of both swelling and erosion on the release characteristics of the drug from the beads. A 2 factors-3 levels central composite design (CCD) was employed to evaluate the effect of critical formulation variables, namely drug loading (X1) and concentration of calcium chloride (X2) on various responses. Multiple linear regression analysis generated polynomial mathematical models for various response variables and the corresponding response surface and contour plots were drawn. X1 was found to have more significant effect than X2 on the dependent variables. *In vivo* drug activity studies of the alginate beads demonstrated significant antinociceptive effect of tramadol.

**Keywords**: Sodium alginate beads, ionic cross-linking, tramadol, swelling and erosion, central composite design.

## INTRODUCTION

Alginate is water soluble naturally occurring polysaccharides abundantly found in the surface of seaweeds such as lavar (*Porphyra tenera*), green lavar (*Enteromorpha linza*), agaragar (*Gelidium mansii*), marine brown alga (*Undaria pinnatifida*), and tangleweed (*Kjellmaniella crassifolia*). Alginate becomes water-insoluble in the proximity of polyvalent cations like $Ca^{2+}$, $Hg^{2+}$, $Be^{2+}$, $Cu^{2+}$, $Co^{2+}$, $Al^{3+}$, and $Fe^{3+}$, resulting in the formation of alginate gel. Alginate beads can be formed by drop wise addition of alginate solution to an aqueous solution of di or polyvalent cations. Alginate beads alone or in combination with other polymers have been extensively studied by researchers for their diverse pharmaceutical applications particularly as drug delivery system (Das and Senapati PC 2008; Li *et al*., 2006). Moreover, alginate is reported to be non-toxic and biodegradable along with a protective effect on the mucous membranes of the upper respiratory tract (Mumper *et al*., 1994; Kim and Lee 1992).

Tramadol ((±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol) is a centrally acting analgesic. Tramadol is marketed as a racemic mixture and at the receptor level has a moderate affinity for the μ-subtype of opioid receptors. The (+)-enantiomer is approximately four times more effective than the (-)-enantiomer in terms of μ-opioid receptor binding ability and 5-HT reuptake, whereas the (-)-enantiomer is primarily involved in mediating the noradrenaline reuptake effects. These mechansims have been proposed to cause a synergistic analgesic effect, with (+)-tramadol exhibiting a higher analgesic activity than (-)-tramadol (Goeringer *et al*., 1997).

The present study as designed to prepare sodium alginate beads of tramadol by ionic cross-linking method. Beads formulated were analyzed for particle size, loading efficiency, swelling index. Response surface methodology (RSM) comprises design of experiments (DoE) methodology where formulations are optimized using experimental designs, polynomial equation generation, and mapping of the responses (Singh *et al*., 2004; Kumar and Singh 2010). The technique is advantageous in terms of reduced experimentation and time, thereby making it more effective than the conventional methods of formulating dosage forms.

In-vitro release studies and in-vivo pharmacodynamic studies were also performed. Tail flick latency test using the tail flick apparatus is a widely reported and a thoroughly standardized model for studying the analgesic activity of drugs. Moreover, tramadol is a well-known analgesic mediating its effect via the activation of opioid receptors. Therefore, the pharmacodynamic assessment of the analgesic effect of tramadol was done using tail flick assay in rats.

## MATERIALS AND METHODS

### *Materials*

Tramadol was received as a gift sample from Indswift Laboratories Ltd. (Derabassi, Punjab, India). Sodium

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alginate and calcium chloride were procured from Loba Chemie, Mumbai, India. All the reagents were of analytical grade and were used as and when received.

***Formulation of sodium alginate beads***

Ionic cross-linking technique was used to formulate sodium alginate beads of tramadol (Das and Senapati, 2008). Polymer solution was prepared by dissolving 2% sodium alginate in deionized water using gentle heat followed by stirring on magnetic stirrer for 30 min. Once complete solution of the polymer was prepared, accurately weighed quantity of drug was dispersed in the polymer solution with stirring followed by sonication (Raj Analytical Service, Mohali, India) for removing the air bubbles. A 20-gauge hypodermic needle fitted with a 5 ml syringe was used to add the polymer-drug solution (20 ml) into 100 ml of (0.5-1.5 % w/v) $CaCl_2$ being stirred at 200 rpm for bead formation. As soon as the polymer-drug solution got in contact with the solution of cross-linking agent, an instantaneous gel was formed which later on transformed into discrete uniform beads. The stirring was continued for another 1 hour. Alginate beads were filtered followed by washing with deionized water (4 x 50 ml). The beads were then dried at 60°C for 3 hours in a hot air oven. Different batches of alginate beads were prepared by varying polymer drug ratio and cross-linking agent concentration.

***Particle size determination***

The prepared drug loaded alginate beads (after drying) were characterized for size determination using optical microscopy. A minimum of 100 beads were analyzed and their mean was noted as particle size. All the reading were average of three trials ± SD.

***Swelling index***

100 mg of dry beads were soaked in pH 7.4 phosphate buffer and the beads were reweighed at regular intervals of time, carefully wiping off the excess liquid with a tissue paper. The under given expression was used for swelling index determination:

$$\text{Swelling Index} = (W_t - W_o)/ W_o$$

where $W_t$ and $W_o$ are the weight of the beads at time 't' and under dry state, respectively.

***Determination of drug incorporation efficiency***

About 50 mg of drug loaded alginate beads from the formulated batches were crushed in a glass mortar and digested in 50 ml of phosphate buffer pH 7.4 for 24 hours. The solution was filtered through a G-2 filter and aliquot of the filtrate was suitable diluted with pH 7.4 phosphate buffer for spectrophotometric quantification of drug content at 272 nm. The incorporation efficiency (%) was determined by dividing actual quantity of drug present in the beads by theoretical quantity of drug in the beads. All the values were average of three trials ± SD.

***In vitro drug release studies***

*In vitro* drug release from the beads was performed in USP XXIII apparatus I (37±0.5°C; 50 rpm) using 0.1 N HCl (pH 1.2; 500ml) as dissolution media for first 2 hours followed by phosphate buffer (pH 7.4 ; 500 ml) for next 8 hours. Alginate beads (all formulated batches) carrying drug equivalent to 100 mg were employed in the dissolution study. 5 ml aliquots were withdrawn at specified time interval followed by replacement with the 5 ml of prewarmed phosphate buffer for maintaining sink conditions. The aliquots were analyzed spectrophotometrically (Systronics 2202, India) at 272 nm and percentage drug released at different time intervals was calculated using the Lambert-Beer's equation ($y = 0.0061 x - 0.0041$, $R^2 = 0.9993$) of the calibration curve of tramadol in phosphate buffer pH 7.4. The $t_{80\%}$ was calculated using the Higuchi's equation (Higuchi 1963).

The *in vitro* release data were fitted to various kinetic equations like zero-order equation $Q_t = Q_o + K_o t$; first-order equation (Gibaldi and Feldman 1967; Wagner 1969) $Q_t = Q_o e^{-Kt}$ ; and Higuchi's square root model $Q_t = K_H \sqrt{t}$, where, $Q_t$ is the amount of drug released in time 't', $Q_o$ is the initial amount of drug in dissolution medium, and $K_o$, K and $K_H$ are respective release constants. The

**Table 1**: Formulation compositions and physical characteristics of the formulated sodium alginate beads

| Batch | Sod Alginate (% w/v) | Tramadol (% w/v) | $CaCl_2$ (% w/v) | Dry Bead Size (mm) | Incorporation Efficiency (%) | Swelling Index | Release Exponent (n) | $t_{80\%}$ |
|---|---|---|---|---|---|---|---|---|
| I | 2 | 0.5 | 0.5 | 0.82±0.03 | 72.63±2.09 | 32.86±1.23 | 1.0008 | 4.95 |
| II | 2 | 0.5 | 1.0 | 0.80±0.06 | 75.25±3.11 | 29.32±0.72 | 1.0797 | 5.29 |
| III | 2 | 0.5 | 1.5 | 0.78±0.05 | 80.52±2.14 | 24.80±1.18 | 0.9873 | 5.33 |
| IV | 2 | 1 | 0.5 | 0.81±0.10 | 74.22±2.39 | 36.15±1.33 | 0.9700 | 4.96 |
| V | 2 | 1 | 1.0 | 0.80±0.08 | 76.41±1.95 | 34.64±0.98 | 1.0086 | 5.11 |
| VI | 2 | 1 | 1.5 | 0.75±0.04 | 84.15±2.61 | 30.18±1.63 | 0.9557 | 4.88 |
| VII | 2 | 2 | 0.5 | 0.84±0.05 | 80.00±1.58 | 34.20±1.41 | 0.7896 | 4.57 |
| VIII | 2 | 2 | 1.0 | 0.82±0.07 | 83.68±2.00 | 30.45±1.05 | 0.8604 | 4.81 |
| IX | 2 | 2 | 1.5 | 0.79±0.06 | 86.43± 3.47 | 28.22±0.86 | 0.9148 | 4.88 |

mechanism of drug release from the polymer matrix was studied using the Power law (Korsmeyer *et al*., 1983; Peppas, 1985) $M_t/M_\infty = Kt^n$, where, $M_t/M_\infty$ is the fraction of drug released in time 't', K is structural and geometric constant, and n is the release exponent.

***In vivo drug activity studies***

Analgesic effect of tramadol was selected as a parameter for assessment of the time dependent pharmacological activity of the treatments. Tail flick assay was used to quantitate the antinociceptive effect of tramadol. Nociceptive threshold in rats was measured using the tail flick apparatus (D'Amour and Smith, 1941). The time that elapsed between tail exposure to the source of radiant heat and its withdrawal were defined by the tail flick latency. Radiant heat emerging from electrically heated nichrome wire was used in the analgesiometer (INCO, Ambala, India) to elicit nociception. The magnitude of thermal stimuli was adjusted so as to obtain basal latency between 2 and 3 seconds in the rodents. A cut off latency time was fixed at 10 seconds. Tail flick latency was recorded as a percentage of the maximum possible effect (MPE) as deduced from the following formula:

$$\text{MPE (\%)} = \frac{\text{(Post treatment latency - pre treatment latency)}}{\text{(Cut off time - pre treatment latency)}} \times 100$$

Thus, tail flick latency was observed immediately before and 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180 min after the respective treatment(s) according to the *in vivo* study protocol. The study protocol was approved by the institutional animal ethics committee and the experiments were carried out as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forest, Govt. of India (Chitkara College of Pharmacy Animal Facility Registration Number: 1181/ab/08/CPCSEA).

***In vivo* study protocol**

**Group I (Vehicle control group)**

Tail flick latency was observed immediately before and at the various time points after vehicle (10 ml/kg, oral) administration.

**Group II (Tramadol control group)**

Tail flick latency was observed immediately before and at the various time points after tramadol (20 mg/kg, oral) administration.

**Group III (Tramadol beads treatment group)**

Tail flick latency was observed immediately before and at various time points after alginate beads containing tramadol (the amount of drug equivalent to 20 mg/kg, oral) administration. The beads used for testing belonged to the batch number V.

## STATISTICAL ANALYSIS

The results were analyzed using Student's t-test and one-way ANOVA, wherever necessary followed by turkey's multiple range post hoc test to determine statistical difference between the results of various groups. A probability value $p<0.05$ was considered statistically significant.

## RESULTS

***RSM optimization and mathematical modeling***

Mathematical relationships generated using Multiple Linear Regression Analysis (MLRA) for the studied response variables are expressed as Equations 1 through 5.

$$\mathbf{d} = 0.79 + 5.13\ X_1 + 0.073\ X_2 - 0.046\ X_1X_2 + 6.13\ X_1^2 - 0.042\ X_2^2 - 0.013\ X_1X_2^2 + 0.026\ X_1^2X_2 \quad (1)$$

$$\mathbf{I.E.} = 83.82 - 18.76\ X_1 - 21.13\ X_2 + 20.88\ X_1X_2 + 8.23\ X_1^2 + 12.29\ X_2^2 - 4.77\ X_1X_2^2 - 4.92\ X_1^2X_2 \quad (2)$$

$$\mathbf{S.I.} = 26.68 + 14.85\ X_1 + 2.03\ X_2 + 0.986\ X_1X_2 - 5.10\ X_1^2 - 6.32\ X_2^2 - 2.53\ X_1X_2^2 - 1.86\ X_1^2X_2 \quad (3)$$

$$\mathbf{n} = 0.572 + 0.455\ X_1 + 0.955\ X_2 - 0.632\ X_1X_2 - 0.195\ X_1^2 - 0.445\ X_2^2 + 0.206\ X_1X_2^2 + 0.124\ X_1^2X_2 \quad (4)$$

$$\mathbf{T_{80\%}} = 204.51 + 115.37\ X_1 + 172.41\ X_2 - 136.93\ X_1X_2 - 48.55\ X_1^2 - 51.44\ X_2^2 + 10.40\ X_1X_2^2 + 45.33\ X_1^2X_2 \quad (5)$$

The polynomial equations generated using MLRA (Design Expert Software 7.1.4) were found to be statistically significant ($P<.05$), as determined using analysis-of-variance. The sign and magnitude of coefficients for intercept, first-order main effects, interaction terms, and higher order effects imply the relative influence of each factor on the dependent variables.

***Particle size***

The size of dry sodium alginate beads were determined and recorded (table 1). The mean particle size of the various batches of dried sodium alginate beads was found to be between 0.75±0.04 to 0.84±0.05 mm. The equation generated (equation 1) revealed that both factors independently exerted a significant influence on the mean particle size. The influence of the main effects on the particle size was also evident from the response surface plot (fig. 1a) and contour plot (fig. 1b).

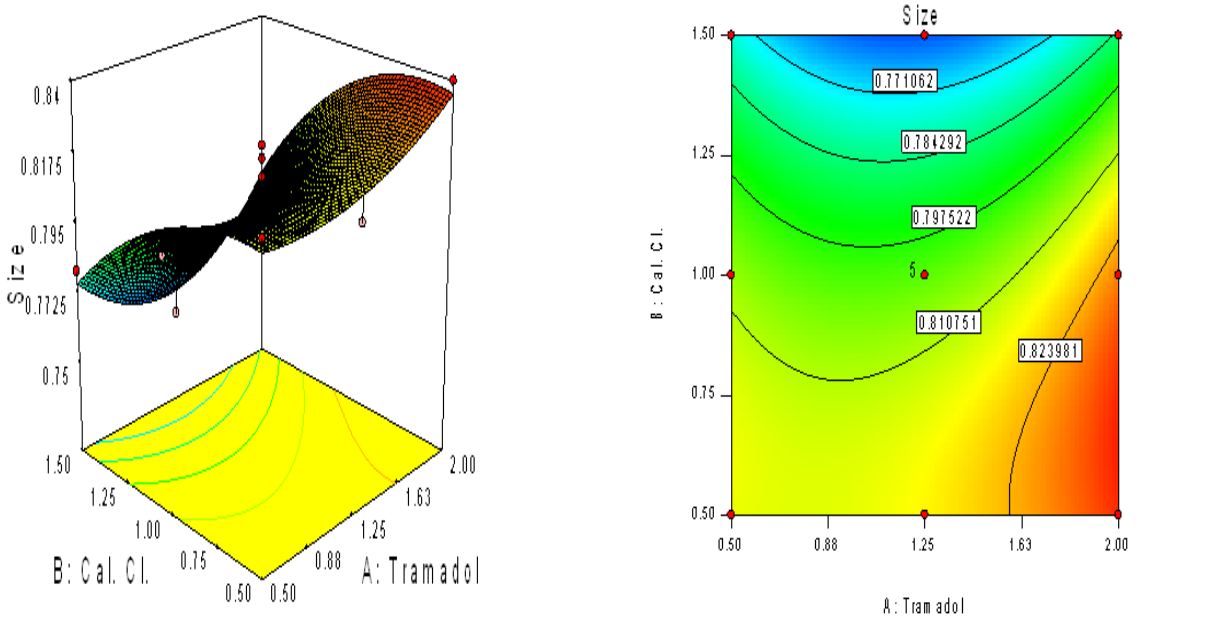
**Incorporation efficiency**

The percent incorporation efficiency was found to be between 72.63±2.09 and 86.43± 3.47. The quadratic model generated (equation 2) revealed that the concentrations of drug and cross-linking agent had a significant influence on the incorporation efficiency

without producing any interaction. The response surface plots (fig. 2a) and the contour plot (fig. 2b) illustrates a dependence on the concentration of cross-linking agent and amount of drug added.

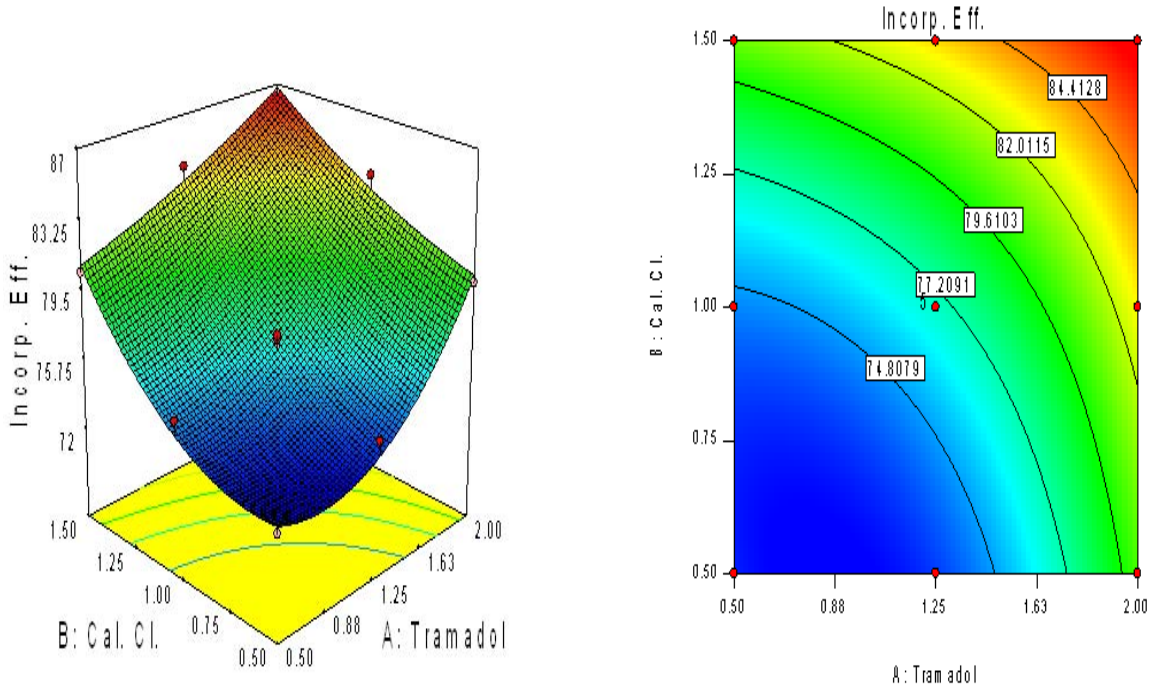
***Swelling index***

Swelling index is an indicator of water uptake capacity of the beads, varied from 36.15±1.33 to 24.80±1.18 amongst the prepared batches of sodium alginate beads (as shown in table 1). The mathematical model generated (equation3) indicated that both the factors were found to exert independently a significant influence on swelling index. The influence of calcium chloride concentration on swelling index is clearly demonstrated by the response surface plots (fig. 3a) and the respective contour plot (fig. 3b).



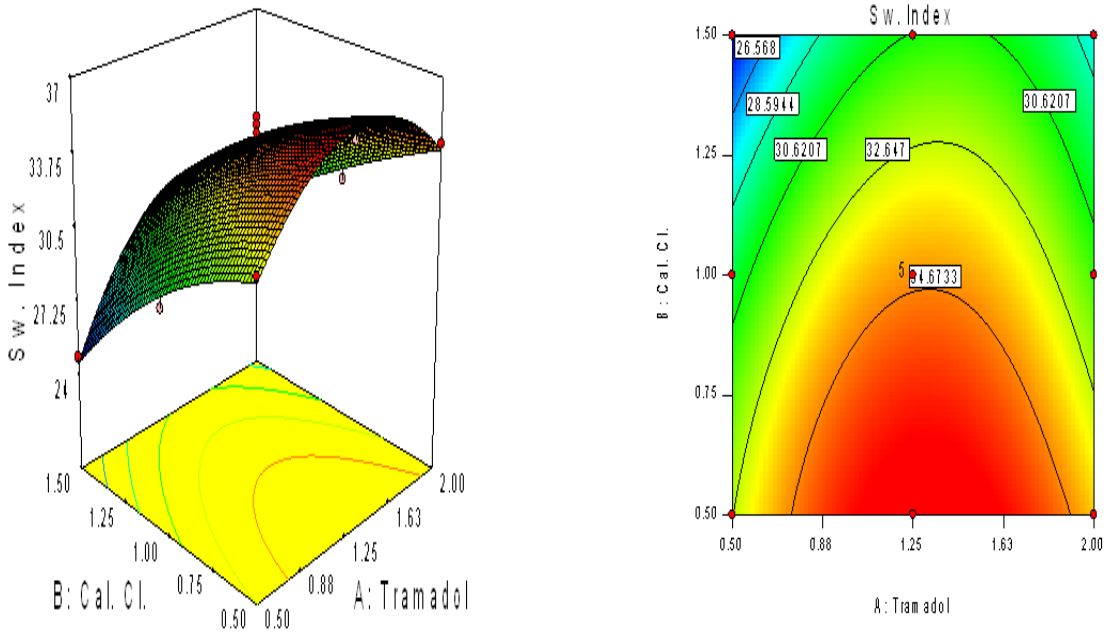

(A) (B)

**Fig. 1**: (A) 3-D plot and (B) Contour plot, depicting the effect of concentration of Tramadol ($X_1$) and Calcium Chloride ($X_2$) on bead size.



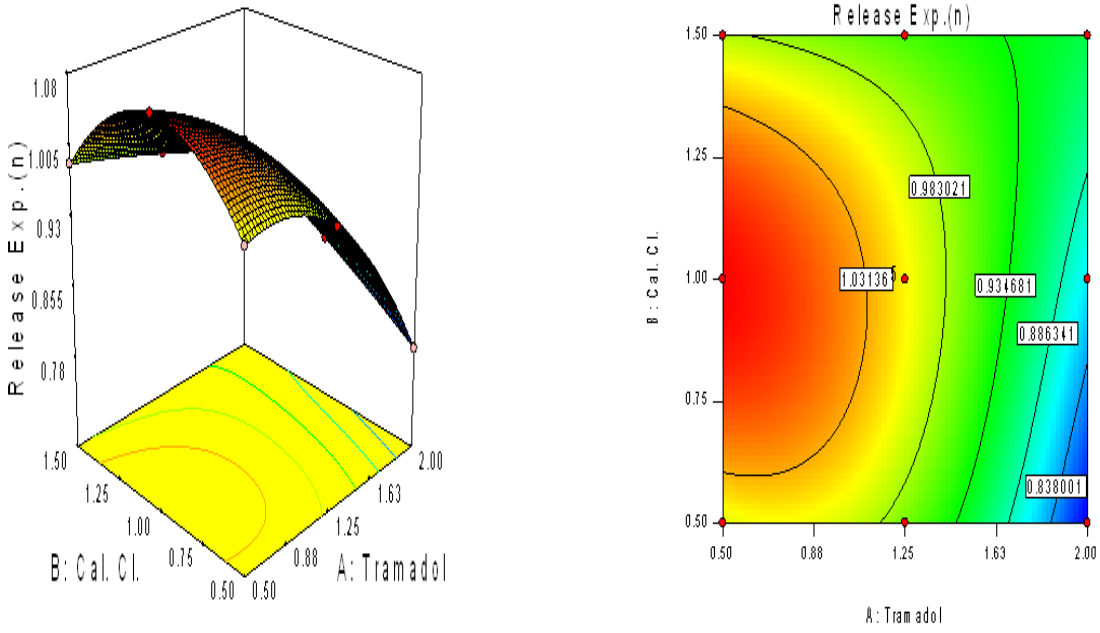

(A) (B)

**Fig. 2**: (A) 3-D plot and (B) Contour plot, depicting the effect of concentration of Tramadol ($X_1$) and Calcium Chloride ($X_2$) on incorporation efficiency.




(A) (B)

**Fig. 3**: (A) 3-D plot and (B) Contour plot, depicting the effect of concentration of Tramadol ($X_1$) and Calcium Chloride ($X_2$) on swelling index.




(A) (B)

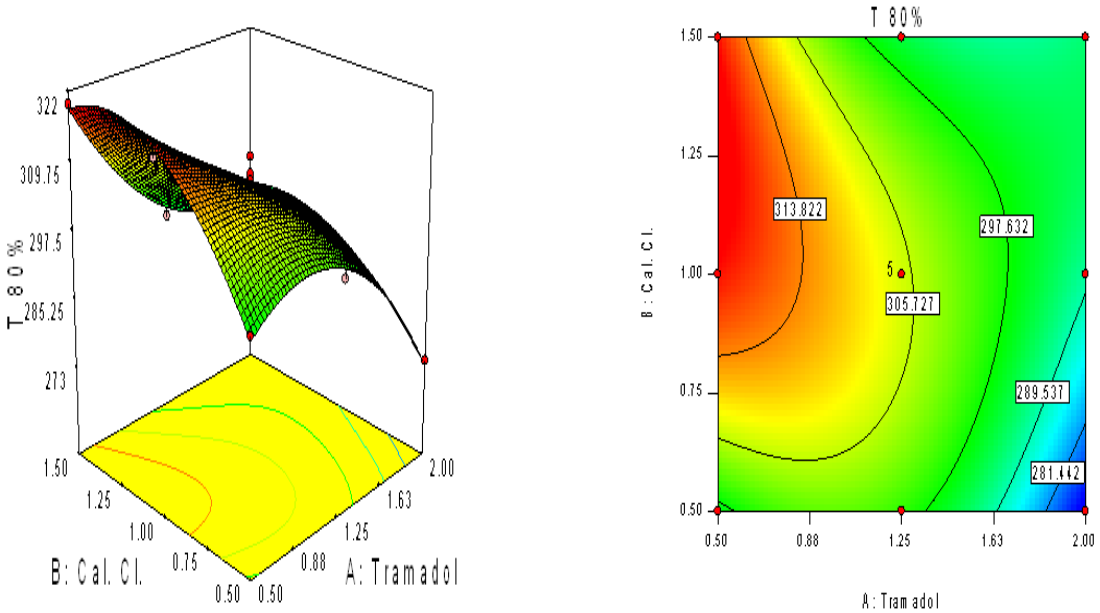
**Fig. 4**: (A) 3-D plot and (B) Contour plot, depicting the effect of concentration of Tramadol ($X_1$) and Calcium Chloride ($X_2$) on release exponent (n).

***Release Exponent (n)***

The predictor equation generated (equation 4), the response surface plot (fig. 4a) and the respective contour plot (fig. 4b) revealed a pronounced effect of drug loading on the release exponent.

***$T_{80\%}$***

The second order polynomial model generated (equation 5) revealed that the levels of polymer ratio and glutaraldehyde had a significant influence on the time for 80 % drug release ($t_{80\%}$) with some obvious interactions. The response surface plots (fig. 5a) and the contour plot (fig. 5b) illustrate that calcium chloride levels were found to have pronounced influence on $t_{80\%}$ as it improved on incorporation of higher amounts. The effect of percentage polymer-to-drug ratio on the release characteristics of drug from the beads is shown in fig. 7.




(A) (B)

**Fig. 5**: (A) 3-D plot and (B) Contour plot, depicting the effect of concentration of Tramadol ($X_1$) and Calcium Chloride ($X_2$) on $t_{80\%}$.

**Table 2**: ANOVA – Influence of formulation variables on the response factors

| Respose factor | Model F-value | Prob>F | Lack of fit F-value | Prob>F |
|---|---|---|---|---|
| Particle Size (µm) | 5.28 | 0.0428 | 4.76 | 0.0945 |
| Incorporation efficiency | 34.29 | 0.0006 | 15.26 | 0.0174 |
| Swelling index | 37.63 | 0.0005 | 6.20 | 0.0675 |
| Release exponent (n) | 5360.72 | 0.0001 | 0.038 | 0.8545 |
| $t_{80\%}$ | 32.75 | 0.0007 | 2.93 | 0.1619 |

**Table 3**: Model Summary Statistics – Influence of formulation variables on the response factors

| Response factor | St. dev. | $R^2$ | Adjusted $R^2$ | Predicted $R^2$ |
|---|---|---|---|---|
| Particle Size (µm) | 0.012 | 0.8807 | 0.7138 | -6.6101 |
| Incorporation efficiency | 0.93 | 0.9796 | 0.9510 | -0.8847 |
| Swelling index | 0.71 | 0.9814 | 0.9553 | -0.3263 |
| Release exponent (n) | 1.355E-003 | 0.9999 | 0.9997 | 0.9997 |
| $T_{80\%}$ | 2.83 | 0.9787 | 0.9488 | -0.0675 |

***Summary statistics for the model***

ANOVA of the selected responses (table 2) indicated that response surface models developed for all responses were significant and adequate. The lack of fit was not significant for all the responses with the exception of incorporation efficiency.

Table 3 details the model summary statistics for the selected significant models. It could be analyzed that higher value of $R^2$ for all the responses suggests a high degree of correlation between the experimental and predicted responses. Furthermore, a negative predicted $R^2$ value in all the responses, with the exception of release exponent (n), implies that the overall mean is a better predictor of our response than the current model. In addition, the predicted $R^2$ value of release exponent (n) is in good agreement with the adjusted $R^2$ value, resulting in reliable model.

***In-vitro release studies***

In-vitro release studies of drug-loaded beads, firstly in 0.1 N HCl followed by phosphate buffer pH 7.4, clearly indicates the pH dependent solubility of sodium alginate. In acidic pH there was no release of the drug from the formulated beads (results in line with *in vivo* drug activity studies). Moreover, release of the drug in phosphate

buffer pH 7.4 clearly demonstrate pH dependent release behavior of the drug from sodium alginate beads. The effect of concentration of cross-linking agent on the release characteristics of Tramadol is shown in fig. 6.

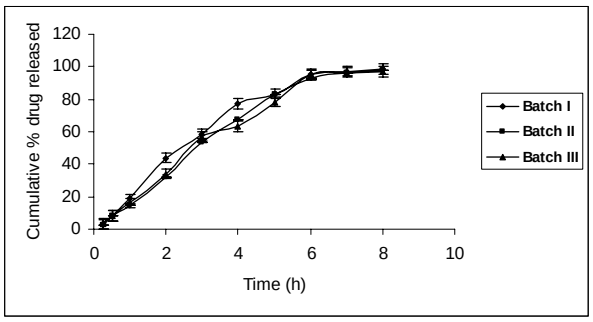



**Fig. 6**: Effect of calcium chloride concentration on the release characteristics of Tramadol from alginate beads.

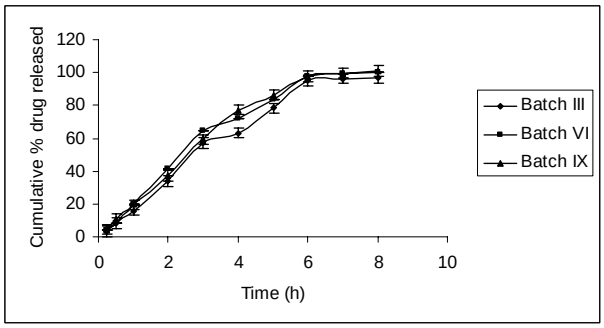



**Fig. 7**: Effect of percentage polymer-to-drug ratio on the release characteristics of Tramadol from alginate beads.

***In vivo drug activity study***

Results of *in vivo* drug activity studies shows that the vehicle administration did not exert any effect on tail flick latency in rats at any of the time points. However, tramadol *per se* did produce a marked analgesic effect in rats. Peak time of analgesic effect of the drug was observed to be 30 min after the administration. Moreover, oral administration of alginate beads of tramadol (Batch V), also elicited a significant analgesic effect in rats. Further the peak time of analgesic effect of the drug-loaded beads was observed to be 150 min after the administration (fig. 8).

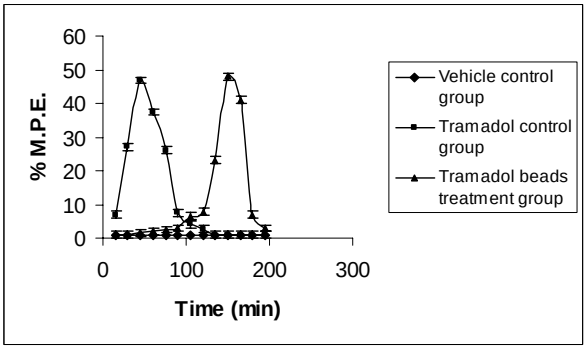



**Fig. 8**: Effect of various treatment(s) on the tail flick latency in rats. Results are expressed as mean % M.P.E. (Maximum possible effect).

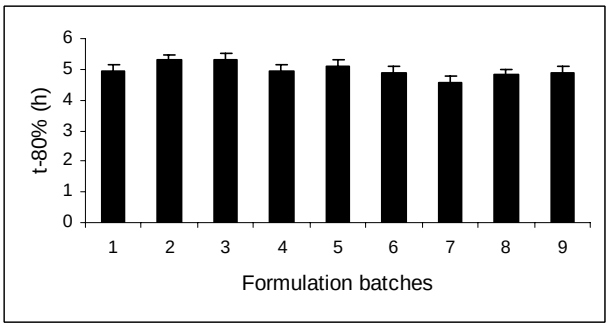



**Fig. 9**: Bar chart depicting significant variation in the $t_{80\%}$ amongst the formulation batches.

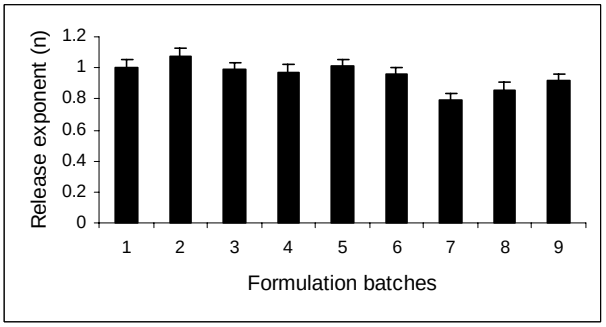



**Fig. 10**: Bar chart depicting significant variation in the release exponent (n) amongst the formulation batches.

## DISCUSSION

The values obtained for main effects of each factor in equations 1 and 3 reveal that $X_1$ has more evident effect on the values particle size and swelling index. Whereas equations 2, 4 and 5 reveals that $X_2$ has a more significant effect on incorporation efficiency, release exponent and $t_{80\%}$. The response surfaces indicated a proportionate reduction in the mean particle size of the beads with increasing concentration of the cross linking agent. This could be attributed to shrinkage of beads caused by high degree of cross-linking linked with the increasing concentration of calcium chloride (Wang and He 2002). Results of incorporation efficiency indicate significant increase in incorporation efficiency with increasing concentration of drug and cross-linking agent. The beads with higher amount of drug exhibited higher incorporation efficiencies that are due to accumulation of more drug molecules within the beads. As the amount of cross-linking was increased, an increase in incorporation efficiency was observed. This may be attributed to the formation of more rigid network structure, which would cause the retention of more drug molecules during the bead preparation (Rokhade *et al*., 2007). With the increasing concentration of cross linking agent, swelling index values were considerably reduced which may be ascribed to surface hardening of the beads linked to concentration (calcium chloride) based degree of cross-linking. Different kinetic models analyzed the in vitro release profiles of alginate beads in order to find out the *n*

value, which is an indicator of the drug release mechanism. The values of *n* (as shown in table 1and fig. 10) for the release of Tramadol at pH 7.4 ranges from 0.7896 to 1.0797 (from power law equation), indicating that the drug release from the beads followed anomalous and super case – II transport mechanism possibly mediated through swelling and erosion (Tonnesen and Karlsen, 2002). The inter batch alteration in polymer-to-drug ratio (1 to 4) depicted significant effect on the *in vitro* drug release characterized by an decrease in percent drug released with an increase in polymer-to-drug ratio. This may be due to the fact that at high levels of polymer-to-drug ratio the cross linking reaction is much favored leading to higher values of $t_{80\%}$ (as shown in table 1 and fig. 9). Moreover, this may further be attributed to the three-dimensional array of lattice points on the surface topology of the beads, playing a vital role in the drug release characteristics. As the drug loading is increased in contrast to the polymer concentration, the drug molecules occupy more lattice points, thereby by acting as filler between the polymer molecules. As the drug molecule is displaced (by dissolution media) from the lattice position, multiple channels are created throughout the polymer matrix thereby aiding in the drug release from the beads. As the concentration of cross-linking agent is increased from 0.5 to 1.5 % (Batch I to III), there is considerable reduction in drug release, which may be ascribed to an increase in the extent of cross linking, leading to the formation of tight junctions and hence denser network structure responsible for retarding the release of drug from the beads (Rokhade *et al*., 2007). Pharmacodynamic assessment of the analgesic effect of tramadol *per se* demonstrated that the peak effect of the drug was observed 30 minutes after the administration. However, it was also found out that by formulating the alginate beads of tramadol, the analgesic effect of the drug was found to be delayed by 2 hrs. Such an observation might be attributable to a possibility that the beads might be staying intact in the gastric pH but are releasing the drug later in the distal part of the gastrointestinal tract. These observations are further supported by the present *in-vitro* release studies of the alginate beads of tramadol, which demonstrated the poor release of the drug from its beads in the gastric pH. The said results further showed that the beads disintegrated more effectively in a more basic pH similar to that of the milieu inside the lumen of the intestines. However, such a supposition needs further experimental justification in the form a more specific study to delineate the pharmacokinetic profile of the beads and its exact relation with the site of release of the drug in question.

## CONCLUSION

It may be concluded from the present investigation that preparation of beads by ionic cross-linking technique requires proper selection of formulation parameters in order to achieve high entrapment efficiency and to control the release of drug from the alginate beads. The release kinetics of the beads indicated involvement of both swelling and erosion processes in mediating the release of drug from the beads. The central composite design was found to be satisfactory for describing the relationships between formulation variables and individual response variables. For future suggested work blends of sodium alginate with other biopolymers could be employed for better controlled release and site specific drug delivery application. At lower drug loading, there is less probability of formation of a continuous network and thus restricting the drug diffusion. Whereas at higher drug loading, there occurs the formation of channels/pores which might be responsible for faster drug release from the dosage form (Kim, 2005). Also with an increase in drug loading, the release kinetics is mechanized through polymer erosion and drug diffusion there by reducing the value of release exponent (value of n is 1.0008, 0.9700 and 0.7896 for batch I, IV and VII respectively).

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