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Sodium Alginate Based *In-Situ* Gelling System of Ketorolac Tromethamine: Formulation, Evaluation and Optimization Using 2D Contour Plot

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Abstract

The present investigation concerns with the development and optimization of p^H specific sodium alginate based *in-situ* gelling system containing ketorolac tromethamine. The experiments were designed using 3^2 full factorial designs with an objective to retain in stomach for an extended time period. Based on preliminary trial, the concentration of sodium alginate (X1) and calcium carbonate (X2) were selected as formulation variables. The effect of selected independent factor on response variables such as percentage drug release at 1h (Q1), time required to release 80% of drug ($t_{80\%}$) and viscosity, were studied from the two dimension (2D) contour plot. Results of analysis of variance conformed that both formulation variable had a significant effect on studied response, as p- value less than 0.05. The validation of proposed model were performed by designing two check point formulation (A1, A2) based on the visual inspection of 2D contour plot of studied response. The comparison of observed and predicted response of A1 and A2 showed good similarity in response variable. Results of accelerated stability study showed no significant change in response variables. Hence, it was concluded that controlled release of ketorolac tromethamine can be achieved by sodium alginate based *in-situ* gelling system.

Keywords: In-situ gel, ketorolac tromethamine, check point, counter plot.

Introduction

A property of aqueous alginates solution has been widely exploited for the fabrication of vehicles for the sustained delivery of bioactive molecules is their ability to form firm gels on the addition of di- or tri- valent metal ions by a co-operative process involving consecutive guluronic residues in the G- blocks of the alginate chain (Morris et al. 1993, Grant et al. 1993, Rees et al. 1994, Liang et al. 1998). There have been many investigations of the use of alginate gels for the sustained release of drugs. Nakano and Ogata investigated tablets containing sodium alginate for the sustained release of theophylline (Nakano et al. 1994). *In-vitro* release from capsules containing sodium alginate and calcium phosphate and from solid beads consisting of a calcium alginate gel matrix has been reported (Nicholson et al. 1990, Stockwell et al. 1986, Yotsuyanagi et al. 1987). There have been very few reports on the use of alginates in liquid sustained release preparations for oral administration (Segi et al. 1989, Johnson et al. 1985).

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Zatz and Woodford developed a suspension formulation of theophylline which contained sodium alginate and which formed a gel when in contact with simulated gastric fluid (Zatz 1987). A liquid sustained release formulation containing sodium alginate intended for the eradication of helicobacter pylori has recently been reported (Katayama et al. 1999). The formulation depends for its action on *in-situ* gelling induced by the separate oral administration of a solution of a calcium salt immediately following that of the sodium alginate solution. The present work focused on use of Ca^{2+} ions and sodium alginate based ketorolac tromethamine *in-situ* gelling system for sustained release delivery.

Ketorolac tromethamine (KET) is a nonsteroidal anti-inflammatory drug widely prescribed in gastric ulcer, stomach inflammation, pain, and fever through inhibition of prostaglandin synthesis. It is mainly absorbed in stomach or proximal part of small intestine. As PK_a of KET is 3.49, it remains unionized in stomach and maximum absorption take place from stomach only (Ruckmani et al. 2000, Vatsaraj et al. 2000, Bhaskaran et al. 2001). Hence, ketorolac tromethamine was selected as a model drug to design sodium alginate based *in-situ* gelling system.

Materials and Methods

Materials

Ketorolac tromethamine (KET) was received as a gift sample from Sun Pharmaceutical Ltd., Vadodara (India). Sodium alginate was received as a gift sample from Signet Chemicals Corpn. Pvt. Ltd., Mumbai (India). Calcium carbonate and other excipients were procured from S.D. fine chemicals, Mumbai (India).

Methods

Fourier transforms infrared spectroscopy (FTIR) study

Drug - excipients compatibility studies were performed by FT-IR spectroscopy. IR spectra of KET loaded *in-situ* gel was recorded in a fourier transform infrared (FTIR) spectrophotometer (FTIR-8400 S, Shimadzu, Japan).

Differential scanning calorimetry (DSC) study

The DSC analysis of KET alone and KET loaded *in-situ* gel were carried out using automatic thermal analyzer system (DSC 60, Shimadzu, Japan) in order to evaluate drug-excipients compatibility (Kawashia et al. 1991).

Preliminary trials for KET in-situ gel

Preliminary trial was carried out in order to determine effect of sodium alginate and calcium carbonate concentration on drug content, viscosity of the solutions, p^H and other physical properties of the gel. In the trial, the concentration of sodium alginate was varied from 1.0 - 3.0 % w/v with respect to solution containing 2 % w/v calcium carbonate and 0.25 % w/v sodium citrate. The results are shown in Table 2.

A 3^2 full factorial design

On the basis of the preliminary trials, a 3^2 full factorial design was employed to study the effect of formulation variables, i.e. concentration of sodium alginate (X_1) and the concentration of calcium carbonate (X_2) on response variables % drug release at 1h (Q1), time required to release 80% of drug ($t_{80\%}$), viscosity (n) as shown in Table 1. A statistical model (eq.1) incorporating interactive and polynomial terms was utilized to evaluate the study responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (1)$$

Where, Y is the dependent variables, b_0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor X_1. 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 how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity (Patel et al. 2004). The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative. The high values of correlation coefficient for the dependent variables indicate a good fit.

Table 1. A 3^2 full factorial design for KET *in-situ* gel

Batch No.	Variables levels in coded form		
	X_1		X_2
F1	-1		-1
F2	-1		0
F3	-1		+1
F4	0		-1
F5	0		0
F6	0		+1
F7	+1		-1
F8	+1		0
F9	+1		+1
Translation of coded levels in actual units			
Variables level	Low (-1)	Medium (0)	High (+1)
Sodium alginate content (X_1)	1.5 %	2.0 %	2.5 %
Calcium carbonate content (X_2)	1.0 %	2.0 %	3.0 %

All the batches contained KET 20 mg/5 ml, viscosity measured at 150 rpm and pH 7.0 ± 0.3.

Preparation of the in-situ gel

Various *in-situ* gel forming solution were prepared by dissolving 1.5–2.5 % w/v sodium alginate in deionised water containing 0.25 % w/v sodium citrate and heated at 70°C with continuous stirring. After cooling this polymer solution (below 40°C), different proportion of calcium carbonate in range of 1.0-3.0 % w/v was added. To each solution 0.4 % w/v KET was added and stirred continuously for 45 min. The resulting solution was finally stored in amber colour bottles with proper labelled until further use.

Evaluation of KET in-situ gel

Physical properties

Each factorial batch was evaluated for its clarity and type of gel formed. The p^H of solution was measured using a calibrated digital p^H meter at 27°C.

Determination of viscosity

Viscosity of each factorial batch was measured using a brookfield digital viscometer (Model no. LVDV 2P230) at 100 rpm of splinder. The solution temperature was controlled at 25±1°C before the each measurements.

Determination of drug content

The 5 ml solution of each factorial batch was placed in a 100 ml volumetric flask containing small quantity of 0.1N HCl and shake it for 10 min. Final volume of solution was made to the mark with 0.1N HCl. From the above solution, 1ml aliquot was withdrawn and diluted into 10 ml volumetric

flask. The resulting solution was then subjected for absorbance measurement at 322 nm using spectrophotometer against 0.1N HCl.

In-vitro buoyancy study

The *in-vitro* buoyancy study was determined using USP dissolution apparatus II in 900 ml of simulated gastric fluid (p^H 1.2). The medium temperature was kept at 37±0.5 °C. The 5 ml of *in-situ* gel forming solution were drawn up with help of disposable syringe and placed in to Petri dish and then kept in the dissolution vessel containing dissolution medium without any disturbance. The time required for the *in-situ* formed gel to buoyant at the medium surface (floating lag time) and the time required for the gel to remain float on the dissolution medium surface (floating time) were noted (Rajinikanth et al. 2000).

In-vitro drug release study

The drug release study was carried out using modified USP XXVI paddle apparatus (Labindia, Disso 2000, Mumbai, India) at 37±0.5 °C. The 900 ml of simulated gastric fluid (p^H 1.2) were utilized as a dissolution medium as per paddle dissolution test. The medium were stirred at 50 rpm. The 5 ml of *in-situ* forming formulation was withdrawn using disposable syringe. The syringe end was then placed into the petridish and plunger pushes slowly to remove 5 ml formulation. The formulation containing petridish was kept in the dissolution vessel without any disturbance. The sample solution was withdrawn at different time intervals and filtered through a 0.45 µm membrane filter, diluted suitably and analyzed spectrophotometrically at 322 nm. The same amount of pre-warmed (37±0.5 °C) fresh dissolution medium was replaced after each withdrawal of the sample.

Kinetics modelling of drug release

The dissolution profile of each factorial batch was fitted to zero order, first order and higuchi model, korsmeyer peppas model and hixson crowell model to ascertain the mechanism of drug release from various factorial batches (Higuchi 1963, Wagner 1969, Gibaldi 1967, Higuchi 1996).

Statistical analysis

The statistical analysis of the factorial batches were performed by using Design Expert software (Design Expert Trial Version 8.0.3.1. State-Ease Inc, Minneapollis, MN). To evaluate contribution of each factor on response variables, the analysis of variance (ANOVA) was performed using the Design Expert software. The optimization of formulation was carried out from the two dimensional contour plot. The contour plots were generated to demonstrate the influence of each formulation variable on response variable. The model was considered significant, if p value found less than 0.05.

Comparison of dissolution profiles

The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are considered to be similar when f_2 is between 50 and 100. Similarity factor was calculated by following formula (Higuchi 1963),

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5}\times 100\right\} \quad (2)$$

Where, n is the number of dissolution time and R_t and T_t are the reference and test dissolution values at time t.

Stability study

The optimized *in-situ* gel forming solution was stored in a glass containers (well stoppered) for one months and the stability of the aqueous solutions was monitored up to 1 months at accelerated stability conditions (45°C and 75±5% RH). Periodically (initial, 1, 2, and 3 week interval) samples were removed and characterized for p^H, viscosity and drug content. Effect of accelerated stability condition on release profile of ketorolac was monitered by comparing similarity factor (f_2) of optimized batch before and after stability study.

Results and Discussion

Fourier transform infrared spectroscopy (FTIR) Study

Drug and other excipients were checked for its competibility by FTIR spectroscopy. Figure 1 shows IR spectra of physical mixture of KET included, sodium alginate, sodium citrate. There was no interaction between KET and other excipients observed and results showed that selected excipients are compatiled with KET.

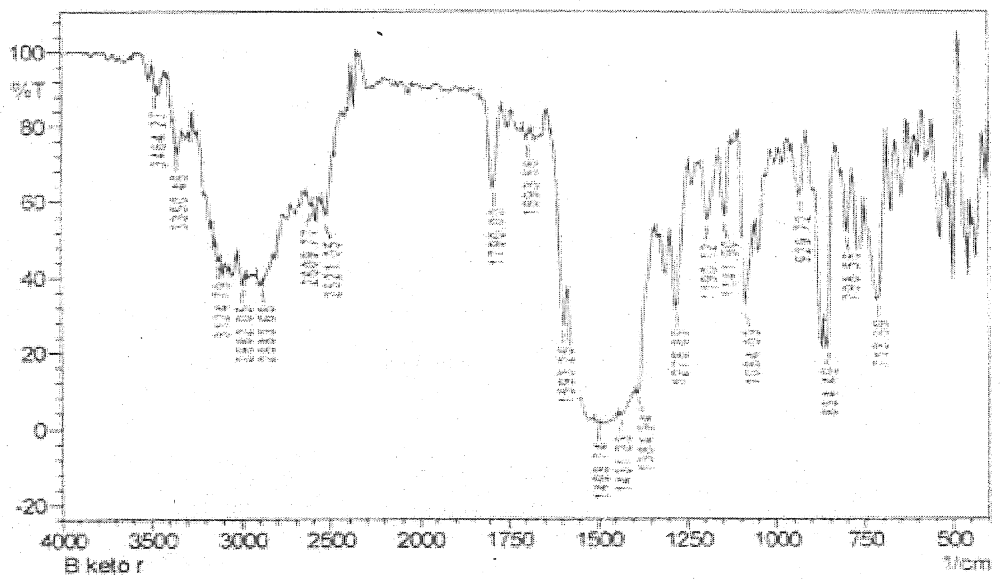

Figure 1. FT-IR spectra of physical mixture of KET *in-situ* forming formulation

Differential scanning calorimetry (DSC) study

DSC provides qualitative information about the physicochemical state of drug inside the formulation. Figure 2 shows DSC thermograms of KET, sodium alginate, sodium citrate and physical mixture of formulation. The thermogram of pure ketorolac shows melting endotherm at 160.10°C. Thermogram of KET loaded formulation shows three different endothermic peak at 162°C, 151.03°C and 294.41°C. This confirmed that the presence of excipients had not influenced on stability of KET.

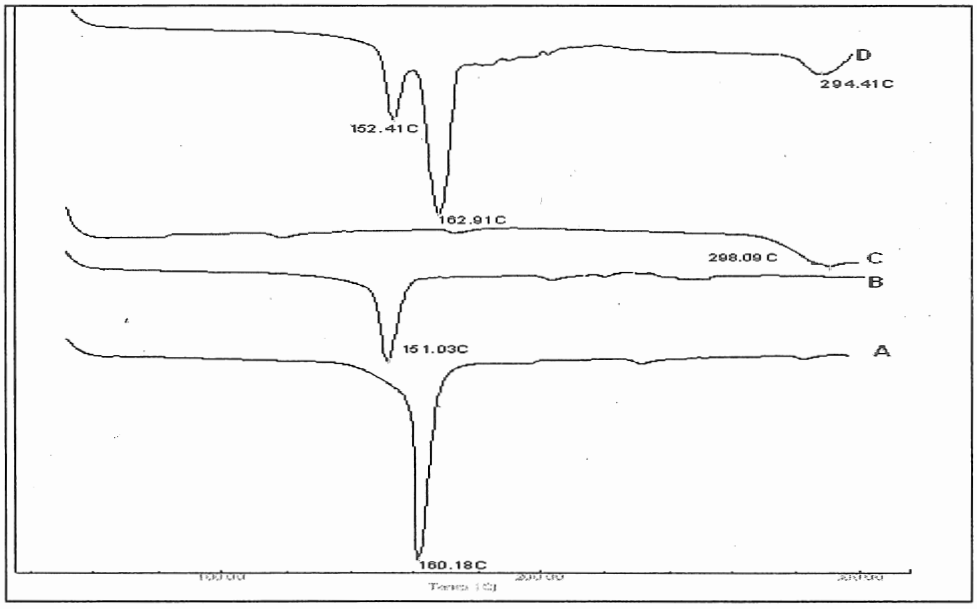

Figure 2. DSC curve for (A) ketorolac tromethamine-drug, (B) sodium citrate, (C) sodium Alginate, (D) physical mixture of KET with sodium citrate, sodium alginate

Preliminary trials of sodium alginate based in-situ gelling system of KET

The results of preliminary work are shown in Table 2. Batch P1 showed improper gellation and more time required for gellation compared to other batches. The obtained drug content of batch P1 was found lower than the other batches. Batch P2 showed more gellation and less time for gellation compared to batch P1. The obtained drug content for batch P2 was slightly better than batch P1. While batch P3 showed excellent gellation and less time for gellation as compared to above batches. Batch P5 showed more viscous solution compared to others. This might be due to higher content of sodium alginate which was difficult to pour from bottle. From the above finding, it was observed that content of sodium alginate and calcium carbonate had greater influenced on gellation, viscosity, drug content. Hence, it was decided to optimize content of sodium alginate and calcium carbonate for KET *in-situ* gelling formulation.

Table 2. Preliminary trial batches for KET *in-situ* gel

Batch No.	Conc.of Na alginate (%)	pH	Viscosity (cp)	Drug content (%)	Characteristic of *in-situ* gels
P_1	1.0	7.4	90	83.25	Gel is not form properly and less drug content
P_2	1.5	7.1	150	91.92	Gel formation and drug content are slightly better
P_3	2.0	7.0	236	97.87	Gel formation and drug content are excellent
P_4	2.5	6.8	331	96.56	Gel formation and drug content are good
P_5	3.0	6.8	347	98.55	Gel formation and drug content are good and stiff (Solution is too viscous to pour)

Note: All the batches were prepared using $CaCO_3$ 2.0 %

Optimization by 3^2 full factorial design

A 3^2 full factorial design was employed to study the effect of independent variables, i.e. concentration of sodium alginate (X_1) and the concentration of $CaCO_3$ (X_2) on dependent variables viscosity, % drug release in 1 h (Q1), time required to release 80% of drug ($t_{80\%}$). The results clearly indicated that selected dependent variables are strongly dependent on the independent variables as they showed a wide variation among the nine batches (F1 to F9). The high values of correlation coefficient for the dependent variables indicate a good fit. The equation may be used to obtain estimate of the response because small error of variance was noticed in the replicates.

Table 3. Results of study response for experimental batches

Batch No.	n (cp)	Drug content (%)	Q1 (h)	t_{80}% (h)	Floating lag time (sec)
F1	112	94.12	37.12	6.1	75
F2	134	95.65	35.01	6.8	68
F3	155	96.78	31.34	7.5	57
F4	227	97.92	28.42	7.7	58
F5	236	100.72	26.51	8.3	42
F6	266	97.54	22.03	9.1	45
F7	296	98.22	19.1	9.3	60
F8	335	99.95	16.32	10	58
F9	365	97.75	12.4	10.8	49

In-vitro buoyancy study

In-vitro buoyancy study was carried out in simulated gastric fluid. Floating lag time was found to decrease with increasing content of calcium carbonate. This might be due to upon contact with an acidic media, calcium carbonate ionized into Ca^{++} ions and released carbon dioxide. The released carbon dioxide is entrapped in the gel network producing buoyant formulation and then calcium ion reacted with sodium alginate produced a cross linked three-dimensional gel network that may restrict further liberation of carbon dioxide and drug molecules, resulting an extended period of floating and drug release, respectively (Grasdalen 1987, Singh 2000). The floating ability of the formulation mainly depends on calcium carbonate and sodium alginate concentrations. Floating lag time of factorial batches F1 to F9 are shown in Table 3.

In-vitro dissolution profile of factorial batch

The release profile of KET from various factorial batches are shown in Figure 3. release rate of KET was found to be related with content of sodium alginate, study response Q1 and $t_{80\%}$ was found to be greater influenced by content of sodium alginate. The batch F5 released 26.51 % of KET at the end of 1 h and showed 8.3 h for 80% of KET release which was similar to theoretical release profile. The drug release rate was found to decrease with increasing content of sodium alginate and calcium carbonate. This might be due to formation of cross linking network of gelling barrier increased by increasing the content of sodium alginate and calcium carbonate that restrict the release rate of ketorolac. Release profile of factorial batches are expressed in Figure 3.

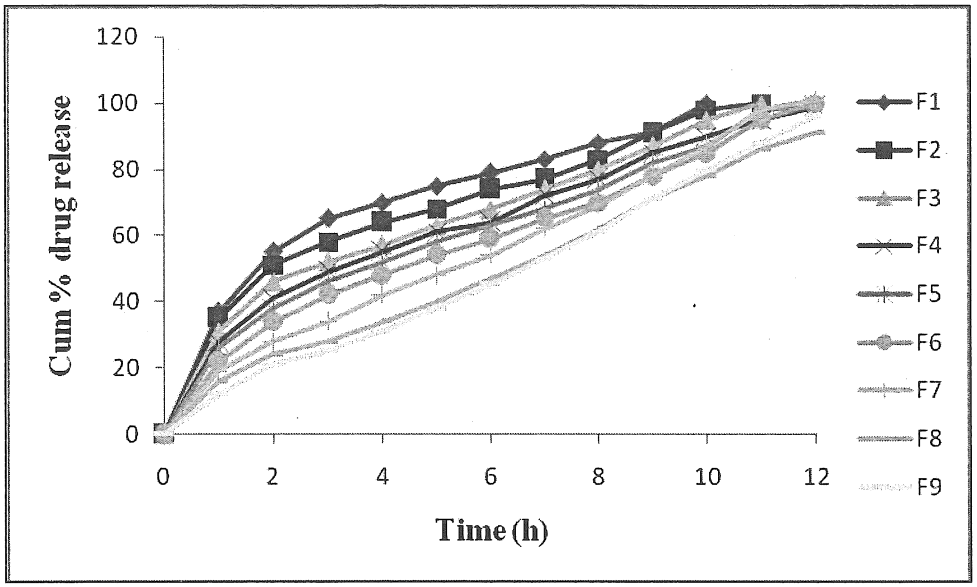

Figure 3. *In-vitro* KET release profile of factorial batches F1 to F9

Drug release mechanism

The obtained KET release profiles were extrapolated by Zero order, Higuchi, First order, Korsmeyer-Peppas model, and Hixon crowell equations to know the mechanism of drug release from these formulations. Table 4 showed the results of kinetic modelling of factorial batches F1 to F9. The release rate of drug could be best expressed by Higuchi's equation as it showed good linearity (R^2: 0.949 to 0.995). To confirm the diffusion mechanism, the data were fitted into Korsmeyer peppas equation. All batches showed good linearity (R^2: 0.980 to 0.993) with slope (n) values ranging from 0.392 to 0.840, indicated that at low level of sodium alginate and calcium carbonate, drug release rate was diffusion controlled. As the proportion of sodium alginate and calcium carbonate increased in the formulation, diffusion release mechanism sifted towards erosion mechanism. These allowed near zero order drug release achieved.

Table 4. Kinetic modelling of drug release

Batch	Zero order		First order		Highuchi		Korsmeyer peppas		Hixon crowell	
	K_0	R^2	K_1	R^2	K_H	R^2	N	R^2	K_{HC}	R^2
F1	7.81	0.828	-0.14	0.811	29.5	0.977	0.392	0.98	-0.33	0.837
F2	7.4	0.881	-0.15	0.834	28.79	0.988	0.416	0.987	-0.32	0.877
F3	7.54	0.921	-0.13	0.797	28.75	0.991	0.463	0.985	-0.31	0.839
F4	7.07	0.934	-0.12	0.825	28.21	0.995	0.498	0.993	-0.25	0.98
F5	7.2	0.951	-0.13	0.78	28.38	0.987	0.529	0.991	-0.26	0.916
F6	7.31	0.968	-0.12	0.758	28.41	0.978	0.587	0.99	-0.28	0.816
F7	7.89	0.989	-0.13	0.755	29.88	0.949	0.685	0.983	-0.3	0.752
F8	7.2	0.992	-0.07	0.902	27.03	0.976	0.719	0.985	-0.19	0.955
F9	7.71	0.994	-0.09	0.815	28.55	0.981	0.84	0.993	-0.22	0.914

Statistical analysis

The mathematical relationship was generated using Design Expert software for all study responses and express as equation 3 to 5.

$$\text{Viscosity} = 241.77 + 99.17 * X1 + 25.17 * X2 - 10.17* X1*X2 + 1.83*X1^2 + 6.5 * X2^2$$

$$(R^2_{adj} = 0.9925; F = 214.46; F(5,3,95\%) = 9.01) \quad (3)$$

$$Q1 = 25.88 - 9.33*X1 - 3.17*X2 - 0.33*X1*X2 - 0.83*X1^2 - 0.25*X2^2$$

$$(R^2_{adj} = 0.9991; F = 1804.2; F(5,3,95\%) = 9.01) \quad (4)$$

$$t_{80\%} = 8.33 + 1.61*X1 + 0.72*X2 + 0.05*X1*X2 + 0.05*X1^2 + 0.025*X2^2$$

$$(R^2_{adj} = 0.9994; F = 2703.72; F(5,3,95\%) = 9.01) \quad (5)$$

For the estimation of significant of the model, the analysis of variance (ANOVA) was determined as per the provision of Design Expert software as shown in Table 5. Using 5% significance level, a model is considered as a significant, if p value is less than 0.05. From the polynomial equation of Q1, the negative sign of coefficient of independent variables showed that release rate of drug at 1 h decreased by loading sodium alginate and calcium carbonate. Calculated F value suggested that both independent variables had a significant effect on Q1. It was further confirmed from higher value of R^2_{adj}. Polynomial equation for $t_{80\%}$ showed that as loading of sodium alginate and calcium carbonate increased, the time required to release 80 % of drug increased. It was further confirmed from p value as shown in Table 5. Viscosity of the solutions was significantly affected by the content of sodium alginate and calcium carbonate. The higher value of coefficient correlation for all study response clearly indicated that all studied responses were strongly depended on both formulation variables.

Table 5. Result of two ways ANOVA for dependent variables

Source of variation	DF	SS	MS	F	P
Q_1					
Regression	5	584.6944	116.9389	1804.2	2.06E-05
Residual	3	0.194444	0.064815		
Total	8	584.8889			
$t_{80\%}$					
Regression	5	18.77583	3.755167	2703.72	1.12E-05
Residual	3	0.004167	0.001389		
Total	8	18.78			
Viscosity					
Regression	5	63186.78	12637.36	214.4617	0.000499
Residual	3	176.7778	58.92593		
Total	8	63363.56			

Contour plot analysis

The graphically representation of the influence of sodium alginate and calcium carbonate on study responses were generated using provision of Design Expert software.

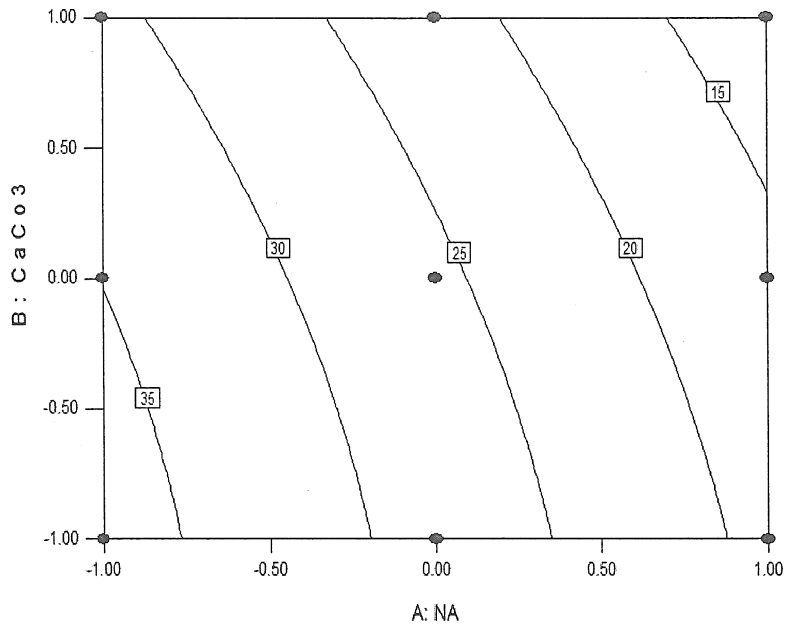

Figure 4. Counter plot showing the effect of Na-alginate polymer(X_1) and $CaCo_3$(X_2) on Q_1

Figure 4 shows the effect of independent variables on release rate at 1 h. The results demonstrate that sodium alginate has a more significant effect than the calcium carbonate on release rate of drug at 1 h. As loading of sodium alginate increases, the release rate of drug decreases.

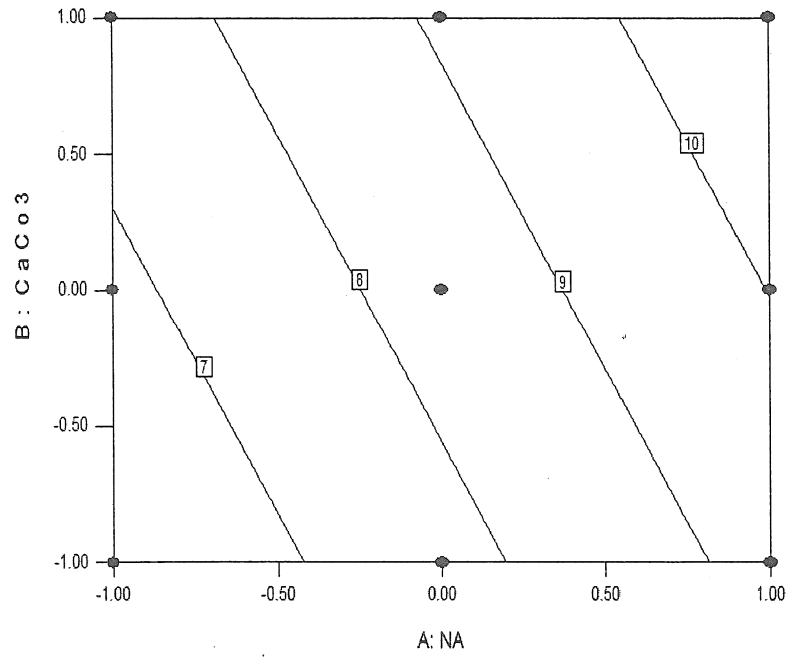

Figure 5. Counter plot showing the effect of Na-alginate polymer(X_1) and $CaCo_3$(X_2) on $t_{80\%}$

Figure 5 shows the effect of independent variable on time required to release 80 % of KET. These demonstrate that as loading of sodium alginate increase, the time required to release 80% of drug increase in linear fashion. These may be attributed to increase in the density of the polymer matrix and also an increase in the diffusion path length which the drug molecules have to travel. The results of polynomial equation showed that both independent variables had significant effect on the study response variable as p value was less than 0.05.

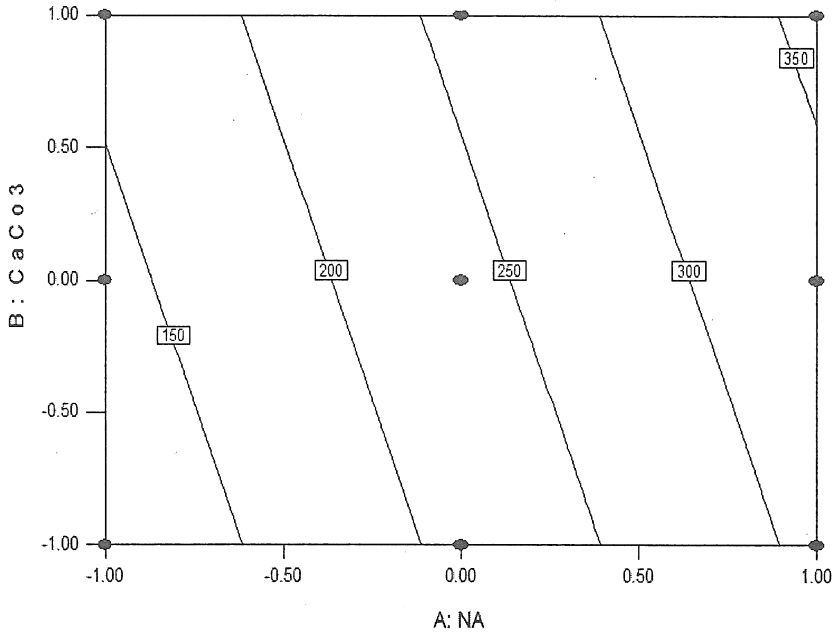

Figure 6. Counter plot showing the effect of Na-alginate polymer (X_1) and $CaCo_3$ (X_2) on viscosity

Figure 6 shows effect of independent factor on viscosity of solution. It was observed that calcium carbonate had significant effect on viscosity as $p < 0.05$. As calcium carbonate concentration increased in formulation, viscosity of solution was found to increase simultaneously. This might be due to insoluble dispersion of calcium carbonate increased the number of disperse particles that contributing in viscosity.

Validation and optimization of in-situ gelling system

Based on visual inspection of the two dimension contour plot, two check point formulation were designed. Batch A1 contained 2.25% w/v sodium alginate and 2.0% w/v calcium carbonate, while A2 contained 2.25 % w/v sodium alginate and 2.25 % w/v calcium carbonate. Both checkpoint formulations were evaluated under same condition as outlined for other factorial batches. The Comparison of predicted and observed response of both checkpoint formulations is expressed in Table 6. Results showed good similarity between studied response and predicted value for optimized batches. Drug content and other physical parameters of both formulations found within acceptable range. Similarity factor (f_2) was calculated by considering the ideal release profile as reference and optimized batches as test formulation. The obtained similarity value (f_2) for optimized formulation A1 and A2 were 65.42, 70.35, respectively, which revealed more similarity of the dissolution profile with theoretical release profile that presented in Figure 7.

Table 6. Comparison of predicted and observed response for checkpoint batches A1, A2

Parameters	Predicted	Observed (A1)	Observed (A2)
Drug content (%)	100	99.89	100.15
Q1(%)	8.33	21.15	19.38
$t_{80\%}$	9.6	9.2	9.56
Viscosity (cp)	250	286	297
Floating lag time (sec)	30	25	32
Similarity factor (f_2)	100	65.42	70.35

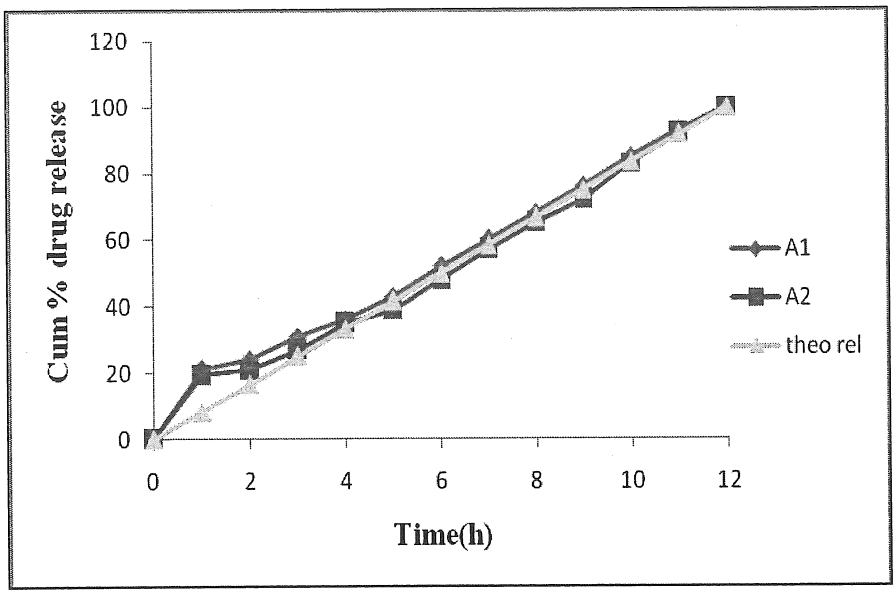

Figure 7. Comparison of dissolution profile of theoretical release to checkpoint formulations

Stability study

The stability study of both A1 and A2 were performed for one month as per the ICH accelerated stability. Both checkpoint batches were monitored for the same parameters as outlined in factorial batches. Results of physical parameters are shown in Table 7. It revealed that no significant changes take place throughout the stability period. *In-vitro* release study of both optimized batches before and after stability study was performed and then compared with theoretical release profile as shown in Figure 8.

Table 7. Stability study of checkpoint formulation A1 and A2

Time period for sampling	pH		Viscosity (cp)		Drug content (%)	
	A1	A2	A1	A2	A1	A2
Initial	7	7	282	293	99.72	100.12
After 1 month	7	7.01	284	295	98.8	99.26
After 2 month	7.09	7.1	286	296	99.1	99.21
After 3 month	7.1	7.14	288	296	98.75	98.82

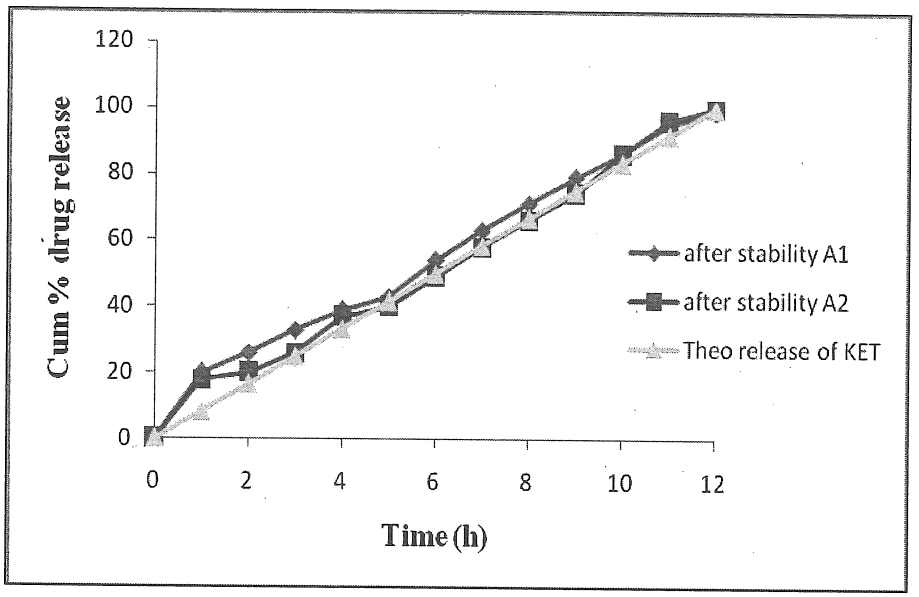

Figure 8. Comparison of *In-vitro* release profile of A1 and A2 after stability period and theoretical release of KET

Conclusion

The present investigation has demonstrated the feasibility of formation of p^H specific *in-situ* gelling system of KET using sodium alginate containing calcium carbonate aqueous solution. The release rate of KET could be controlled up to 12h from above stated solution having buoyancy for more than 12 h in stomach. From the present study, it was concluded that sustained delivery of KET in stomach can be achieved by using sodium alginate and calcium carbonate containing *in-situ* gel forming solution.

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References

Bhaskaran, S., Sanmathi, B.S. (2001). Poly (lactic acid) microspheres of ketorolac tromethamine for parenteral controlled drug delivery system. *Int. J. Phar. Sci.* 63: 538-530.

Gibaldi, M., Feldman, S. (1967). Establishment of sink conditions in dissolution rate determinations- theoratical considerations and application to nondisintegrating dosage forms. *J. Pharm. Sci.* 56: 1238-1242.

Grant, G.T., Morris, E.R., Rees, D.A., Smith, P.J. (1993). Biological interactions between polysaccharides and divalent cations: the egg-box model. *FEBS Lett.* 32: 195-198.

Grasdalen, H., Smidsroed, O. (1987). Gellation of gellan gum. *Carbophyr Polym.* 7: 371-393.

Higuchi, T. (1963). Mechanism of sustained-action medication, Theoratical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.* 52: 1145-1149.

Higuchi, T., (1996). Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci.* 50: 874-875.

Johnson, M., Medlin, J. (1985). Attempts to control the release of the dyestuff proflavine hemisulphate from calcium alginate gels I. Physical co-entrapment of polymers. *Eur. Polym. J.* 21: 147-150.

Katayama, H., Nishimura, T., Ochi, S. (1999). Sustained release liquid preparation using sodium alginate for eradication of helicobacter pylori. *Biol. Pharm. Bull.* 22: 55-60.

Kawashia, Y., Niwa, T., Takeuchi, H., Hino, T. (1991). Characterization of polymorphs of tranilast Anhydrate amd tranilast monohydrate when crystallized by two solvent change spherical Crystallization techniques. *J. Pharm. Sci.* 81: 472-478.

Liang, J.N., Stevens, E.S., Frangou, S.A., Morris, E.R., Rees, D.A. (1998). Cation-specific vacuum ultraviolet circular dichronism behavior of alginate solutions, gels and solid films. *Int. J. Bio Macromol.* 2: 204-208.

Morris, E.R., Rees, D.A., Thom, D. (1993). Characterisation of polysaccharide structure and interaction by circular dichronism: order–disorder transition in the calcium alginate system. *J. Chem. Soc. Chem. Commun.* 7: 245-246.

Nakano, M., Ogata, A. (1994). Examination of natural gums as matrices for sustained release of theophylline. *Chem. Pharm. Bull.* 3: 782-785.

Nicholson, S.J., Horder, R., Attwood, D., Collett, J.H. (1990). In-vestigation of drug release from sodium alginate-sodium calcium alginate matrices. *J. Pharm. Pharmacol. 72*, 2P.

Patel, J., Bharadia, P., Avani, A., Patel, M. (2004). Formulation optimization and evaluation of controlled release mucoadhesive microspheres of glipizide for oral drug delivery using factorial design. *Drug Deliv Tech.* 4: 48-53.

Rajinikanth, P.S., Balasubramaniam, J., Mishra, B. (2000). Development and evaluation of a novel in situ gelling system of amoxicillin for eradication of Helicobacter pylori. *Int. J. Pharm.* 335: 114-122.

Rees, D.A., Thom, D., Boyd, J. (1994). Chiroptical and stoichiometric evidence of a specific, primary dimerisation process in alginate gelation. *Carbohyd. Res.* 66: 145-154.

Ruckmani, K., Muneera, M.S., Vijaya, R. (2000). Eudragit matrices for sustained release of ketorolac tromethamine: formulation and kinetics of release. *Boll. Chim. Farm.* 139: 205-208.

Segi, N., Yotsuyanagi, T., Ikeda, K. (1989). Interaction of calcium induced alginate gel beads with propranolol. *Chem. Pharm. Bull.* 37: 3092-3095.

Singh, B.M., Kim, K.H. (2000). Effect of monovalent and divalent cations on the rheological Properties of gellan gels. *J. Control. Release.* 63: 235-259.

Stockwell, A.F., Davis, S.S., Walker, S.E. (1986). In-vitro evaluation of alginate gel systems as sustained release drug delivery systems. *J. Control. Rel.* 3: 167-176.

Vatsaraj, N., Hossein, Z., Needham, T. (2000). Developed a sustained-release tablet of ketorolac tromethamine. *Drug delivery,* 9: 153-159.

Wagner, J.G. (1969). Interpretation of percent dissolved-time plots divided from in vitro testing of conventional tablets and capsules. *J. Pharm. Sci.* 58: 1253-1257.

Yotsuyanagi, T., Ohkubo, T., Ohhashi, T., Ikeda, T. (1987). Calcium induced gelation of alginic cid and pH sensitive reswelling of dried gels. *Chem. Pharm. Bull. 35:*1555-1563.

Zatz, J.L., Woodford, D.W. (1987). Prolonged release of theophylline from aqueous suspensions. *Drug Dev. Ind. Pharm.* 132: 159-2178.

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