ORIGINAL ARTICLE

Potato starch-blended alginate beads for prolonged release of tolbutamide: Development by statistical optimization and *in vitro* characterization

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The work investigates the development and optimization of novel beads of potato starch-alginate blend containing tolbutamide by ionotropic gelation using 3^2 factorial design. The optimized beads exhibited 85.57 ± 3.24% drug encapsulation efficiency and 50.42 ± 2.18% drug release after 8 h. The *in vitro* drug release followed controlled-release (zero-order) pattern with super case-II transport mechanism over 8 h. The swelling and degradation of the optimized beads were influenced by pH of test mediums. These were also characterized by SEM and FTIR analysis. These newly developed beads are suitable for controlled delivery of tolbutamide for prolonged period.

Key words: *Alginate, potato starch, polymer-blend, tolbutamide, controlled release, optimization*

INTRODUCTION

The use of natural starch continues to be an area of active research despite the advent of synthetic polymers. It does remain attractive, primarily because they are inexpensive, readily available, degradable, biocompatible and non-toxic.[1,2] Starch obtained from potatoes is one of such natural polysaccharides with potential applications in pharmaceutical and food technology.[3,4] Potato starch is a very refined starch, containing minimal protein or fat. This gives the powder a clear white color. Potato starch contains approximately 800 ppm phosphate bound to the starch; this increases the viscosity as well as swelling power.[5]

Alginate is a natural, hydrophilic, high molecular weight, anionic heteropolysaccharide obtained from brown marine algae composed of β-D- mannuronic acid monomers (M), regions of ∞-L-guluronic acid residues (G), and regions of interspersed M and G units.[6,7] Alginates undergoes ionotropic gelation in aqueous solution in the presence of various metal ions like Ca^{2+}, Ba^{2+}, Zn^{2+}, Al^{3+}, *etc*., due to an ionic interaction and intermolecular bonding between the carboxylic acid groups located on the polymer back-bone and these cations.[8,9] However, the drug release from ionotropically cross-linked alginate hydrogels suffer from some serious problems like low drug encapsulation due to drug leakage during cross-linking, and burst release of drugs due to the quick degradation.[7] Therefore, to formulate various cross-linked alginate beads by ionotropic gelation, blending with other polymers is a common practice.[8,10] From the review of literature, it was found that a few investigations had been carried out to formulate gel beads of natural starch-alginate blends.[11,12] However, reports are not available regarding formulation of ionotropically-gelled beads using potato starch as polymeric-blend with alginate. In the present study, the utility of potato starch as a polymeric blend with

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sodium alginate to develop ionotropically-gelled potato starch-alginate beads for the use in oral drug delivery was evaluated. Tolbutamide is used as model drug in this study, which was incorporated into potato starch-alginate beads to analyze its drug release profiles.

Tolbutamide, 1-butyl-3-(p-tolysulfonyl) urea, is an oral hypoglycemic agent and used in the management of type-II diabetes. Tolbutamide stimulates the secretion of insulin by the pancreas. This drug has low $t_{1/2}$ i.e., 4.5 to 6.5 h, and requires administration in multiple daily doses.[13] Thus, tolbutamide is an ideal candidate for incorporation in controlled-release device.

In the development of drug delivery formulations, an important issue was to design an optimized pharmaceutical formulation with desired properties within a short time period and minimum trials. The optimization procedure involves systematic formulation design to minimize the number of trials, and analyze the effect of various formulation variables by the response surfaces for each response to obtain the appropriate formulations of optimum properties with target goals.[14,15] Therefore, in order to quickly obtain the optimized formulation, a computer aided optimization technique using two-factors and three-levels (3^2) factorial design was employed to investigate the effects of two independent formulation variables (factors), *i.e.,* amount of sodium alginate, and potato starch on the properties of potato starch-blended alginate beads containing tolbutamide like drug encapsulation, and drug release.

MATERIALS AND METHODS

Materials

Tolbutamide was a gift sample from Chembiotech. Pvt. Ltd., India. Sodium alginate (Central Drug House, India), and calcium chloride (Mark Specialties Pvt. Ltd, India) were used. Potatoes were purchased from Jharpokharia, India market. All chemicals and reagents used were of analytical grade.

Isolation of potato starch from potatoes

Potato starch was isolated from potato tubers according to the previously reported method with little modification.[4] Potatoes (1 kg) were washed carefully in tap water to remove adhering dirt or soil. The potatoes were cut into smaller pieces, macerated with added distilled water in a blender equipped with razor blades and filtered through two layer of gauze. The filtrate was washed extensively with distilled water, in order to separate potato cell debris. The residual containing the starch was further washed by several cycles of centrifugation (2000 rpm, 10 min) and air dried over night at 27°C. The dried starch agglomerates were grounded with a mortar and passed through an 80 mesh sieve. The isolated potato starch powders were packed in a plastic bag and kept airtight desiccators until further use.

Preparation of potato starch-blended alginate beads containing tolbutamide

The potato starch-blended alginate beads containing tolbutamide were prepared using calcium chloride ($CaCl_2$) as cross-linker by ionotropic gelation method. Briefly, required amount of sodium alginate was dissolved in deionized water (20 ml) using magnetic stirring for 20 min to form proper gel. Then, required amount of potato starch was added into the previous gel with continuous magnetic stirring for 30 min. Afterwards, tolbutamide (100 mg) was added to the mixed gel of sodium alginate and potato starch for each formulation and mixed thoroughly using a homogenizer (Remi Motors, India). The final potato starch-sodium alginate mixture gels containing tolbutamide were ultrasonicated for 5 min for debubbling. The resulting dispersion was then added via a 21-gauge needle drop wise into100 ml of 5% w/v $CaCl_2$ solution. Added droplets were retained in the $CaCl_2$ solution for 15 min to complete the curing reaction and to produce rigid beads. The wet beads were collected by decantation, and washed two times with distilled water and dried at 40°C for 24 h. The dried potato starch-alginate beads containing tolbutamide were stored in a desiccator until used.

Experimental design

To reduce the number of trials necessary to attain maximum numbers of information on product properties, the screening was performed applying a 3^2 factorial design. The amount of sodium alginate (X_1, 650 to 750 mg) and potato starch (X_2, 50 to 250 mg) as polymeric blend were defined as the selected independent variables, which were varied at three levels, low level (–1), medium level (0), and high level (+1). The drug encapsulation efficiency (DEE, %), and drug release at 8 h (R_{8h}, %) were used as dependent variables (responses). The formulation variables (factors) and levels with experimental values are reported in Table 1. The response and factors of all trial formulations were treated by Design-Expert8.0.6.1 software (Stat-Ease Inc., USA).

Determination of drug encapsulation

Accurately weighed, 100 mg of beads were taken, and were crushed using pestle and mortar. The crushed powders of beads containing drug were placed in 500 ml of phosphate buffer, pH 7.4, and kept for 24 h with occasionally shaking at 37 ± 0.5°C. After the stipulated time, the mixture was stirred at 500 rpm for 20 min using a magnetic stirrer. The polymer debris formed after disintegration of beads was removed filtering through Whatman® filter paper (No. 40). The drug content in the filtrate was determined using a UV-VIS spectrophotometer (Shimadzu, Japan) at 228 nm. The drug encapsulation efficiency (DEE, %) of beads was calculated using this following formula:

$$\text{DEE}\,(\%) = \frac{\text{Actual drug content in beads}}{\text{Theroetical drug content in beads}} \times 100 \qquad (1)$$

Table 1: Experimental plan of 3^2 full factorial design (coded values in bracket) with observed response values for different formulations of potato starch-blended alginate beads containing tolbutamide

Experimental formulation codes	Normalized levels of factors		Responses[a]	
	Sodium alginate (mg, X_1)	Potato starch (mg, X_2)	DEE (%)[b]	R_{8h} (%)[c]
F-1	650.00 (-1)	50.00 (-1)	60.54±2.16	75.05±2.62
F-2	650.00 (-1)	150.00 (0)	64.91±2.63	70.40±2.33
F-3	650.00 (-1)	250.00 (+1)	69.02±3.20	62.98±1.60
F-4	700.00 (0)	50.00 (-1)	62.18±2.26	71.37±2.36
F-5	700.00 (0)	150.00 (0)	68.80±3.03	67.85±2.86
F-6	700.00 (0)	250.00 (+1)	70.02±3.19	60.25±2.02
F-7	750.00 (+1)	50.00 (-1)	65.54±2.72	68.63±2.98
F-8	750.00 (+1)	150.00 (0)	67.23±2.55	65.37±2.67
F-9	750.00 (+1)	250.00 (+1)	72.54±3.27	56.84±1.46

[a]Observed response values: Mean±S.D., *n*=3, [b]DEE (%): Drug encapsulation efficiency (%), [c]R_{8h} (%): % Drug released from potato starch-blended alginate beads containing tolbutamide after 8h

Bead size measurement and morphology analysis

The diameters of dried beads were measured using digital slide calipers (CD-6″ CS, Mitutoyo Corporation, Japan) by inserting the beads in between the space of two metallic plates and diameter of resultant beads were displayed in the digital screen of the previously calibrated equipment. The average size was then calculated by measuring the diameter of 3 sets of 20 beads from each batch.

Potato starch-blended alginate beads containing tolbutamide were gold coated by mounted on a brass stub using double-sided adhesive tape and under vacuum in an ion sputter with a thin layer of gold (3 ~ 5 nm) for 75 sec and at 20 kV to make them electrically conductive and their morphology was examined by scanning electron microscope (ZEOL, JSM-5800, Japan).

Fourier transform-infrared spectroscopy

Samples were reduced to powder and analyzed as KBr pellets by using a Fourier transform–infrared (FTIR) spectroscope (Perkin Elmer Spectrum RX I, USA). The pellet was placed in the sample holder. Spectral scanning was taken in the wavelength region between 3750, and 400 cm^{-1} at a resolution of 4 cm^{-1} with scan speed of 1 cm/sec.

In vitro drug release studies

The release of the drug (tolbutamide) from various potato starch-blended-alginate beads containing tolbutamide was tested using a dissolution apparatus USP/BP/IP (Campbell Electronics, India). The baskets were covered with 100-mesh nylon cloth to prevent the escape of the beads. The dissolution rates were measured at 37 ± 1°C below 50 rpm speed. Accurately weighed quantities of potato starch-blended-alginate beads containing tolbutamide equivalent to 100 mg were added to 900 ml of simulated gastric fluid (pH 1.2). The test was carried out in simulated gastric fluid (pH 1.2) for 2 h, and then, continued in simulated intestinal fluid (pH 7.4) for next 6 h. Five ml of aliquots was collected at regular time intervals, and the same amount of fresh dissolution medium was replaced into dissolution vessel to maintain the sink condition throughout the experiment. The collected aliquots were filtered, and suitably diluted to determine the absorbance using a UV-VIS spectrophotometer (Shimadzu, Japan) at 228 nm.

Analysis of *in vitro* drug release kinetics and mechanism

In order to predict and correlate the release behavior of tolbutamide from these potato starch-blended alginate beads containing tolbutamide, it is necessary to fit into a suitable mathematical model. The *in vitro* drug release data were evaluated kinetically using various important mathematical models like zero order, first order, Hixson-Crowell, Weibull, Baker-Lonsdale, Higuchi, and Korsmeyer-Peppas models.[16]

Zero-order model: $Q = kt + Q_0$; where Q represents the drug released amount in time t, and Q_0 is the start value of Q; k is the rate constant.

First-order model: $Q = Q_0 e^{kt}$; where Q represents the drug released amount in time t, and Q_0 is the start value of Q; k is the rate constant.

Hixson-Crowell model: $Q^{1/3} = kt + Q_0^{1/3}$; where Q represents the drug released amount in time t, and Q_0 is the start value of Q; k is the rate constant.

Weibull model: $m = 1 - \exp[-(t)^b/a]$; where m represents the drug released amount in time t, a is the time constant and b is the shape parameter.

Baker-Lonsdale model: $3/2\ [1-(1-Q)^{2/3}] - Q = kt$; where Q represents the drug released amount in time t, and k is the rate constant.

Higuchi model: $Q = kt^{0.5}$; where Q represents the drug released amount in time t, and k is the rate constant.

Korsmeyer-Peppas model: $Q = kt^n$; where Q represents the drug released amount in time t, k is the rate constant and *n* is the diffusional exponent, indicative of drug release mechanism.

The accuracy and prediction ability of these models were

compared by calculation of squared correlation coefficient (R^2) and root mean squared error (RMSE) using KinetDS 3.0 Rev. 2010 software.

Again, The Korsmeyer-Peppas model was employed in the *in vitro* drug release behavior analysis of these formulations to distinguish between competing release mechanisms: Fickian release (diffusion-controlled release), non-Fickian release (anomalous transport), and case-II transport (relaxation-controlled release). When n is ≤ 0.43, it is Fickian release. The n value between 0.43 and 0.85 is defined as non-Fickian release. When, n ≥ 0.85, it is case-II transport.[10]

Swelling behavior measurement

Swelling measurement of optimized potato starch-blended alginate beads containing tolbutamide were carried out in two different aqueous media: simulated gastric fluid (pH 1.2), and simulated intestinal fluid (pH 7.4). 100 mg beads were placed in vessels of dissolution apparatus (Campbell Electronics, India) containing 500 ml respective media. The experiment was carried out at 37 ± 1°C below 50 rpm paddle speed. The swelled beads were removed at predetermined time interval and weighed after drying the surface by using tissue paper. Swelling index was determined using the following formula:

$$\text{Swelling index} = \frac{\text{Weight of beads after swelling} - \text{Dry weight of beads}}{\text{Dry weight of beads}} \times 100 \quad (2)$$

Statistical analysis

Statistical optimization was performed using Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA). All measured data are expressed as mean ± standard deviation (S. D.) and each measurements were done in triplicate ($n = 3$).

RESULTS AND DISCUSSION

Optimization by 3^2 factorial design

Factorial design is an experimental design by which all factors involved in a process are studied in all possible combinations by analyzing the influence of individual variables and their interactions using minimum experiments.[17] Thus, the construction of factorial design involves the selection of factors and the choice of responses. For the 3^2 factorial design, a total 9 trial formulations were proposed by Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA) for two independent variables: amount of sodium alginate (X_1), and amount of potato starch (X_2), which were varied at three levels: low level (–1), medium level (0), and high level (+1). The DEE (%), and R_{8h} (%) were evaluated as dependent variables (responses). According to this trial proposal, various potato starch-blended alginate beads containing tolbutamide were prepared by ionotropically gelation technique. Overview of matrix of the design including investigated responses i.e., DEE (%), and R_{8h} (%) were presented in Table 1. The values of investigated responses measured for all trial formulations were fitted in the 3^2 factorial design to get model equations for responses analyzed in this investigation. The Design-Expert 8.0.6.1 software suggested two quadratic model equations involving individual main factors and interaction factors for all response parameters as best-fitting mathematical models based on the comparison of several statistical parameters like multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted-R^2), predicted multiple correlation coefficient (predicted-R^2), and predicted residual sum of squares (PRESS). The model summary statistics for best-fitting model selection is presented in Table 2. The results of the ANOVA based on the two quadratic models indicated that these models were significant for all response parameters [Table 3]. The model equation relating DEE (%) as response became:

$$\text{DEE (\%)} = 193.84 - 0.43X_1 + 0.09X_2 - 7.40 \times 10^{-5}X_1X_2 + 3.47 \times 10^{-4}X_1^2 + 1.13 \times 10^{-5}X_2^2$$

[$R^2 = 0.9995$; F-value = 1135.10; $P < 0.05$]

The model equation relating R_{8h} (%) as response became:

$$R_{8h}\ (\%) = 125.33 - 0.09X_1 - 7.50 \times 10^{-3}X_2 + 1.40 \times 10^{-5}X_1X_2 + 2.20 \times 10^{-5}X_1^2 - 2.02 \times 10^{-4}X_2^2$$

[$R^2 = 0.9972$; F-value = 213.82; $P < 0.05$]

Model simplification was carried out by eliminating non-significant terms ($P > 0.05$) in model equations resulting from the multiple regression analysis,[18] giving:

$$\text{DEE (\%)} = 58.67 - 1.26X_1 + 4.31X_2 - 0.59X_1X_2$$

$$R_{10h}\ (\%) = 108.45 + 2.44X_1 - 7.94X_2 + 0.49X_1X_2$$

The influences of main effects (factors) on responses (here, DEE, and R_{8h}) were further elucidated by response surface methodology. Response surface methodology is a widely proficient approach in the development and optimization of drug delivery devices.[19-21] The purpose of the response surface methodology is to understand a model as fully as possible the effect of factors and their levels, over the whole of the experimental domain, and to predict the response inside the domain. Moreover, it can be used for optimizing a formula (i.e., maximizing one or more of the responses, keeping the formulation variable setting within a satisfactory range), carrying out simulations with the model equations and plotting the responses.[22] The three-dimensional response surface graph is very useful in learning about the main and interaction effects of the independent variables (factors), whereas two-dimensional contour plot gives a visual representation of values of the response.[15] The three-dimensional response surface plots [Figures 1 and 2] and corresponding contour plots [Figures 3 and 4] were

Table 2: Model summary statistics for measured responses in 3^2 full factorial design

	DEE (%)[a]				R_{8h} (%)[b]			
	Adjusted		Predicted		Adjusted		Predicted	
	R^2	R^2	R^2	PRESS[c]	R^2	R^2	R^2	PRESS[c]
Linear	0.9819	0.9759	0.9577	5.01	0.9662	0.9550	0.9298	18.75
2FI[d]	0.9865	0.9784	0.9478	6.19	0.9663	0.9461	0.8751	33.04
Quadratic	0.9995	0.9986	0.9941	0.70	0.9972	0.9925	0.9659	9.02

[a]DEE (%): Drug encapsulation efficiency (%), [b]R_{8h} (%): % Drug released from potato starch-blended alginate beads containing tolbutamide after 8h, [c]PRESS: Predicted residual sum of squares, [d]2FI: Two factor interactio

Table 3: Summary of ANOVA for the response parameters

Source	Sum of squares	d.f.[a]	Mean square	*F* value	*P*-value Prob >*F*
(a) For DEE (%)[b]					
Model	118.39	5	23.68	1135.10	<0.0001
X_1	25.67	1	25.67	1230.53	<0.0001
X_2	90.64	1	90.64	4345.17	<0.0001
X_1X_2	0.55	1	0.55	26.25	0.0144
X_1^2	1.51	1	1.51	72.29	0.0034
X_2^2	0.03	1	0.03	1.23	0.3481
(b) For R_{8h} (%)[c]					
Model	263.69	5	52.74	213.82	0.0005
X_1	51.57	1	51.57	209.08	0.0007
X_2	203.93	1	203.93	826.83	<0.0001
X_1X_2	0.02	1	0.02	0.08	0.7963
X_1^2	6.05×10^{-3}	1	6.05×10^{-3}	0.03	0.8855
X_2^2	8.16	1	8.16	33.09	0.0104

[a]d.f.: Degree of freedom, [b]DEE (%): Drug encapsulation efficiency (%), [c]R_{8h} (%): % Drug released from potato starch-blended alginate beads containing tolbutamide after 8h, X_1 and X_2 represent the main effects (factors), X_1^2 and X_2^2 are the quadratic effect, X_1X_2 is the interaction effect

presented to estimate the effects of the independent variables (factors) on each response investigated.

The three-dimensional response surface graph relating DEE [Figure 1] indicates the increment in both the values with the increasing of sodium alginate amount (X_1), and potato starch amount (X_2) in the formulated potato starch-blended alginate beads containing tolbutamide by ionotropic gelation technique. However, a decrease in R_{8h} values with the increasing sodium alginate amount (X_1), and potato starch (X_2) is indicated by the three-dimensional response surface graph relating R_{8h} [Figure 3]. All the two-dimensional contour plots [Figures 2 and 4] were found to be nonlinear indicating nonlinear relationships between two independable variables (here, sodium alginate amount, X_1 and potato starch, X_2) on all measured responses, investigated for this study.

A numerical optimization technique using the desirability approach was employed to develop new formulations with desired response (optimum quality). The desirable ranges of the undependable variables (factors) were restricted to X_1 = 500 mg, and X_2 = 425 mg; whereas the desirable ranges of responses were restricted to 60 ≤ DEE ≤ 100%, and 45 ≤ R_{8h} ≤ 75%. The optimal values of responses were obtained by numerical analysis using the the Design-Expert

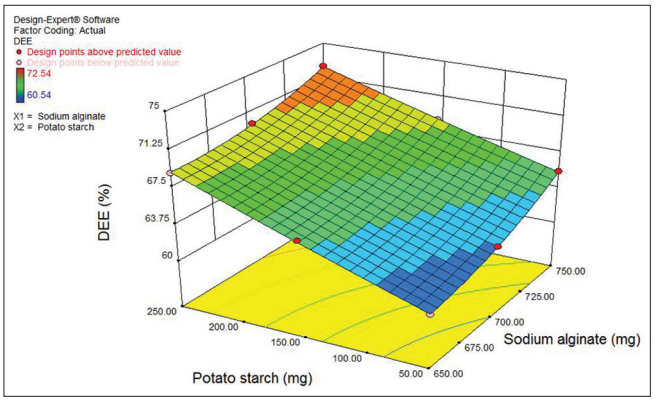

Figure 1: Effect of sodium alginate and potato starch amount on DEE (%) presented by response surface plot

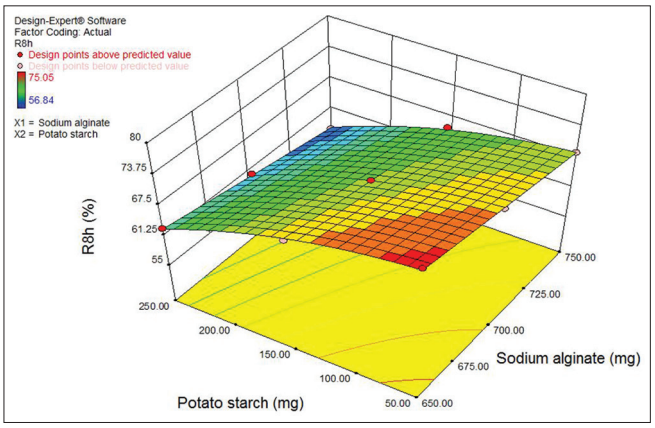

Figure 2: Effect of sodium alginate and potato starch amount on R_{8h} (%) presented by response surface plot

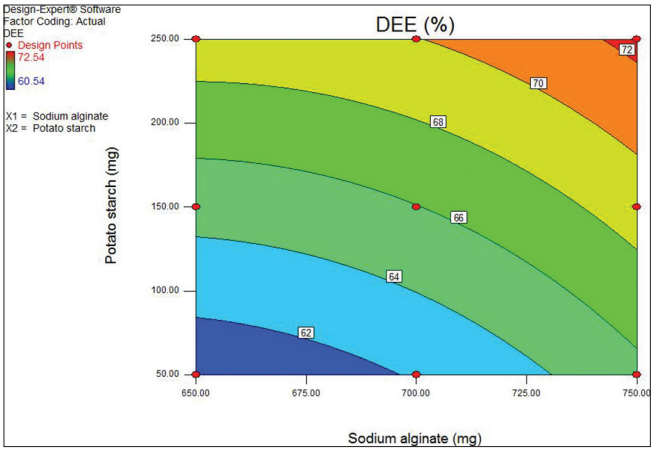

Figure 3: Effect of sodium alginate and potato starch amount on DEE (%) presented by contour plot

8.0.6.1 software based on the criterion of desirability. In order to evaluate optimization capability of models generated in accord to the results of the full 3^2 factorial design, optimized potato starch-blended alginate beads containing tolbutamide was prepared by ionotropic gelation technique using these optimal formulation variable settings. The optimized potato starch-blended alginate beads containing tolbutamide (F-O) was evaluated for DEE (%), and R_{8h} (%). Table 4 lists the results of experiments done with predicted responses by the mathematical model and those actually observed. The optimized potato starch-blended alginate beads containing tolbutamide (F-O) showed DEE of 85.57 ± 3.24%, and R_{10h} of 50.42 ± 2.18% within small error-values (−1.85, and 4.11, respectively), indicating that mathematical models achieved from the full 3^2 factorial design were well fitted.

Drug encapsulation

The DEE (%) of all these potato starch-blended alginate beads containing tolbutamide ranged between 60.54 ± 2.16 (F-1) to 85.57 ± 3.24 (F-O) % w/w [Tables 1 and 4]. From the results, it was observed that the drug encapsulation in the potato starch-blended alginate beads containing tolbutamide was increased by increasing sodium alginate and potato starch amount as polymer-blend. The increased drug encapsulation with the increment of sodium alginate and potato starch amount may be due to the increase in viscosity of the polymeric solution, so that, it might have been prevented drug leaching to the cross-linking solution at the time of preparation.[8,10] Again, the drug encapsulation in the potato starch-blended alginate beads may also be attributed to the greater availability of active calcium binding sites in the alginate chain and greater degree of cross-linking as the amount of sodium alginate in the polymer-blend increased.[23]

Bead size and morphology

The size of potato starch-blended alginate beads containing tolbutamide for each formulation was measured using digital slide calipers (CD-6″ CS, Mitutoyo Corporation, Japan), and the average size of these dried beads were within the range between 1.02 ± 0.04 to 1.41 ± 0.07 mm [Table 5]. Increasing the bead size was found with the increasing amount of sodium alginate and potato starch into formulations. This could be attributed due to the increase in viscosity of polymer-bled solution with incorporation of sodium alginate and potato starch in increasing amount that in turn increased the droplet size during addition of the polymer blend solution to the cross-linking solution.

The morphological analysis of potato starch-blended alginate beads containing tolbutamide was visualized by SEM at different magnifications and is presented in [Figures 5a and b]. The SEM photograph of these beads at lower magnification (×60) showed spherical shape with a rough surface, which was also noticed even at higher magnification (×500). Detailed examination of the bead surface topography revealed cracks and wrinkles, which might be caused by partly collapsing the polymeric gel network during drying.[24] In addition, pores with diameters of few micrometers were found on the bead surface.

FTIR spectroscopy

The FTIR spectra of tolbutamide, potato starch-blended alginate beads containing tolbutamide, and potato starch-blended alginate beads without drug, are shown in [Figures 6a-c, respectively]. The FTIR spectrum of tolbutamide [Figure 6a] showed that principal peaks at

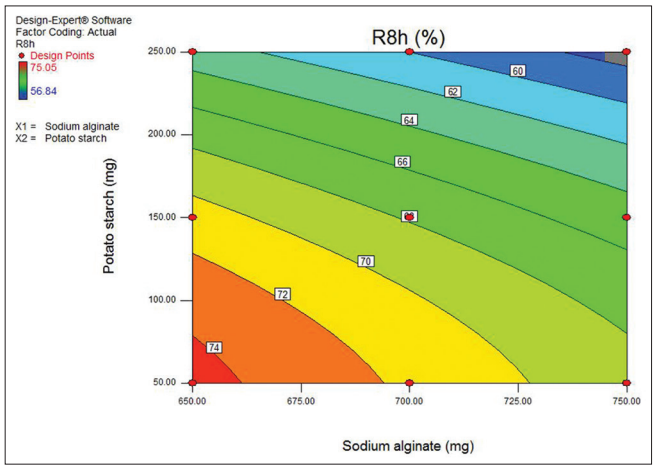

Figure 4: Effect of sodium alginate and potato starch amount on R_{10h} (%) presented by contour plot

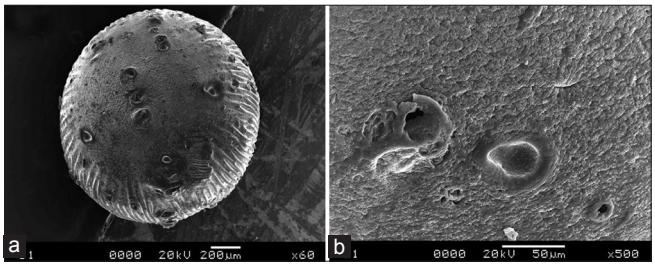

Figure 5: (a) Scanning electron microphotograph of optimized potato starch-blended alginate beads containing tolbutamide (F-O) in different magnifications: ×60, (b) and ×500

Table 4: Results of experiments for confirming optimization capability

Code	Factors		Responses					
	Sodium alginate (mg)	Potato starch (mg)	DEE (%)[a]			R_{8h} (%)[b]		
			Predicted value	Observed value[c]	Error(%)[d]	Predicted value	Observed value[c]	Error (%)[d]
F-O	500.00	425.00	87.18	85.57±3.24	−1.85	48.43	50.42±2.18	4.11

[a]DEE (%): Drug encapsulation efficiency (%), [b]R_{8h} (%): % Drug released from potato starch-blended alginate beads containing tolbutamide after 8h, [c]Mean±S.D., *n*=3, [d]Error (%): (observed value – predicted value)/predicted value ×100

3326.61 cm^{-1} (due to -N-H stretching of urea group), 1703.90 and 1663.62 cm^{-1} (due to C = O stretching of urea group), 1335.11 and 1158.44 cm^{-1} (due to S = O stretching of sulphonamide group), which were almost similar with the previously reported literature by Keraliya *et al*.[25] In the FTIR spectrum of potato starch-blended alginate beads containing tolbutamide [Figure 6b], various characteristic peaks of tolbutamide were appeared without any significant shifting. In both the FTIR spectra of potato starch-blended alginate beads containing tolbutamide [Figure 6b] and potato starch-blended alginate beads without drug [Figure 6c], the strong and broad absorption band peaks had been observed between 3600-3200 cm^{-1} due to –OH stretching along with some complex bands in the region 1200-1030 cm^{-1} due to-C-O and C-O-C stretching vibrations, which are the characteristic of the natural polysaccharides. In addition, the absorption bands in the region 930-820cm^{-1} and 785-730cm^{-1} were also been observed due to vibrational modes of pyranose rings of polysaccharides. The presence of strong asymmetric stretching absorption band between 1650 cm^{-1} and 1620 cm^{-1}, and weaker symmetric stretching band near 1420 cm^{-1} supported the presence carboxylate anion of alginate structure. In short, the potato starch-blended alginate beads containing tolbutamide had significant characters of tolbutamide in the FTIR spectrum, suggesting, there were no interaction between the tolbutamide and the polymers used (sodium alginate and potato starch). The FTIR analysis confirmed the compatibility of the tolbutamide with sodium alginate and potato starch used to prepare the potato starch-blended alginate beads containing tolbutamide by ionotropic gelation technique.

In vitro drug release

The *in vitro* drug release studies were carried out for all potato starch-blended alginate beads containing tolbutamide in the 0.1 N HCl (pH, 1.2) for first 2 h and then, in phosphate buffer (pH, 7.4) for next 8 h. All these beads showed prolonged release of tolbutamide over 8 h [Figure 7]. Tolbutamide release from these beads in the acidic medium was slow (less than 19% after 2 h) due to the shrinkage of alginate at acidic pH (as alginate is pH sensitive). The trace amount of release could probably be due to the release of surface adhered drug. After that, drug release was observed faster in phosphate buffer (pH, 7.4) comparatively. The percentage drug released from potato starch-blended alginate beads containing tolbutamide in 8 h (R_{8h}, %) was within the range of 50.42 ± 2.18% (F-O) to 75.05 ± 2.62% (F-1), and this was found to be lower with the increasing of both sodium alginate and potato starch in the polymer-blend used. In case of beads containing higher potato starch amount, the more hydrophilic property of potato starch bind better with water to form viscous gel-structure, which might blockade the pores on the surface of beads and sustain the drug release profile.

The *in vitro* drug release data from various potato starch-blended alginate beads containing tolbutamide were evaluated kinetically using various important mathematical models like zero-order, first-order, Hixson-Crowell, Weibull, Baker-Lonsdale, Higuchi, and Korsmeyer-Peppas models. The R^2 and RMSE values of these models were determined

Table 5: Mean diameter of potato starch-blended alginate beads containing tolbutamide

Formulation codes	Mean diameter (mm)[a]
F-1	1.02±0.04
F-2	1.08±0.05
F-3	1.12±0.06
F-4	1.10±0.04
F-5	1.15±0.04
F-6	1.26±0.05
F-7	1.17±0.06
F-8	1.32±0.05
F-9	1.41±0.07
F-O	1.16±0.05

[a]Mean±S.D

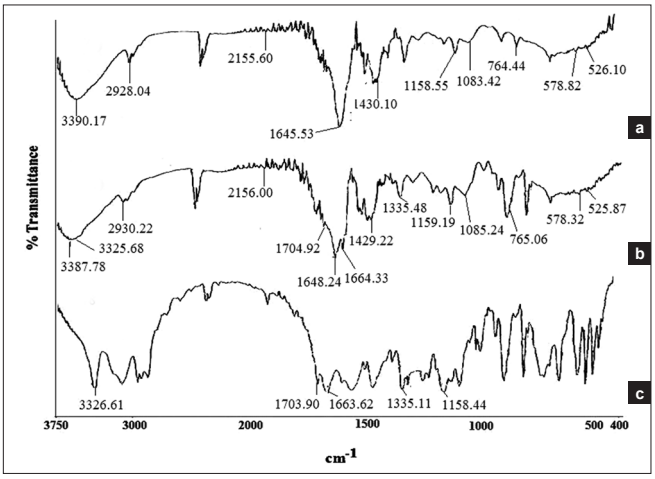

Figure 6: (a) FTIR spectra of tolbutamide, (b) potato starch-blended alginate beads containing tolbutamide, and (c) potato starch-blended alginate beads without drug

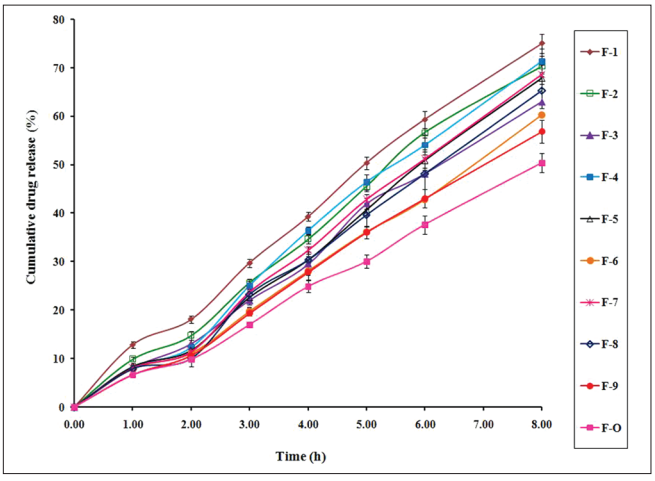

Figure 7: *In vitro* drug release from various potato starch-blended alginate beads containing tolbutamide (Mean ± S.D., *n* = 3)

for evaluation of accuracy and prediction ability of these models using KinetDS 3.0 Rev. 2010 software. The result of the curve fitting into various mathematical models is given in Table 6. When the respective R^2 of potato starch-blended alginate beads containing tolbutamide were compared, it was found to follow the zero-order model (R^2 = 0.9912 to 0.9959; RMSE = 1.02 to 1.86) as best-fit model over a period of 8 h. In addition, this was also observed to be closest to some other models like Weibull model (R^2 = 0.9575 to 0.9820; RMSE = 1.52 to 3.04) and Korsmeyer-Peppas model (R^2 = 0.9585 to 0.9891; RMSE = 1.20 to 2.12). The best fit of zero-order model indicated that the drug release from these beads followed controlled-release pattern. The values of diffusional exponent (*n*) determined from Korsmeyer-Peppas model ranged from 0.90 to 1.12, indicating the drug release from these beads followed the super case-II transport mechanism controlled by swelling and relaxation of polymeric-blend (alginate-potato starch) matrix. This could be attributed due to polymer dissolution and polymeric chain enlargement or relaxation.

Swelling behavior

The swelling behavior of optimized potato starch-blended alginate beads containing tolbutamide was evaluated in 0.1 N HCl, pH 1.2, and phosphate buffer, pH 7.4. The swelling behaviors of these beads in both the pH, 0.1 N HCl (pH 1.2), and phosphate buffer (pH 7.4) are shown in Figure 8. The swelling index of optimized beads containing tolbutamide was lower in 0.1 N HCl in comparison with that of in phosphate buffer, initially. This was occurred due to shrinkage of alginate at acidic pH. Maximum swelling of beads was noticed at 2-3 h in phosphate buffer, pH 7.4 and after which, erosion and dissolution took place. The swelling behavior of optimized potato starch-blended alginate beads in alkaline pH could be explained by the ion exchange phenomenon between the calcium ion of cross-linked potato starch-blended alginate beads and the sodium ions present in phosphate buffer, with the influence of calcium-sequestrant phosphate ions. This could result in disaggregation of potato starch-alginate matrix structure leading to matrix erosion and dissolution of swollen beads.[8] These results clearly suggested that the optimized potato starch-blended alginate beads containing tolbutamide might have the capability to swell slightly in the stomach pH as they subsequently move to the upper intestine and swell more in the intestinal pH, where the absorption of tolbutamide take place.

CONCLUSION

In this study, the potato starch-blended alginate beads containing tolbutamide by ionotropic gelation technique was

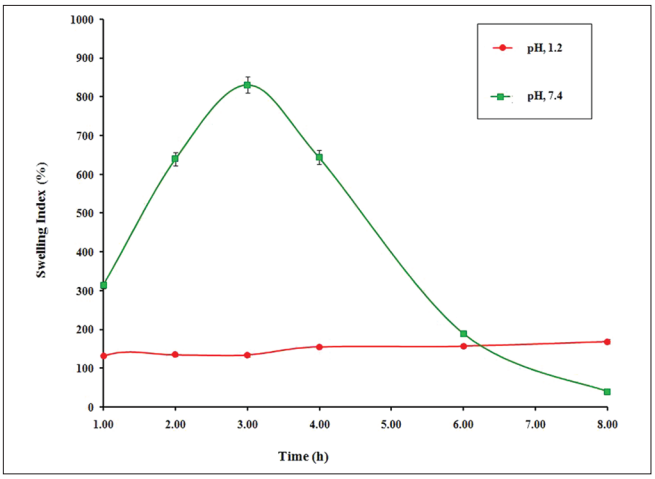

Figure 8: Swelling behavior of optimized potato starch-blended alginate beads containing tolbutamide in 0.1 N HCl, pH 1.2 and phosphate buffer, pH 7.4 (Mean ± S.D., *n* = 3)

Table 6: Results of curve fitting of the *in vitro* drug release data from different potato starch-blended alginate beads containing tolbutamide

Models		Formulation codes									
		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-O
Zero order	R^2	0.9947	0.9924	0.9959	0.9923	0.9928	0.9940	0.9936	0.9912	0.9955	0.9950
	RMSE	1.51	1.79	1.16	1.86	1.69	1.34	1.61	1.80	1.12	1.02
First order	R^2	0.9335	0.9295	0.9327	0.9033	0.9374	0.9412	0.9184	0.9136	0.9200	0.9366
	RMSE	8.15	9.03	7.69	11.13	8.18	6.50	9.50	8.68	7.91	5.76
Hixson-Crowell	R^2	0.9654	0.9645	0.9703	0.9481	0.9726	0.9757	0.9597	0.9557	0.9616	0.9719
	RMSE	4.77	5.06	4.02	6.05	4.06	3.15	4.93	4.50	4.16	2.94
Weibull	R^2	0.9684	0.9726	0.9804	0.9761	0.9626	0.9689	0.9677	0.9545	0.9820	0.9754
	RMSE	2.98	2.72	2.20	2.04	3.04	2.57	2.45	2.64	1.52	1.79
Baker-Lonsdale	R^2	0.9206	0.9163	0.9066	0.9101	0.8813	0.8778	0.8935	0.8880	0.9154	0.9048
	RMSE	45.69	42.10	36.80	42.01	38.71	34.10	39.60	37.44	31.14	29.07
Higuchi	R^2	0.7169	0.6376	0.6199	0.5763	0.5737	0.5981	0.5695	0.5655	0.5885	0.6150
	RMSE	11.07	12.33	11.22	13.80	12.97	10.91	13.27	12.63	10.71	8.96
Korsmeyer-Peppas	R^2	0.9822	0.9831	0.9891	0.9794	0.9734	0.9782	0.9738	0.9585	0.9861	0.9812
	RMSE	1.83	1.97	1.36	2.12	2.02	1.72	1.72	1.93	1.20	1.28
	n	0.90	1.00	1.03	1.12	1.06	1.03	1.10	1.09	1.08	1.02

RMSE: Root mean squared error, *n*: Diffusional exponent, all results were obtained using KinetDS 3.0 Rev. 2010 software

successfully developed and optimized using 3^2 factorial design based on response surface methodology. The optimized beads exhibited 85.57 ± 3.24% DEE, and 50.42 ± 2.18% drug release after 8 h. The drug release from these newly developed beads containing tolbutamide were found to be sustained over 8 h and followed a controlled release (zero-order) pattern with super case II transport mechanism. The ionotropic gelation technique for the preparation of potato starch-blended alginate beads containing tolbutamide was found to be simple, reproducible, easily controllable, economical and consistent process. In addition, the excipients used for the formulation of these newly developed beads were cheap and easily available. The conditions used in this development process of potato starch-blended alginate beads were very mild and would be appropriate for encapsulation of other drugs for controlled drug release. Thus, potato starch is proved as a potential polymeric blend with alginate in the development of ionotropically-gelled beads for the use in controlled drug delivery.

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