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Performance Optimization of Sustained Release Arginine Alginate Microbeads with a Natural Polysaccharide

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Authors' contributions

This work was carried out in collaboration between all authors. Author RKT designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors LS and VS managed the analyses of the study. Author VS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Objectives: The design of effective and safe novel drug delivery systems has become an integral part for the development and formulating of new medicines. So, research continuously keeps on searching for new ways to deliver drugs over a long period of time or for a well-controlled release profile, to minimizing the loss of drug, to reduce the side effect. The objective of this study was to develop suitable microbeads of L-arginine for sustained release delivery by varying the alginate concentrations, starch concentrations using analytical and statistical approaches.
Materials and Methods: The work investigates the development and optimization of novel microbeads of potato starch-alginate blend containing L-arginine by ionotropic gelation using response surface methodology. Response surface methodology was found to be satisfactory for describing the relationships between formulation set variables and response variables. The influence of various formulation factors such as *In vitro* drug release, entrapment efficiency, SEM,

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analysis, swelling study and micromeritic properties, was investigated. These were also characterized by SEM, analysis.
Results: L-arginie containing microbeads were in the size range of 0.175 ± 0.02 to 0.226 ± 0.02 mm. The drug entrapment efficiencies were found in the range of 42.5 ± 1.83% to 91.2 ± 1.05% and the drug release were found at 10 h in the range 84.568 ± 2.75% to 99.761 ± 1.99%. The release pattern observed was a biphasic, characterized by an initial burst effect followed by slow release. No significant change was found during stability studies of optimized formulation at different temperature and humidity conditions as per ICH guidelines.
Conclusion: The data suggest that sweet potato flour is a potentially useful natural material for making sustained release L-arginine loaded microbeads by the ionotropic gelation technique.

Keywords: Sodium alginate; potato starch; ionotropic gelation technique; optimization.

1. INTRODUCTION

A controlled release drug delivery system is usually designed to deliver the drug at particular rate in a specific time in to the body. Safe and effective blood levels are maintained for a specific period as the system continuous to deliver the drug. Controlled drug delivery usually results to achieve constant blood levels of the drug as compared to the uncontrolled fluctuations observed when multiple doses of conventional dosage forms are taken by the patient, thus, in controlled release dosage form, release of the drug in to the body at a rate profile that is only predictable kinetically, [1,2]. These delivery systems show various significant advantages, compared with conventional dosage forms, which is improved efficacy, minimized toxicity, and improved patient compliance and overall cost. Thus the controlled drug delivery systems objective and aim to improve effectiveness of drug therapies. The main goal in designing of controlled or sustained delivery system is to reduce the repetition of dosing or to maximize effectiveness of the drug by localization at the site of action minimized the dose required, or providing the constant release drug delivery [3].

Controlled release drug delivery systems show one of the very important areas of health care. The controlled drug delivery systems are needed when the drug has to be delivered for a prolonged period of specified time. Repeated dosage of medicines has to be taken simultaneously in case of chronic patients. Frequent administration of such medicine is necessary when those have shorter half life and all these leads to decrease in patient's compliance [4].

The present scenario points to an increasing interest in the use of natural ingredients in food, drugs, and cosmetics formulation. The naturally occurring alginate polymers have a mostly used in drug formulation due to their major application as food additives and their identified lack of toxicity. Alginate is a naturally occurring polymer which is biocompatible, biodegradable, bioadhesive biopolymer and is capable to use in rate and/or time controlled drug release formulations. They are generally used in food and pharmaceutical industries, such as disintegrating agent and tablet binder, thickening agent, stabilizing agent in mixtures and as gelling agent in confectionary. Recently they have been employed as a matrix for entrapment of drugs, macromolecules and biological cells [5]. The most important advantage of using alginate as a matrix for controlled release preparations is its biodegradability, because it is degraded and is absorbed by the body during and/or after drug release without showing any toxic effects [6].

Multiparticulate delivery systems for oral use have been employed to sustain the drug release delivery, and it play important role to minimizing or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems more uniformly distributed out in the gastrointestinal tract thus results in more reproducible drug absorption and reduce local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Microbeads oftenly called microspheres thus present a novel approach for such delivery systems. Microbeads may be defined as "Monolithic sphere or therapeutic agent uniform distributed in the matrix either as a molecular dispersion of particles" or can also be defined as structure consist of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level [7].

2. MATERIALS AND METHODS

The following chemicals were procured from: Sodium alginate (Loba Cheime pvt ltd), Calcium chloride (Thermo fisher scientific India pvt. ltd.), L-arginine (Central drug house India), Starch Soluble (Thermo fisher scientific India pvt ltd.), Sodium hydroxide (Thermo fisher scientific India pvt ltd.), Potassium dihydrogen orthophosphate (Qualigens fine chemicals), Methanol (Thermo fisher scientific India pvt ltd), HPLC grade water (Thermo fisher scientific India pvt. ltd). All organic solvents used in HPLC were of high-performance liquid chromatography (HPLC) grade. All other ingredients were of analytical grade. Double distilled water was used throughout the study.

2.1 Preparartion of Microbeds by Ionoic Gelation Technique

Weigh accurately all materials required for the experiment, at first; Distilled water was then added to the weighed quantity of sodium alginate and starch to make aqueous mucilage of it in a beaker. The aqueous mucilage of sodium alginate and starch is then stirred in a magnetic stirrer at a suitable speed. Distilled water was also added to the weighed quantity of calcium chloride to make a solution in it. L- arginine was dispersed in the aqueous mucilage of sodium alginate subsequently and stirred at suitable speed in the magnetic stirrer. The microbeads are formed by dropping the bubble free dispersions through a glass syringe with the help of a needle into the gently agitated calcium chloride solution. The prepared microbeads was filtered & washed thoroughly with distilled water [8]. (Table 1).

2.2 Experimental Design

The screening was performed applying response surface methodology. The amount of sodium alginate (X_1, 3.5-4.5%) and potato starch (X_2, 1-3%) 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 and drug release at 10 h, and particle size, angle of repose 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 trial version of Design-Expert 8.0.7.1 software (Stat-Ease Inc., USA).

2.3 Evaluation

2.3.1 Shape and colour of microbeads

All the formulated batches of starch blended alginate microbeads of L-arginine were visually analyzed.

2.3.2 Flowability

The flow properties were determined by measuring the angle of repose of drug loaded microbeads. Microbeads were pouring to fall freely through a funnel fixed at 1cm above the horizontal plane until the apex of the conical pile just touches to the tip of funnel [9]. The angle of repose was determine by-

$$\tan\theta = h/r$$

Where the h = cone height, r = radius of circular base formed by the microbeads on the ground.

2.3.3 Size analysis

The particle sizes of the prepared microbeads were determined by using Vernier calipers. It is the most direct method for size distribution measurement was calculated. The prepared microbeads were taken and the diameters of 100 particles were measured by calibrated vernier caliper and the mean diameter was calculated [10].

2.3.4 Scanning electron microscopy (SEM)

Morphological examination of the surface and internal structure of the dried microbeads was carried out using a scanning electron microscope (LEO 430) equipped with secondary electron detector at an accelerating voltage of 15 kV. The samples were coated with gold Palladium. The internal structure of beads was examined by cutting them with a steel blade [11].

2.3.5 Swelling index

Swelling measurement of optimized potato starch-blended alginate microbeads containing L-Arginine were carried out in two different aqueous media: phosphate buffer (pH 6.8). 100 mg beads were placed in vessels of dissolution apparatus (Electrolab Tdt-08l Mumbai, India) containing 500 ml respective media. The experiment was carried out at 37 ± 1℃ below 50 rpm paddle speed. The swelled microbeads were removed at predetermined time interval and

Table 1. Experimental design of with coded and actual value of different formulations

S. No	Batch code	Coded level		Actual amount		Drug (mg)
		Factor A	Factor B	Factor A	Factor B	
		Sodium alginate	Potato starch	Sodium alginate (%)	Potato starch (%)	
1	f1	-1	-1	3.5	1	500
2	f2	-1	0	3.5	2	500
3	f3	-1	1	3.5	3	500
4	f4	0	-1	4	1	500
5	f5	0	0	4	2	500
6	f6	0	1	4	3	500
7	f7	1	-1	4.5	1	500
8	f8	1	0	4.5	2	500
9	f9	1	1	4.5	3	500

weighed after drying the surface by using tissue paper. Swelling index was determined using the following equation [12].

Swelling index = {(Weight of microbeads after swelling – Dry weight of microbeads)}/ Dry weight of microbeads × 100

2.3.6 Drug entrapment efficiency (DEE)

Accurately weighed, 100 mg of microbeads were taken, and crushed using pestle and mortar. The crushed powders of microbeads containing drug were placed in 100 ml of phosphate buffer, pH 6.8, and kept for 24 h with occasionally shaking. After the stipulated time, the mixture was stirred at 100 rpm for 20 min using a magnetic stirrer. After disintegration of microbeads were removed by filteration through Whatman filter paper (No. 40). The drug content in the filtrate was determined using a HPLC (ACME 9000 Younglin, China) at 210 nm [13]. The drug encapsulation efficiency of microbeads was calculated using this formula:

DEE = (Actual drug content in microbeads/ Theoratical drug content of microbeads) X 100

2.3.7 In–vitro drug release study

The release of (L-Arginine) from various potato starch-blended-alginate microbeads containing L-arginine was tested in phosphate buffer of pH 6.8 using a dissolution apparatus United States Pharmacopoeia (USP) XXIV 8-station dissolution test apparatus (Model TDT - 08L, Electro lab, Mumbai, India) with a rotating paddle stirrer at 50 rpm and 37℃ ± 1℃ temperature. The baskets were covered with nylon cloth to prevent the escape of the beads. Accurately weighed quantities of potato starch-blended-alginate microbeads containing L-arginine equivalent to 100 mg were added to 900 ml phosphate buffer. The test was carried out in Phosphate buffer (pH 6.8) for 10 hr. 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 HPLC (ACME9000 Younglin, China) at following chromatographic condition, Stationary phase: column – C18; mobile phase: methanol: distilled water = 1: 1 v/v (before using is filtered thought membrane filter with pore size 0.45 mm); flow rate – 1.0 ml/min; column temperature – 25 ^{o}C; analytical wavelength l = 210 nm, retention time-2.2-2.4 [14].

2.4 Optimization and Data Analysis

Optimization is done by the response surface methodology and it is a widely acceptable approach in the development and optimization of drug delivery devices. It can be used for optimizing a formula by maximizing one or more of the responses, keeping the formulation variable setting within a valid satisfactory range, carrying out simulations with the model equations and plotting the responses. The three-dimensional response surface graph is very effective in study 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 and overlay plot. The optimal values of responses were obtained by numerical analysis using the Design-Expert 8.0.6.1software based on the criterion of desirability, and to evaluate optimization capability of models generated in accord to the results of the design [15].

2.5 Stability Studies

Stability testing has become an integral part of formulation development. Determine the long term physical stability selected batch of microbeads from at a various storage conditions like as room temperature 25℃/60℃% RH, 40℃ /75% RH for 3 months (zone II conditions as per ICH Q1 guidelines) in an environment chamber. [16].

3. RESULTS AND DISCUSSION

3.1 Shape and Color of Microbeads

All the formulation show spherical shape and some are showing tailing and the color of microbeads in pale yellow and light yellow, (Table 4).

3.2 Fowability

From the results, it was observed that the angle of repose in the potato starch-blended alginate microbeads containing L-arginine was decreases by increasing sodium alginate (Table 4) and potato starch amount as polymer-blend. All the formulation showed excellent flowability represented in term of angle of repose. Sodium alginate concentration also has a significant positive effect on angle of repose. The decreases the angle of repose with the increment of sodium alginate and potato starch amount may be due to the increase the particle size and it tend to decreases the angle of repose.

3.3 Size Analysis

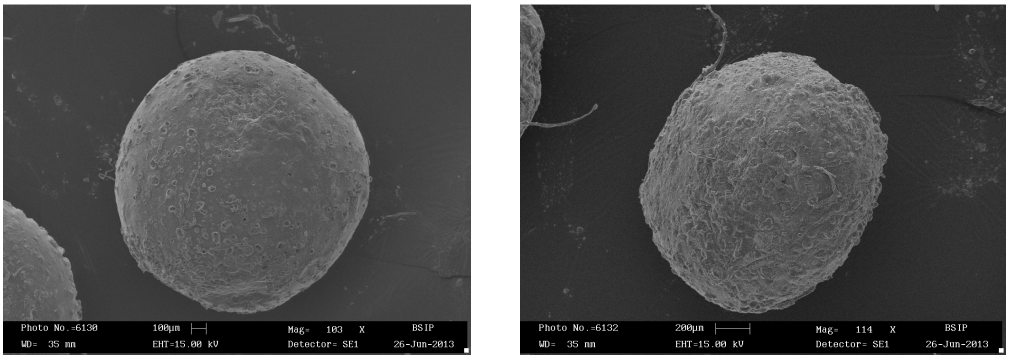
The size of microbeads containing L-arginine for each formulation was measured using slide caliper, and the average size of these dried microbeads were within the range between 0.175 ± 0.02 to 0.226 ± 0.02 mm (Table 4). Increasing the bead size was found with the increasing amount of sodium alginate and potato starch into formulations. This could be attributed due to the increase in viscosity of polymer 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.

3.4 Scanning Electron Microscopy (SEM)

The morphological analysis of potato starch-blended alginate microbeads containing L-arginine was visualized by SEM at different magnifications (Fig. 1). The SEM photograph of these microbeads (batch f4) at magnification (×103) showed spherical shape with a rough surface, detailed examination of the bead surface topography revealed cracks and wrinkles, which might be caused by partly collapsing the polymeric gel network during drying.

3.5 Swelling Index

Both factors sodium alginate and starch showed positive effects on the swelling index and it indicating that increasing the concentrations of starch and sodium bicarbonate led to an increase in the swelling properties of the microbeads, and increasing the concentration of sodium alginate (Table 2). This could be due to the high water sorption capacity of the starch and the surface characteristics of the microbeads. The swelling behavior of optimized microbeads in alkaline pH could be explained by the ion exchange phenomenon between the calcium ion of cross-linked microbeads and the sodium ions present



(a) **(b)**

Fig. 1. SEM photography of different prepared microbeads (a) batch f4 (b) batch

in phosphate buffer, with the influence of calcium-sequestrate phosphate ions, this result in disaggregation of potato starch-alginate matrix structure leading to matrix erosion and dissolution of swollen microbeads.

Table 2. Swelling study of all formulations

Batch code	% Swelling index		
	1hr	2hr	3hr
f1	110	215	310
f2	125	230	315
f3	140	245	325
f4	165	255	335
f5	175	270	348
f6	183	280	351
f7	190	286	356
f8	194	290	358
f9	199	296	365

3.6 Drug Entrapment Efficiency (DEE)

From the results, it was observed that the drug entrapped in the microbeads containing L-arginine was increased by increasing sodium alginate and potato starch amount as polymer-blend. The increased entrapment efficiency 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, (Table 4).

3.7 *In –vitro* Drug Release Study

The percentage drug released from microbeads containing L-arginine in 10 h (R_{10h}, %) was within the range of 84.568 ± 2.75% (F9) to 99.761 ± 1.99% (F1), 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 microbeads 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 microbeads and sustain the drug release profile (Fig. 2, Table 3,Table 4).

3.8 Optimization by Response Surface Methodology and Data Analysis

Factorial design by which all factors involved in a process are studied in all possible combinations by analyzing the effect of individual variables and their interactions using minimum experiments. Thus, the factorial design involves the selection of factors and the choice of responses. For the Response surface methodology, a total 9 trial formulations were proposed by Design-Expert 8.0.7.1 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 drug entrapment, *In-vitro* drug release and particle size, angle of repose were evaluated as dependent variables (responses). Overview of matrix of the design including investigated responses i.e., drug entrapment efficiency, and release, particle size, angle of repose were presented in (Table 4). The values of investigated responses measured for all trial formulations were fitted in the Response surface methodology to get model equations for responses analyzed in this investigation. The Design-Expert 8.0.7.1 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 shown in (Table 3).

Response surface methodology is a most useful approach in the development and optimization of drug delivery system. The influences of main effects (factors) on responses (here, drug entrapment efficiency, and *in vitro* drug release, Size analysis and Flowability) were further elucidated by response surface methodology. The three-dimensional response surface graph relating to DEE Indicates the increasing with the increasing of sodium alginate concentration (X_1), and potato starch concentration (X_2) in the formulated potato starch-blended alginate beads containing L-arginine by ionotropic gelation technique. However, a decrease in R_{10} values with the increasing sodium alginate concentration (X_1), and potato starch (X_2) is indicated by the three-dimensional response surface graph relating release. Then increasing the sodium alginate concentration and potato starch particle size also increases and the same effect were found on flowability (Fig. 3).

3.9 Data Analysis

The values of investigated responses measured for all trial formulations were fitted in response surface methodology to get model equations for responses analyzed using statistical tool Design-Expert 8.0.7.1 software by applying one way ANOVA. ANOVA of the selected responses

indicated that response surface model developed for all response was significant and adequate (Table 5). The results of the ANOVA based on the two cubic models indicated that these models

Table 3. *In-vitro* % drug release data of all formulation

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	50.502	45.388	39.929	49.14	41.294	38.223	47.094	40.270	37.200
1	59.315	49.393	42.198	57.94	46.641	41.165	55.249	45.953	40.136
2	69.878	51.713	45.502	65.43	49.969	44.122	63.389	47.936	44.452
3	73.674	54.385	52.281	71.00	52.291	51.894	69.249	51.252	49.225
4	77.674	61.506	57.648	75.48	55.307	53.894	74.081	54.945	50.564
5	81.665	65.595	61.683	79.84	63.455	59.638	77.936	62.402	55.350
6	86.203	74.821	67.513	84.47	70.964	65.453	81.453	69.571	61.760
7	89.058	82.733	76.067	86.02	77.490	74.319	85.621	76.089	70.598
8	91.925	90.345	82.960	89.05	85.074	79.839	88.822	82.324	76.790
9	97.194	93.220	84.843	96.48	92.697	82.069	92.333	88.550	79.356
10	99.761	96.814	90.150	98.71	95.948	87.568	97.602	94.166	84.648

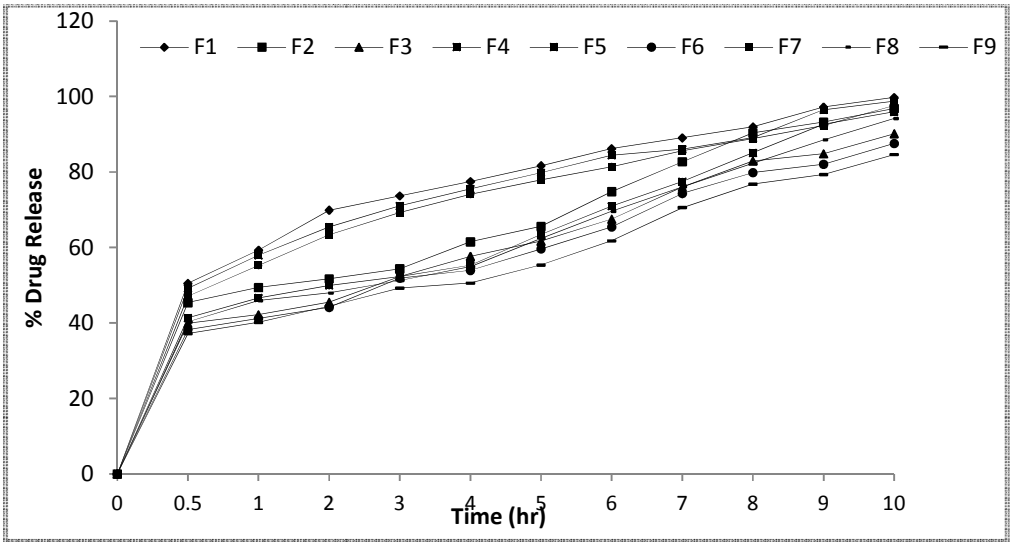


Fig. 2. Cumulative % drug release VS time profile

Table 4. Evaluation of all the formulation parameter as per the experimental design

Batch	Shape	Colour	Size (mm)	DEE (%)	Flowability (degree)	R_{10h} (%)
f1	Spherical	Whitish Yellow	0.175±0.02	42.5±1.8	18.9±1.3	99.76
f2	Spherical	Pale Yellow	0.179±0.02	61.2±1.5	21.8±1.6	96.81
f3	Spherical	Pale Yellow	0.184±0.01	81.2±1.68	24.98±1.5	90.15
f4	Spherical	Light Yellow	0.182±0.02	45.3±2.0	18.4±1.0	98.71
f5	Spherical	Light Brownish	0.187±0.01	70.5±1.3	20.14±2.5	95.94
f6	Spherical	Pale Yellow with tail	0.191±0.02	86.2±2.1	23.4±2.2	87.64
f7	Spherical	Light Yellow	0.192±0.01	54.2±1.3	16.3±1.4	97.62
f8	Spherical	Pale Yellow	0.197±0.01	76.2±1.1	18.4±0.8	94.16
f9	Spherical	Brownish with tail	0.226±0.02	91.2±1.05	21.8±0.9	84.56

Note; $R_{10h=}$ Release in 10 hrs

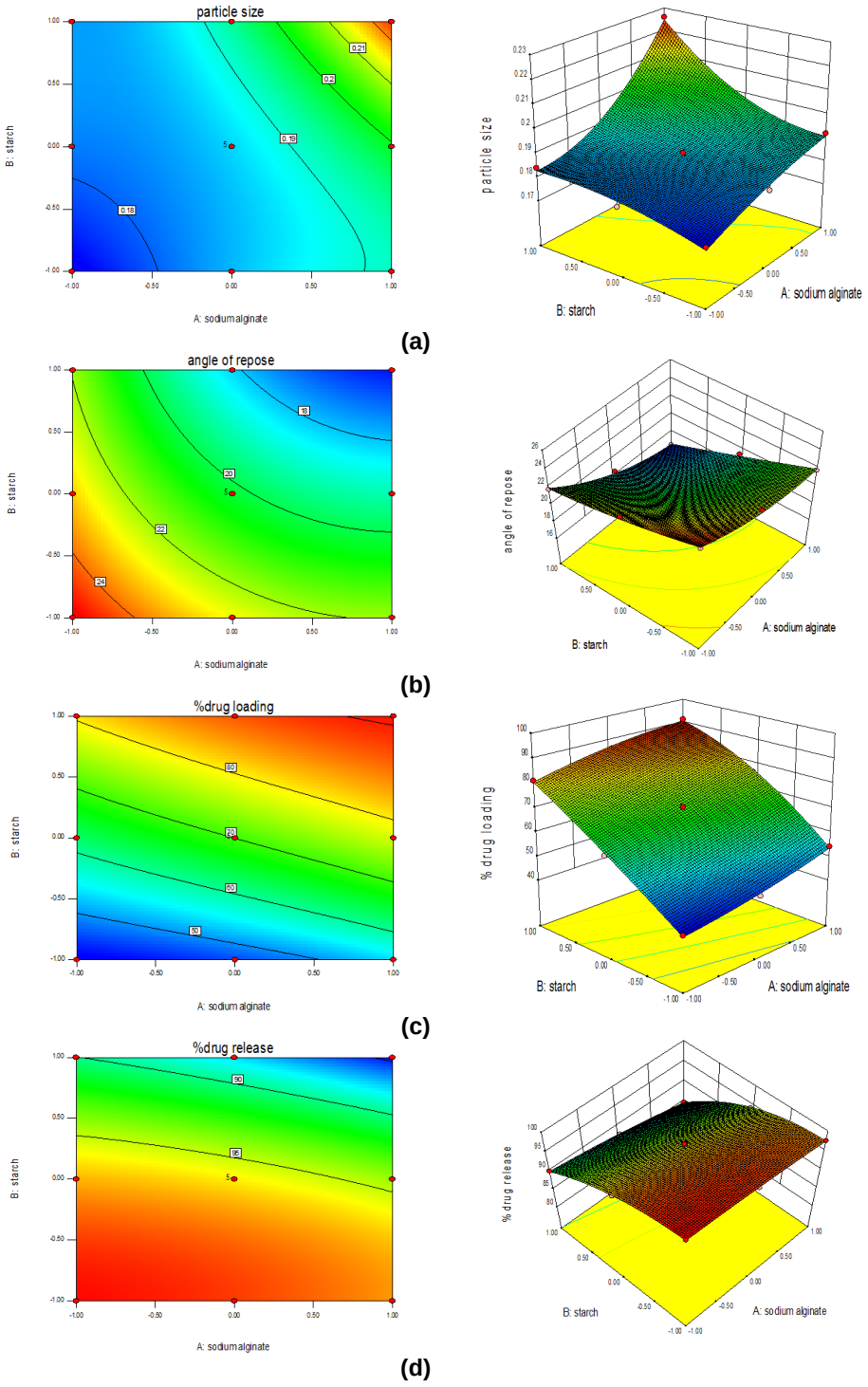


Fig. 3. Response surface and counter plots for (a) Size analysis (b) Flowability (c) Drug entrapment efficiency (d) Drug release

were significant for all response parameters. It can be noticed that all the coefficients of the model equation. The model equation all response shown in-

Size analysis = 0.19 + 9.000 X1 + 4.500 X2 + 6.250 X1 X2 + 4.259$X1^2$ +2.759$X2^2$ + 6.250 $X1^2$ X2+ 5.750 X1 $X2^2$

Flowability =20.24 - 2.00 X1 - 2.28 X2 - 0.56 X1 X2 + 0.92 $X1^2$ + 0.21 $X2^2$ +0.13 $X1^2$ X2 - 0.15 X1 $X2^2$

% DEE = 70.04 + 7.50 X1 + 20.45 X2 - 0.43 X1 X2 - 0.19 $X1^2$ - 3.14 $X2^2$ - 1.52 $X1^2$ X2- 2.07 X1 $X2^2$

% DR = 96.07 - 1.32 X1 - 5.57 X2 - 0.84 X1 X2 - 0.39 $X1^2$ - 2.74 $X2^2$ - 0.070 $X1^2$ X2- 0.59 X1 $X2^2$

The Design-Expert 8.0.7.1 software suggested cubic 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). The model summary statistics for best-fitting model selection was presented in (Table 6).

3.10 Design Validation

The checks point variables and by comparing all the predicted and observed value show in (Table 6). The optimized potato sodium alginate microbeads containing L-arginine A1 was evaluated for DEE (%), and R_{10h} (%) particle size and angle of repose. The results of experiments done with predicted responses by the mathematical model and those actually observed. The optimized formulation potato sodium alginate microbeads containing L-arginine A1 batch was selected by trading off various response DEE of 81.12%, R_{10h} of 90.19%, particle size 0.190 and angle of repose 19.16 (shown in (Table 7, Fig. 4) with in small error-values (-1.0, and -0.11, -0.003 and -1.0 respectively), indicating that mathematical models achieved from the full 3^2 factorial design were well fitted.

3.11 Stability Studies

All the parameters viz., content, TFT, BS and DR remained quite well within the desirable limits, showing negligible and random variation over three months of storage under accelerated conditions. Stability studies were carried out in accordance to ICH guidelines at temperature 40±2℃ and relative humidity 75±5%. The all parameter that is was no change in the appearance of the microbeads indicating that the formulations were stables at all the condition to which they were exposed. In-vitro drug release studies for all the formulations were carried out at the end of 3 months and did not reveal any significant change in the drug release from all the formulation. Stability studies revealed that the microbeads kept at room temperature (25℃) and 40℃ /75% RH showed the maximum stability. Thus, we may conclude that the drug does not undergo degradation on storage.

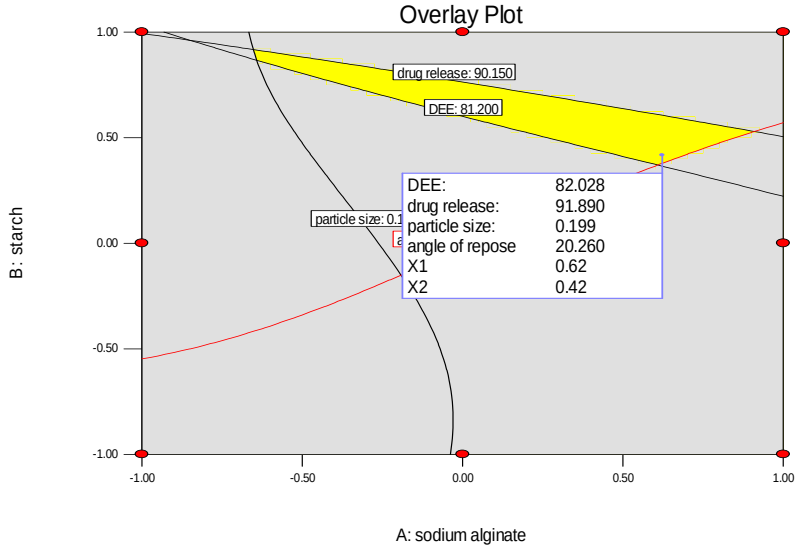


Fig. 4. Overlay plot showing optimized batch

Table 5. Summary of ANOVA for the response parameters

Response factor	Sum of square	d.f	Mean square	f-value	Prob.> F
DEE	2533.56	7	361.94	235.35	<0.0001
Drug release	237.68	7	33.95	167.15	<0.0001
Size Analysis	1.803	7	2.56	40.99	0.0004
Flowability	60.03	7	8.58	119.12	<0.0001

Table 6. Model summary statistics for measured responses in response surface methodology

Response factor	St. dev.	R^2	Adjusted R^2	Predicted R^2
Drug Entrapment	1.23	0.997	0.9928	0.6513
Drug Release	0.45	0.9957	0.9898	0.8901
Particle size	2.507	0.9829	0.9589	-0.9901
Angle of Repose	0.27	0.994	0.9857	0.3073

Table 7. Validation check point batches composition and their results

Check point batch	X1 CC	X2 CC	Response variables	Prediction values	Experimental values	Percentage error
A1	4.36	2.31	DEE	82.02	81.02	-1.01
			R_{10} (%)	91.89	91.78	-0.11
			Size analysis	0.199	0.196	-0.003
			Flowability	20.26	19.26	-1.01
A2	3.62	2.8	DEE	84.71	82.71	-2.01
			R_{10} (%)	90.48	89.4	-1.08
			Size analysis	0.206	0.2	-0.006
			Flowability	20.16	19.08	-1.1
A3	4.05	2.71	DEE	81.39	80.29	-1.1
			R_{10} (%)	90.54	88.54	-2.01
			Size analysis	0.184	0.184	0.0
			Flowability	23.82	22.82	-1.0
A4	4.15	2.5	DEE	81.54	80.52	-1.2
			R_{10} (%)	90.42	90.12	-0.3
			Size analysis	0.185	0.175	-0.1
			Flowability	23.77	23.77	0.0

4. CONCLUSION

The potato starch-blended alginate microbeads were successfully developed and optimized using response surface methodology. Response surface methodology was found to be satisfactory for describing the relationships between formulation variables and individual response variables. Starch is very important excipient and it can fulfill various requirements for the delivery of drug. Various drug delivery systems can be formulated by either native starch or its various derivatives. The applied HPLC method with UV-detector is appropriate for analysis of *in-vitro* drug release study. The drug releases from these newly developed microbeads containing L-arginine were found to be sustained over 10 h and followed a controlled release mechanism. The data suggest that sweet potato flour is a potentially useful natural material for making controlled release L-arginine loaded microbeads by the ionotropic gelation technique. As these microbeads are biocompatible, nontoxic, biodegradable, so they may be better used and i.e. they have paved a better way for controlled/sustained release of drug through the use of natural, biodegradable material. Thus, potato starch is proved as a potential polymeric blend with alginate in the development of ionotropically-gelled microbeads for the use in controlled drug delivery.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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