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Research Article

EMBRACING THE QUALITY USING QBD: A SYSTEMATIC DEVELOPMENT OF OPTIMIZED ARGININE BEADS

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A B S T R A C T

Purpose of the research work was aimed to develop a optimised controlled release dosage form of L-arginine with minimum efforts by using a combination of statistical and analytical approach by applying Quality by Design (QbD). Controlled release formulation of L- Arginine was developed by using ionotropic gelation technique and effect of various independent variables like concentration of Sodium Alginate (SA) and concentration of Calcium Chloride (CC) was studied employing QbD approach; on dependent variables like Microbeads size (MS), Entrapment Efficiency (EE) and drug release in 10 h (Q_{10}). The comprehensive evaluation of formulated microbeads was done using 3^2 Central Composite design (CCD). The computer optimization process, contour plots and response surface plots predicted the concentration of independent variables SA 7.506 mg and CC 7.92 mg fulfilled the desired criteria by giving best response; MS1.615 mm; EE 95.96%; and Q_{10} 95.52%;. Optimized formulation of L- Arginine was developed without exhaustive experimental study with help of Qbd approach.

INTRODUCTION

Quality by Design (QbD) is a scientific and systemic approach to develop a drug product of predictable quality attribute with desired predetermined specification [1]. QbD-based approach is helpful in developing drug products with minimal expenditure of time, money and efforts [2]. The gist of the expectations from QbD is that the product and process performance characteristics should be scientifically designed to meet specific objectives, not empirically derived from performance of test batches, and good product quality should represent an acceptably low risk of failing to achieve the desired clinical attributes [3]. The design of experiments (DOE) is the design of any task that aims to describe or explain the variation of information under conditions that are hypothesized to reflect the variation [4]. Response surface methodology (RSM) as a tool of designing of experiments is widely practiced approach in the development and optimization of drug delivery devices [5-6]. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient. Thus, in controlled release drug delivery, release of the drug proceeds at a rate profile that is only predictable kinetically, but also reproducible from one unit to another [7-8].

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Arginine is a semi-essential amino acid involved in multiple areas of human physiology and metabolism. Nitric Oxide produced from arginine is helpful in improving outcomes in various diseases[9]. L-arginine is readily available over the counter and is popular as a nutritional supplement. Several researches has proved that L-arginine had potential therapeutic effect in numerous acute and chronic disease states, including sickle cell chest crisis, pulmonary artery hypertension, coronary heart disease, pre-eclampsia and myocardial infarction [10-11].

MATERIAL AND METHODS

Materials

L-Arginine was obtained from CDH Laboratory Chemicals, Sodium Alginate (low viscosity grade, 250 cp of 2% solution at 25°C) from Loba cheime pvt ltd (Mumbai), calcium chloride and sodium hydroxide from Thermo fisher scientific India pvt. Ltd. (Mumbai). HPLC grade water, methanol and potassium dihydrogen orthophosphate from Qualigens fine chemicals (Gujrat).

Design for Formulation

First optimization studies were conducted to find out the optimum concentration of SA and CC by using 3^2 central composite designs (CCD) for the formulation of alginate microbeads. 3^2 CCD is used as to design the experiment to estimate the impact of independent variables over dependent response by using minimum experimentation while centre point was repeated five times. The concentration of Sodium

Alginate and concentration of calcium chloride were taken as independent variables (Table 1). Microbeads were optimised by finding the effects of these formulation variables on drug entrapment efficacy (EE), drug release in 10 hours (Q_{10}) and Microbeads Size (MS).

drug entrapment was calculated in terms of percentage drug entrapment (PDE) as per the following equation:

%DE = (Actual amount of drug loaded/Theoretical amount of drug loaded) ×100 (1)

Table 1 Design for formulations with coded and actual values of independent variables

Batch code	Level of factor		Actual amount (%)		L-arginine (mg)	Chitosan (%)	Distilled Water (mL to make)
	Sod. Alginate	Cal. Chloride	Sod. Alginate	Cal. chloride			
F1	-1	-1	4	4	1000	0.5	100
F2	-1	0	4	6	1000	0.5	100
F3	-1	+1	4	8	1000	0.5	100
F4	0	-1	6	4	1000	0.5	100
F5	0	0	6	6	1000	0.5	100
F6	0	+1	6	8	1000	0.5	100
F7	+1	-1	8	4	1000	0.5	100
F8	+1	0	8	6	1000	0.5	100
F9	+1	+1	8	8	1000	0.5	100
F10	0	0	6	6	1000	0.5	100
F11	0	0	6	6	1000	0.5	100
F12	0	0	6	6	1000	0.5	100
F13	0	0	6	6	1000	0.5	100

Preparation of Microbeads

The microbeads were prepared by using ionic gelation method [12]. SA solution (4%, 6% & 8% w/v) were prepared by dissolving 4, 6 & 8g of SA in a small amount of distilled water in a mortar pestle as given in table 1. When clear solution was formed, the volume made up to 100 mL. L-Arginine was added in to each SA solution with 15 m stirring on magnetic stirrer to form a clear solution. Chitosan (0.5%) and calcium chloride (4, 6, 8%) were dissolved in 5% acetic acid solution. The pH of solution was adjusted to 5 using 0.1 N NaOH solution and was stirred for further 30 min. Drug containing SA solution was then dropped drop wise through 21 gauge needle into 100 mL solution of CC solution and microbeads were formed. The gelation time of 30 m was allowed to complete the curing reaction in the CC solution containing chitosan and then microbeads were collected, filtered through wattman filter paper and washed thoroughly with water. The time of drying was optimised by weighing the microbeads repeatedly, until a constant weight was obtained [13].

Evaluation of Drug loaded alginate beads

Particle size and Uniformity

Arginine microbeads of the uniform size, shape and density were formulated by keeping various factors constant viz. falling rate of drops, stirring rate, viscosity as well as distance between gelation media and syringe. Any change in these factors may result in non-homogenous and non-uniform microbeads [14]. A number of microbeads (50) were randomly picked up thrice and their size was determined by using a digital vernier (Mitutoyo Japan). The result is expressed as the mean diameter (mm) ± standard deviation [15-16].

Drug Entrapment efficiency

Accurately weighed amount of microbeads (100 mg) were suspended in 50ml of standard phosphate buffer of pH 6.8±0.1 and kept for 24hrs. Next day it was stirred for 5min and then filtered. After suitable dissolution, the drug content in the filtrate was determined by HPLC [17-18]. Efficiency of

Swelling properties

The swelling properties of the microbeads were determined in simulated gastric fluid (0.1 N HCl) standard phosphate buffer (SPB) pH 6.8. Samples of microbeads (10mg) were placed in a glass vial containing 10 ml of swelling solution and allowed to swell at 37^0C. The swollen beads were removed. The weight of wet swollen microbeads was determined immediately after blotting them with filter paper to remove moisture adhering to the surface. The percentage of swelling of the beads was calculated from the formula [19-22].

Swelling ratio = weight of wet microbeads/weight of dried microbeads (2)

Topographic study

The shape and surface characteristics were determined by scanning electron microscopy (Phillips 1500) using gold sputter technique. The particles were vacuum dried, coated to 200 Å thicknesses with gold palladium using prior to microscopy. A working distance of 20nm, a tilt of zero-degree and accelerating voltage of 15kv were the operating parameters. Photographs were taken within a range of 50-5000 magnifications. The pictures were taken at magnification of 65 and 610X [23].

In vitro drug release study

In vitro release studies were carried out on formulated microbeads using USP XXIV dissolution test apparatus-I (Electrolab, TDT-06T, Maharashtra, India). Accurately weighed quantity of microbeads was suspended in pH 1.2 gastric media. This medium was stirred at 120 rpm and maintained at 37±0.1°C. These formulated microbeads were tested for drug release for 2 h in 0.1 N HCl and then the dissolution medium was replaced with pH 6.8 phosphate buffer and tested for drug release for next 8 h. Samples were withdrawn at appropriate intervals from both media and replaced by fresh media. The amount of L-arginine was determined by HPLC with UV- detector at 210 nm [24]. The release studies were conducted in triplicate. The results of in vitro release data were fitted into various release equations and kinetic models [25-28].

Stability studies

Optimised formulation was also subjected to accelerated stability studies to determine the changes in release profile and floating characteristics on storage; stability studies were carried out at 40±2°C/75±5% relative humidity (RH) for 3 months (zone II conditions as per ICH Q1 guidelines) in an environment chamber (Jindal S.M. Scientific, New Delhi). The samples were withdrawn periodically and evaluated for similarity factor (f2) [29-30].

Data Analysis

3^2 CCD was adopted for optimisation included MS, EE and Q_{10}. Two independent variables were investigated as concentration of sodium alginate (X_1) and calcium chloride (X_2). The effects of these independent variables were investigated on the dependent responses such as MS, EE and Q_{10}. The experimental points used according to the design shown in Table 1. Polynomial equations were generated and used to express the function of independent variables (SA & CC).

For the studied design, 3^2 central composite design was applied using Design Expert 10.0.3 trial version (Stat-Ease, Minneapolis, USA) software to fit polynomial equation with added interaction terms to correlate the studied responses with the examined variables:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2 + b_6X_1X_2^2 + b_7X_1^2X_2 \quad (3)$$

where bo is the intercept while b_1-b_7 are constants, and X_1 and X_2 are taken as variables for the given polynomial equation.

3^2 CCD is a most efficient tool to estimating the influence of individual independent variables and their interactions with minimum experimentation. In the present study, 3^2 CCD was considered to be better as the values of the response surfaces were not known from the previous findings. Hence, 3^2 CCD was chosen for optimization of formulations. Thirteen formulations were formulated by taking nine possible combinations among which centre point was repeated four times and mean values were taken for further study. The models were tested for significance. Four formulations (VC1 to VC4) were selected as the confirmatory check-points, and these were validated by response surface methodology. The observed and predicted responses were critically compared. Linear correlation plots were constructed for the chosen check-point formulations. The residual graphs between predicted and observed responses were also constructed separately and the percent bias (% prediction error) was calculated with respect to the observed responses. After studying the responses surfaces for all properties feasibility and grid searches through MS-excel (Microsoft, USA) utility and overlay plot generation method through design expert were used for finding the optimized product.

Stability Studies

Optimised formulation was also subjected to accelerated stability studies to determine the changes in release profile and floating characteristics on storage; stability studies were carried out at 40±2°C/75±5% relative humidity (RH) for 3 months (zone II conditions as per ICH Q1 guidelines) in an environment chamber (Jindal S.M. Scientific, New Delhi). The samples were withdrawn periodically and evaluated [30].

RESULTS

Preliminary trail batches of microbeads were prepared by using SA, the stirring speed was varied from 50, 75 and 100 rpm and cross linking time also varied (5, 10 and 15 minutes). From these batches, 50 rpm and 15 minutes were the optimum revolution and cross-linking time used for the preparation of microbeads. The cross linking time did not have a significant effect on the percentage of EE.

Size, Uniformity and Swelling Index of Microbeads

The microbeads were prepared by simple ionotropic-gelation technique using SA a natural polymer followed by coating with chitosan. Polymer concentration (drug: polymer) was an important factor as viscosity of polymer solution effects the size of microbeads. Three different polymer concentrations of 4%, 6% and 8% (w/v) were selected. Particle size and swelling index of all the batches as shown in table 2 and lowest concentration of polymer exhibit least particle size and swelling index of microbeads.

Table 2 Physicochemical properties of alginate beads

Batch code	MS(mm)	Swelling Index		DEE (%)	Q_{10}	Shape
		pH 1.2	pH 6.8			
F1	1.630±0.23	79	300	75.0±2.261	99.435	S
F2	1.569±0.11	76	298	80.0±2.458	98.796	S
F3	1.451±0.03	83	312	82.5±0.794	97.341	S
F4	1.953±1.02	84	318	84.5 ± 1.744	98.663	AS
F5	1.830±0.93	78	300	88.5 ± 1.877	97.216	AS
F6	1.761±0.87	75	296	90.0 ± 1.572	96.262	AS
F7	1.631±1.54	77	299	95.0 ± 0.872	97.753	AS
F8	1.596±1.23	80	304	96.5 ± 0.519	95.194	AS
F9	1.497±0.65	81	306	98.1 ±0.700	94.266	AST
F10	1.859±0.54	78	298	89.0± 0.519	97.56	AS
F11	1.845±1.03	79	303	88.5± 0.519	96.92	AS
F12	1.793±0.68	79	302	87.5± 0.519	97.77	AS
F13	1.833±0.56	80	299	88.0± 0.519	96.83	AS

S- spherical; AS- Almost Spherical; AST- almost spherical with tailing

Surface Topography

Surface topography of prepared microbeads was studied by scanning electron microscopy as shown in Figure 1.

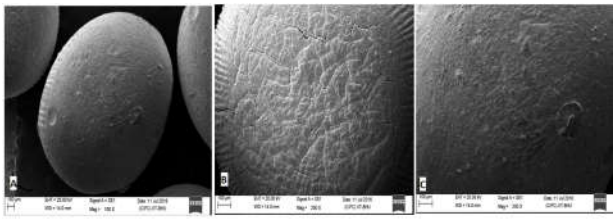

Figure 1 Scanning Electron Micrograph of beads (A) Chitosan-coated alginate beads, (B) Heat dried microbeads; (C) Ethanol dried microbeads

Scanning electron micrographs of chitosan-coated alginate beads are shown in fig. 1A. The size of the microbeads was measured and ranges 1.451±0.03 mm to 1.953±1.02 mm. By observing the surface of microbeads closely small cracks were observed (fig. B) that are may be caused by partial collapsing of the polymer network during dehydration. In contrast, ethanol drying caused significant improvement in maintaining the spherical shape as well as decrement of the cracks on the surface. Ethanol treatment contributed substantial reduction in rough surface of the chitosan membrane and the elimination of the cracks observed on the surface (Figure 1C). Furthermore, ethanol drying maintained the adhesion of the

chitosan membrane with the alginate core and resulted with a smoother outer surface.

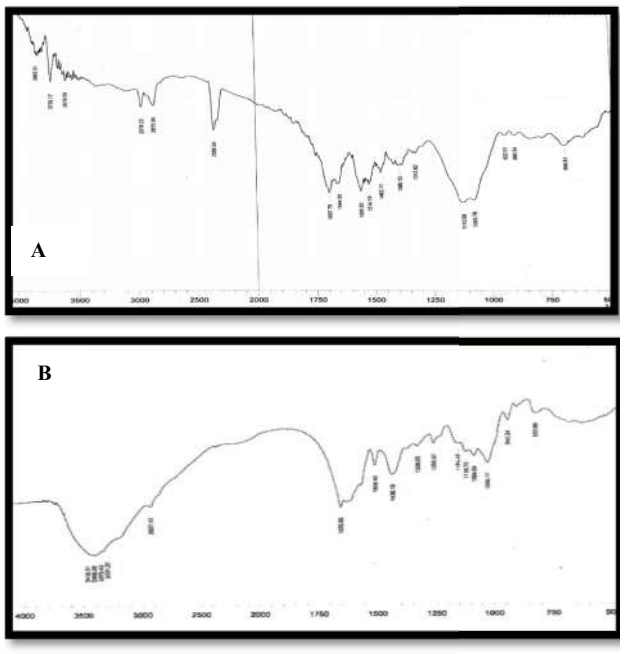

Figure 2 Infra Red Spectra of (A) L-arginine (B) Optimized Batch

Fourier transformed infra red analysis

FTIR spectral data were used to confirm the chemical stability of L-Arginine in alginate beads. FTIR spectra of pure drug and L-Arginine loaded microbeads prepared were compared in Figure 2.

X-ray diffraction study

X-ray diffraction studies of the pure drug, and formulated microbeads containing the drug are shown in Figure 3. Several sharp peaks in XRD spectra of pure drug indicate crystalline nature of L-arginine. XRD pattern of formulated microbeads shows the disappearance of characteristic peaks of drug and also found to be broadened, these finding suggest the changes in the crystalline state of the drug occurred during the formulation of the beads by ionic gelation technique.

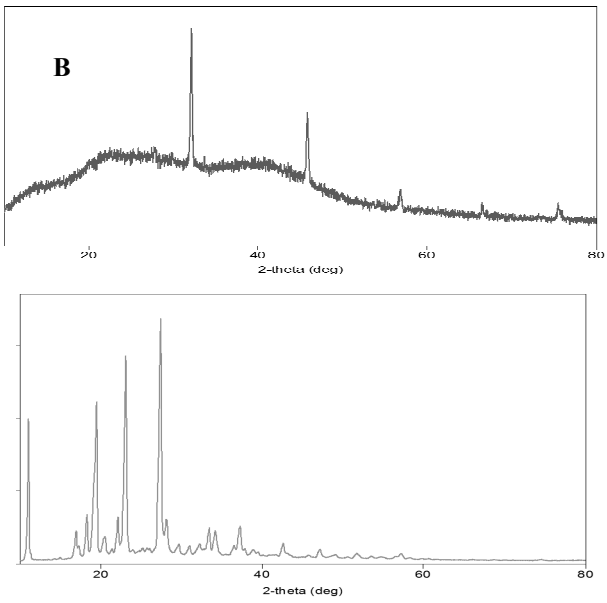

Figure 3 X-ray diffractogram of (A) Pure Drug and (B) Optimized Microbeads

Drug Entrapment Efficiency

Entrapment efficiency is an useful variable used to determine the drug loading capacity of microbeads and their drug release profile. EE depends upon number of variables parameters such as formulation process used, physicochemical properties of the drug and various formulation variables (table 2).

In Vitro Drug Release Studies

In vitro DR study of L-arginine microbeads was carried out in gastric media for 2 h and then in pH 6.8 phosphate buffer for next 8 h. Drug release from all formulations is almost similar. Complexation between SA - chitosan cause delayed release of arginine form the formulations at gastric pH because of poor swelling index of alginate. In the fasted state, gel microbeads exhibited a biphasic release profile as an initial rapid DR phase (burst effect) followed by a slower, gradually decreasing DR phase after 2 hour extending up to 10 hours (Table 3 and Fig. 4).

$$Size=1.84+0.014*A+0.096*B-0.011*AB-0.28*A^2-1.672*B^2-0.018*A^2B-1.75*AB^2 \quad (4)$$

$$DEE=88.24+8.25*A+2.75*B-1.12*AB+0.16*A^2-0.84*B^2-0.13*A^2B+0.62*AB^2 \quad (5)$$

$$Q10=+93.35-6.81*A+3.54*B+3.93*AB-0.97*A^2-0.17*B^2-0.52*A^2B+3.61*AB^2 \quad (6)$$

Table 3 *In vitro* drug release data from different batches

Batch Code	Q_{10}	Korsmeyer R^2	Higuchi R^2	First Order R^2	Zero Order R^2	n
F1	99.435	0.9755	0.9911	0.9471	0.8966	0.4590
F2	98.796	0.9908	0.9945	0.9906	0.9127	0.5055
F3	97.341	0.9767	0.9907	0.9258	0.9003	0.4675
F4	98.663	0.9858	0.9926	0.9790	0.9239	0.5148
F5	97.216	0.9810	0.9935	0.9610	0.8936	0.4626
F6	96.262	0.9893	0.9939	0.9882	0.9131	0.5005
F7	97.753	0.9901	0.9941	0.9869	0.9199	0.5161
F8	95.194	0.9822	0.9939	0.9707	0.8869	0.4566
F9	94.266	0.9419	0.9715	0.9422	0.8843	0.4464
F10	97.56	0.9813	0.9933	0.9689	0.8909	0.4578
F11	96.92	0.9815	0.9932	0.9683	0.8945	0.4632
F12	97.77	0.9813	0.9928	0.9703	0.8918	0.4592
F13	96.83	0.9809	0.9930	0.9724	0.8901	0.4562

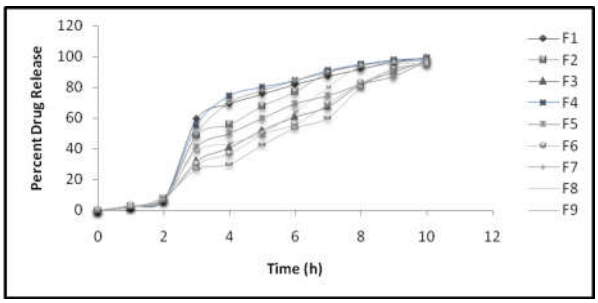

Figure 4 *in-vitro* evaluation of microbeads

Table 4 ANOVA for selected statistical model

Response	Sum of squares	df	Mean square	*F* value	*P*	R^2	Adequate precision
Size	0.29	7	0.042	46.04	0.0003	0.9847	20.052
DEE	501	7	71.57	251.20	<0.0001	0.9972	54.929
Q_{10}	294.23	7	42.03	31.69	0.0008	0.9780	20.284

DEE- Drug Entrapment Efficiency, Q_{10}- Drug Release in 10 h

Response surface analysis

It was observed that microbeads size, DEE and Q_{10} were depend on dependent variables i.e. concentration of SA and

CC. There was an almost linear increment in the size of microbeads with increase in the concentration of cross linking agent i.e. CC while increases upto an extent by increasing the concentration of sodium alginate then start decreasing. The counter plot also shows that combine effect although are decreasing but not totally linear for microbeads [Figure 5a]. Figure 5b suggests that DEE of microbeads sharply increases with increase in SA as well as CC concentration. Figure 5c suggest that Q_{10} of microbeads increases rapidly by increase in SA concentration while its value increases up to some extent and then decrease after reaching upto a limit hence both the independent factors are having significant effect over the release of drug. Overlay plot obtained from design expert software showing area (colored area in the plot, Figure 6) for optimum desired values; also confirm that optimized product is within the area.

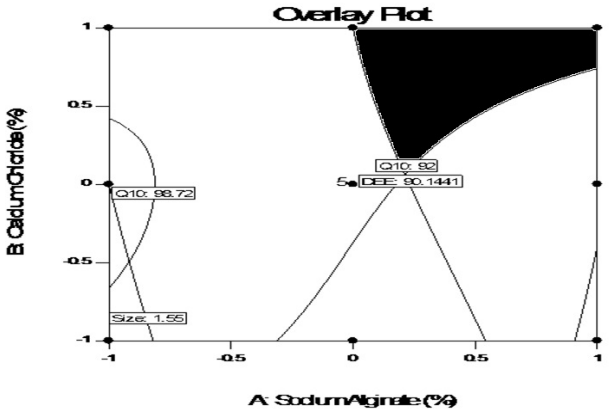

Figure 6 Overlay Plot Showing Area for Optimized batch

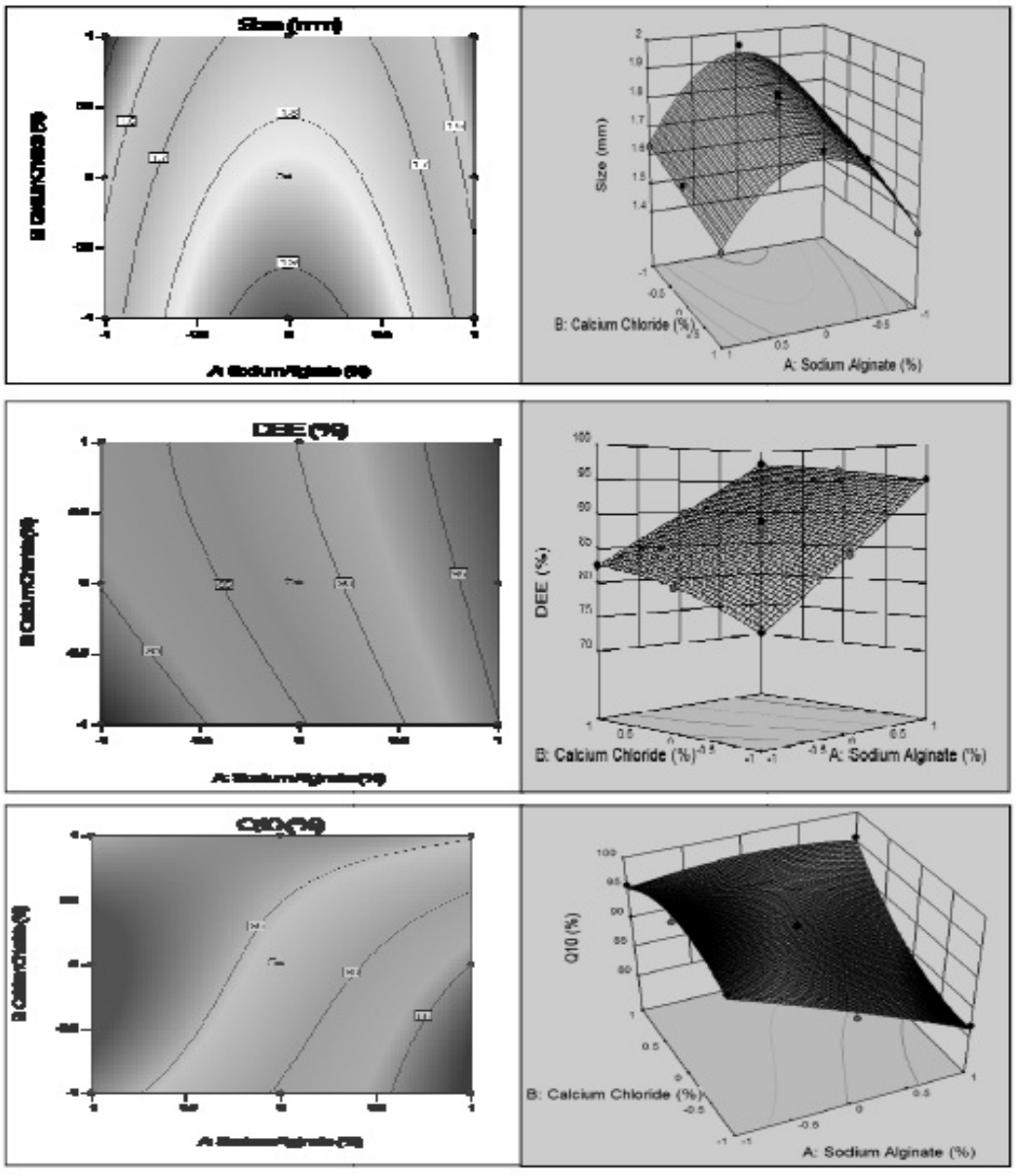

Figure 5 Response Surface and Contour Plots for (A) Microbeads Size, (B) Entraptment Efficiency, (C) Drug Release

Table 5 Validation of response surface methodology

Batch Code	Amount of SA	Amount of CC	Response	Predicted Value	Experimental Value	% Error
			Size	1.93 mm	1.92 mm	0.518
VC1	7.506	7.92	DEE	90.14 %	89.99 %	O.166
			Q_{10}	98.71%	96.73 %	-0.206
			Size	1.84 mm	1.83 mm	0.543
VC2	6.42	6.78	DEE	90.29 %	90.27 %	0.022
			Q_{10}	99.09 %	92.11 %	-0.022
			Size	1.77 mm	1.77 mm	0
VC3	7.34	7.18	DEE	94.83 %	94.80 %	0.032
			Q_{10}	98.21 %	92.19 %	0.022
			Size	1.63 mm	1.62 mm	0.613
VC4	7.98	7.5	DEE	97.60 %	97.57 %	0.031
			Q_{10}	99.13 %	92.10%	0.033
			Size	1.68 mm	1.70 mm	-1.190
VC5	0.94	0.98	DEE	96.80 %	96.83 %	-0.031
			Q_{10}	99.33 %	95.36 %	-0.031

RSM, the three-dimensional response surface graph corresponding contour plot relating MSclearly indicates that increase in concentration of calcium chloride decreases the MS because high concentration of calcium chloride may cause shrinkage of microbeads as well as high degree of cross linking [31].

FTIR spectra of L-Arginine show the characteristic bands of -NH stretching, -CH_3 Asy. stretching, NH_2 Bend, OH bending, CH_3 Asy bend and sym str CCC bond stretching at 3598, 2961, 1689, 1547, 1462 and 1023 cm^{-1}, respectively. The spectra obtained from drug-loaded beads prepared indicate the presence of the characteristic bands of the drug at almost the same wave number. The presence of chitosan in microbeads can be shown by the appearance of the band at 1541 cm^{-1}, attributed to NH_2 and NH of chitosan, also noted in the spectrum of this polysaccharide alone.

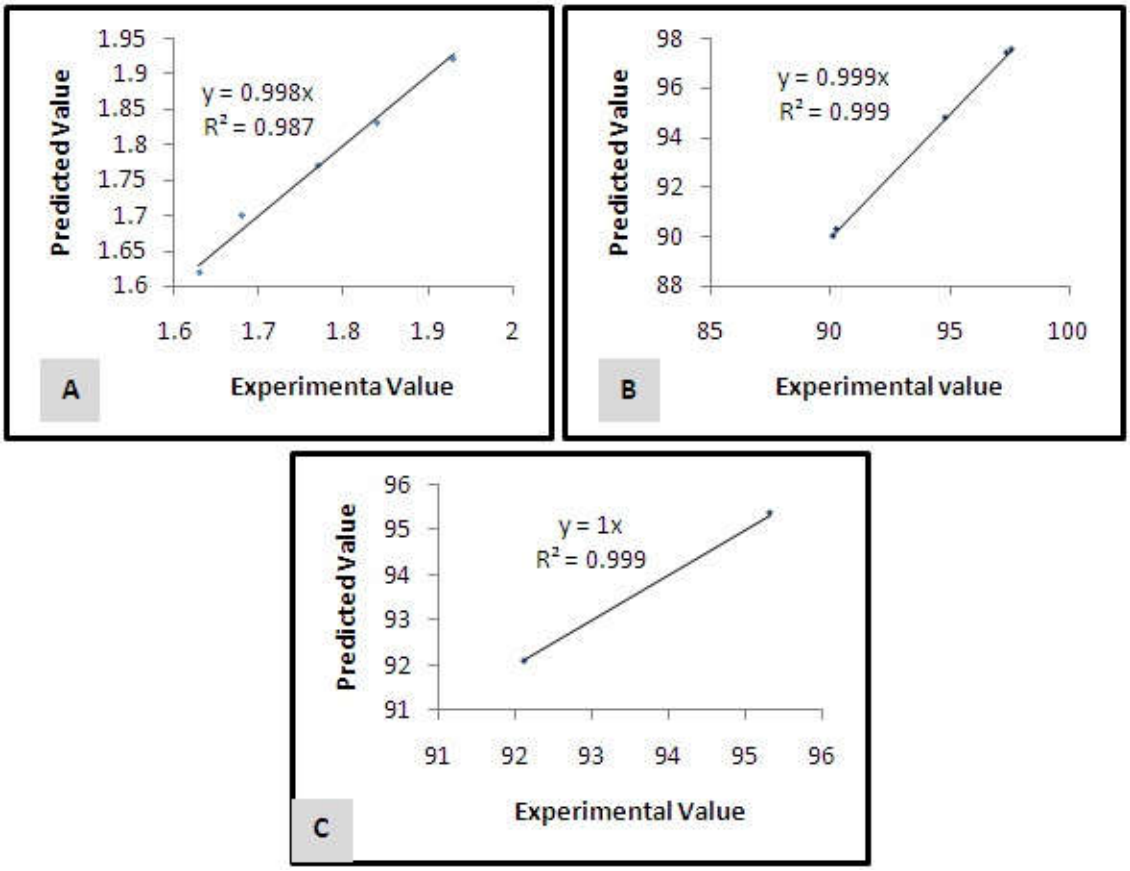

Figure 7 Regression coefficient between anticipated and experimental response: (a) Micro-bead size, (b) Drug Entrapment Efficiency, (c) Drug Release in 10 h

Stability Study of the Optimised Formulation

All the parameters viz., microbead size, drug EE and Q_{10} are found 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°C and relative humidity 75±5% [30].

DISCUSSION

Ionotropic gelation technique was adopted to prepare microbeads loaded with L- Arginine. The influence of independent variables on dependent responses was further elucidated by response surface methodology (RSM). In the

The weak absorptions in the range of 1510-1530 cm^{-1} and near 1630 cm^{-1} indicate the presence of protonate amine group from chitosan in spectra of optimized microbead [32].

XRD spectra of pure drug represent the crystalline nature of drug while XRD pattern of microbeads shows the disappearance of characteristic peaks of drug and also found to be broadened, these finding suggest the changes in the crystalline state of the drug occurred during the formulation of the beads by ionic gelation technique.

The swelling index of microbeads containing L-arginine were evaluated in 0.1 N HCl (pH 1.2) and SPB pH 6.8 after 4 h.. The swelling index values of beads were within the range between 76-84% at pH 1.2 and 296-318% pH 6.8. Hence

increment in pH and alginate mass increases the swelling index, because in acidic medium, the calcium alginate beads were converted to the insoluble alginic acid beads which had a low swelling index. One more cause may that swelling degree is much more influenced by the inner structure of L-arginine than by the chitosan coating layer, which would get more hydrogen bonding in the acidic condition [33,34].

Optimizations of formulated microbeads were done by using QbD utilizing 3^2 CCD. The outcomes for response parameters, that is, microbeads size, EE and Q_{10}, were subjected to regression analysis and statistical models, were found to be significant (Table 5). These observed responses, microbeads size, EE and Q_{10} shows good relation between the dependent and independent variables. The microbeads size, EE and Q_{10} for all formulated batches of microbeads showed a wide variation (i.e., 1.451- 1.953mm, 75 - 98.1% and 81.99-98.72% respectively).

The F value in table 5 is known as the ratio of model mean square to the appropriate error mean square. The F distribution is dependent on the degrees of freedom (df) for the variance in the numerator and the df of the variance in the denominator of the F ratio. In the model, F value is 46.04 for microbead size, 251.20 for DEE and 31.69 for Q_{10}, while high value of regression coefficient, R^2 (0.978-0.997) indicates that these models are significant. Values of "*P*" < 0.05 suggest that model terms are significant. In this case, the models generated for microbeads size, EE and Q_{10} are significant. Adequate precision measures the signal-to-noise ratio. A ratio >4 is desirable. The adequate precision of value 20.052, 54.929 and 20.284 respectively, for microbeads size, EE and Q_{10} models indicate an adequate signal for each. These models can be used to navigate the design space.

It was observed that observed response ie. MSwas dependent on both independent variables like concentration of sodium alginate and calcium chloride. Sizes of the microbeads at first increased with the increasing concentration of sodium alginate and then decreased when concentration of sodium alginate exceeded 6%.

It was observed from the response surface and contour plots that both the independent variables influence the EE of the formulated microbeads. There was a linear increase in the values of EE, as the levels of concentration of sodium alginate and calcium chloride were increased.

The response surface and contour plots reveals a nonlinear decline in the value of Q_{10} with an increase in the amount of the polymers i.e concentration of sodium alginate and calcium chloride. Nonlinear contour lines in figure further show that the variation in Q_{10} is a complex function of the polymers concentration.

Validation of optimized batch was done by formulating five different batches and comparison of the observed responses with those of the anticipated ones was done (Table 5) it was observed that the prediction error varied between -1.1904 and 0.6135 %. The linear correlation curve was drawn between the predicted and observed responses, was a linear line passing through the origin, demonstrated high value of regression coefficient, R^2 (0.987 to 0.999, Fig. 4), indicating excellent goodness of fit ($p < 0.005$). The corresponding residual plots show nearly uniform and random scatter around the mean values of response variables. The slection of optimum formulation was done by trading off dependents response variables and adopting the following range: MS1.451-1.953mm; EE 90-98%; and Q_{10} 92-98.72%. Upon comprehensive evaluation of optimised formulation (X_1: 0.753 and X_2: 0.96) fulfilled the optimal criteria of best response MS 1.615 mm; EE 95.96%; and Q_{10} 95.52% hence, this formulation was taken as optimized formulation.

CONCLUSION

The presented research work result in successful development of optimised microbeads of L-arginine with alginate chitosan coated with desired requirement of the target formulation. The work proves that QbD optimization technique is much helpful for getting optimized product without the need of rigorous experimental work with saves time and a best product may be developed. Thus the hiccup of balancing the two or more variables may be easily surpassed using the CCD. Hence, this study could help pave the way for further development in the manufacture of floating controlled release formulations.

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