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Influence of Pregelatinized Breadfruit Starch-Alginate Blend as a Sustained Release Polymer in Theophylline Microbeads Using Box Behnken Design

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Apart from the coating property of modified starches on drugs, these natural polymers also acts as release rate retardants.

Objectives: To evaluate the potential of pregelatinized breadfruit (*Artocarpus altilis*) starch as a carrier in microbead formulations of theophylline using different blend combinations with sodium alginate and to determine the optimized formulation using Box-Behnken design.

Method: Theophylline microbeads were prepared using the ionic gelation method. The 3 factor-3 level Box-Behnken design was employed for constructing polynomial models to optimize the microbeads, involving 3 independent variables (polymer type, X_1, polymer: drug ratio, X_2, and concentration of calcium chloride, X_3) and 2 dependent variable (entrapment efficiency and quantity of drug released in 12 h, Q_{12}).

Results: Entrapment efficiency was 35 - 71 % while the values of Q_{12} was 38 - 88 %. The three variables, X_1, X_2 and X_3, were positive for entrapment efficiency but negative for Q_{12}, implying that increase from low to medium and then to high level resulted in an increase in entrapment but a decrease in Q_{12} (sustained release), both desirable effects. Factor X_1 had the most significant influence on entrapment efficiency and Q_{12} ($p = 0.002$; $p = 0.0001$, respectively). The optimized formulation with starch:polymer 2:1, polymer:drug 3:1 and 7.5%w/v calcium chloride solution gave an entrapment efficiency 65% with Q_{12} of 38.75%.

Conclusion: Pregelatinized breadfruit starch enhanced entrapment efficiency while retarding drug release, showing its potential as a polymer for sustained release in microbead formulations.

Keywords: Box-Behnken design; Breadfruit starch; Ionic gelation, Microbeads, Pregelatinization

INTRODUCTION

Natural polymers are usually obtained from carbohydrates and proteins and these have been the focus of a large percentage of pharmaceutical investigations as matrices in drug delivery systems (Urhich *et al*, 1999; Clochard et al, 2001; Taylor and Francis, 2006). Examples of such natural polymers include gelatin, collagen, chitosan and starch (Yuryev *et al*, 2004). The ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogel beads forms the basis of ionotropic gelation. Hydrogel microbeads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The cations diffuse into the drug-loaded polymeric drops, forming a three-dimensional lattice of ionically crosslinked moiety (Patil *et al*, 2012). Many natural polyelectrolytes such as starch contain certain anions/cations on their chemical structure. A meshwork structure is formed by combination of these anions/cations with the counter ions; thus inducing gelation by cross linking. Apart from the coating property on the drug core, these natural polymers also acts as release rate retardant.

The undesirable properties of starch such as poor mechanical strength, high water solubility, can be improved by modification as well as by blending with other polymers. Physical modification of starch granules such as the pregelatinization method is relatively easy, cheap, safe and high-yielding. Furthermore, the use of pregelatinized starch in the development of microbead formulations is a good choice since they readily form paste even without heat (Majzoobi *et al*, 2011).

Theophylline, one of the most prescribed drugs for the management of bronchial asthma, is rapidly absorbed after oral administration in solutions. Theophylline has a half-life of about 8 hours. However, its immediate-release dosage forms are associated with quite a number of side effects. This makes sustained release formulations a more desirable option to conventional tablets.

In this study, microbeads of theophylline were prepared using pregelatinized starch obtained from the indigenous food crop, breadfruit (*Artocarpus altilis*), family, Moraceae, in different blend combinations with sodium alginate at different concentrations and polymer: drug ratios. The Box-Behnken design was employed for optimization of theophylline microspheres and this involved 3 independent variables (polymer type, polymer:drug ratio and concentration of calcium chloride, the chelating agent) and 2 dependent variables that determine the release properties of the microspheres (entrapment efficiency and dissolution time). Box-Behnken design was chosen for this study as it generates fewer runs with independent variables (Myers and Montgomery 2002; Hao *et al*, 2011).

METHODOLOGY

Materials

Breadfruit was bought from a local market in Owerri, Imo State (latitude of 5.476310, and longitude of 7.025853). The materials used in this study include: theophylline (Wuhan Hezhong Bio-Chemical Manufacture Co., Ltd. China), sodium alginate (S.D. Fine Chem Mumbai, India), calcium chloride (Loba Chemie Pvt. Ltd., Mumbai, India) All other chemicals used were of analytical grade.

Extraction of Starch.

Mature breadfruits (2 kg) were washed, peeled, cut into small pieces and then soaked in distilled water (10 Litres) at room temperature (27±2^{o}C). The mixture was blended (Panasonic MX-AC400 mixer grinder, MX-AC400, India) to obtain a slurry that was strained through a muslin cloth. The filtrate was suspended in distilled water to enable settling. The supernatant was decanted at 12-hour intervals and the starch slurry re-suspended in distilled water. The starch cake was collected after 72 hours and dried in a hot air oven at 50 °C for 48 hours. The dried mass was pulverized and then screened through a sieve of size 250 µm (Okunlola and Ghomorrai, 2017).

Modification of starch by pregelatinization.

Aqueous slurry of the dry native starch powder was prepared with 100 g of starch powder dispersed in 500 ml of distilled water and then heated at 70°C with constant stirring for 30 minutes. The resulting paste was dried in hot air oven at 50°C for 48 hours and blended into powder (Okunlola and Adewusi, 2019).

Characterization of starches

Morphology

The native and modified breadfruit starches were examined using an optical microscope (Olympus Optical Co, Japan). The size and shape of starch granules were observed.

X-ray Diffraction (XRD) Analysis

The XRD patterns of the starches were recorded using an X-ray diffractometer (ARL X'TRA ThermoFisher Scientific, Landsmeer, The Netherlands) with copper-cobalt radiation. The scanning region of the diffraction angle (2^{0}) was from 5^{o} to 70^{o} at a scan rate of 12^{o}/min.

Formulation of starch-alginate microbeads of theophylline using pregelatinized breadfruit starch as a copolymer

Preformulation studies

Formulation trials of theophylline microbeads containing pregelatinized breadfruit starch were carried out by varying the ratio of the pregelatinized breadfruit starch to sodium alginate, ratio of total polymer to drug, stirring speeds, amount of cross-linking agent and curing times. Final formulations selected were prepared as described below:

Preparation of theophylline microbeads using the ionic gelation method

A 2%w/w aqueous solution of a blend of sodium alginate and pregelatinized breadfruit starch (1g each) in 100 mL distilled water was prepared and mixed thoroughly to produce a homogeneous mixture. Two grams of theophylline was added to the alginate-starch polymer blend (i.e. polymer: drug = 1:1) and stirred continuously for 20 minutes using a magnetic stirrer at to achieve homogeneity. The drug-loaded polymer solution was manually extruded into 200 ml of calcium chloride (5.0 %w/v) inside a 500-mL beaker using a syringe with needle size 21G. This was done under constant stirring (500 rpm) at room temperature (27±2°C). After 15 minutes, the formed microbeads were collected and washed with distilled water to remove the excess calcium ions and then dried overnight at 40°C. The composition of the prepared formulations was varied changing the ratio of starch: alginate (2:1, 0:2) and polymer: drug (2:1, 3:1) as well as the cross-linking agent (7.50, 10.0%w/v)

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Characterization of microbeads.

Microencapsulation yield

The microencapsulation yield was determined by the ratio of the dry weight of the microbeads to the total amount of solid materials used in the preparation of microbeads.

Morphology

The morphology and surface characteristics of the microbeads were observed using a scanning electron microscope (Hitachi Model S-2460N Taichung, Taiwan) at an accelerating voltage of 25 kV. All samples were super coated with Au/Pd prior to examination.

Fourier Transform Infrared (FT-IR) analysis

The drug, pregelatinized starch, alginate and drug-loaded starch-alginate microbeads were analyzed by FT-IR (FT-IR Spectrum BX II MA, USA) in transmission mode. Pellets of the samples were prepared by grinding the sample with KBr under a hydraulic pressure of 600 dynes/m^2. The spectra were scanned between 4000 to 400 cm^{-1} (32 scans with resolution of 8 cm^{-1}).

Entrapment efficiency

Drug - loaded microspheres (50 mg) were accurately weighed, crushed and suspended in 100 ml of phosphate buffer pH 6.8. After 24 hours, the solution was filtered and the filtrate was appropriately diluted with the buffer and analyzed using UV/VIS spectrophotometer (Spectrum lab 752s UV-VIS spectrophotometer China) at 270 nm. The drug entrapment efficiency (E) was calculated as the percentage of actual drug content in microbeads sample to the theoretical content of drug in microbeads sample.

Drug release study

Drug - loaded microspheres (containing 100 mg of theophylline) were accurately weighed and suspended into 900 mL of phosphate buffer pH 6.8. The *in vitro* dissolution studies were carried out using the paddle method (USP XXXVI), rotated at 50 rpm in 900 mL of phosphate buffer pH 6.8, maintained at 37 ± 0.5˚C. Ten milliliter-samples were withdrawn at time intervals and replaced with equal amounts of fresh medium. The amount of theophylline released at each time interval was determined at wavelength of 270 nm, using a UV Spectrophotometer (Spectrumlab 752s UV-VIS spectrophotometer, China).

Experimental design

Box-Behnken design was employed for constructing polynomial models for optimization of theophylline microbeads using the Minitab Statistical Software package (MINITAB 16, USA). The design involved 3 independent and 2 dependent variables (Hao *et al*, 2011; Yasir and Sara, 2013). The effects of the processing variables (polymer type , X_1, polymer: drug ratio, X_2, concentration of calcium chloride, X_3) on the properties of the microbeads (entrapment efficiency and dissolution time, t_{50}) were evaluated using a 3 factor-3-level design. In addition to these, triplicate mid-level of variables, known as center points, were included in the study to improve the statistical significance The factorial Box-Behnken design constituted 15 of the experiments in this study. The software was also used to construct mathematical models for making response predictions for further experiments. The polynomial equation generated by the experimental design is as follows:

$Y = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3 + b_{12} X_1 X_2 + b_{13} X_1 X_3 + b_{23} X_2 X_3 + b_{11} X_1^2 + b_{22} X_2^2 + b_{33} X_3^2$ where Y is

the dependent variable; b_0 is the intercept; b_1 to b_{33} are the regression coefficients; and X_1, X_2 and X_3 are the independent variable that was selected from the preliminary experiments.

A checkpoint analysis was performed to confirm the role of the derived polynomial equations and contour plots in predicting the responses. Values of independent variables were taken at 3 points, one from each contour plot, and the theoretical values of entrapment efficiency and Q_{12} were calculated by substituting the values in the polynomial equation (Elsay *et al*, 2011).

Microbeads of theophylline were prepared experimentally at 3 checkpoints, and evaluated for the responses. After developing the polynomial equations for the responses, formulations were optimized to obtain microbeads that would yield a maximum value of entrapment efficiency with minimum value of Q_{12}.

RESULTS AND DISCUSSION

Characterization of starches

The yield of pregelatinized starch was 91.25%. The native starch had oval-shaped granules with mean size of 8.44 ± 4.00 µm. Modification by pregelatinization produced larger, irregular-shaped starch granules with mean size of 34.45 ± 6.70 µm (Okunlola & Adewusi, 2019).

The XRD spectra of the starches are shown in Fig. 1. In the spectra of XRD, the crystalline parts of native breadfruit starch showed sharp peaks, whereas the amorphous parts had dispersive peaks (Gernat *et al*, 1990). The main diffraction peaks were observed to be between 5 and 23° (2θ) angle. The XRD spectrum of the pregelatinized starch confirmed the disruption of the internal order of the native starch granules, resulting in a more amorphous polymer (Okunlola and Adewusi, 2019).

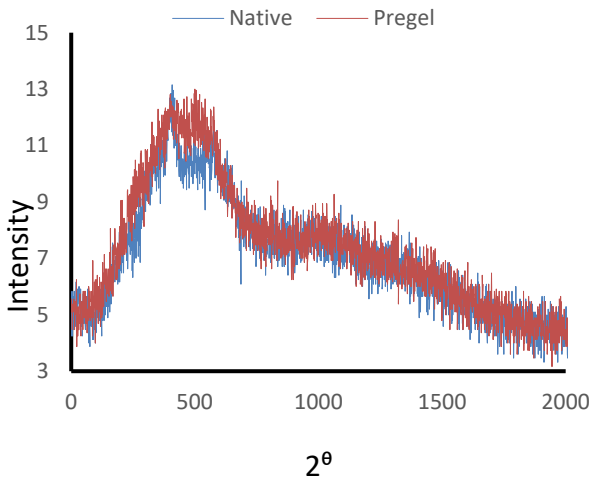

Fig. 1: XRD of native and pregelatinized breadfruit starches.

Characterization of theophylline microbeads containing pregelatinized breadfruit starch

Pregelatinized breadfruit starch was used as a carrier for the preparation of microbeads of theophylline, using the ionic gelation method. This ionic gelation technique was chosen because it is simple, reproducible and avoids the use of harmful organic solvents and high shear during the preparation of the microbeads (Rodrigues *et al*, 2012). Fig. 2a shows SEM images of the microbeads containing a blend of starch and alginate while Fig. 2b shows the SEM of microbeads containing alginate alone. The SEM images of the microbeads containing a blend of starch and alginate revealed a porous surface of the microbeads. Comparison of the morphology of the microbeads containing sodium alginate alone revealed that the surface of the carrier particles appeared to be more uniform and smoother. Most of the microbeads were observed to be mostly spherical, with a few being elongated. The size ranged from 0.96 ±0.09 to 1.37 ± 0.32 mm.

FT-IR studies were carried out to investigate the interaction between drug and the polymers and these are shown in Fig. 3. The FT-IR spectrum of theophylline when compared to that of the microbeads revealed that characteristic peak observed for pure drug remained unchanged, and no significant shift or reduction in the intensity of peak of theophylline was observed. From the results, it was concluded that there was no interaction with the polymer.

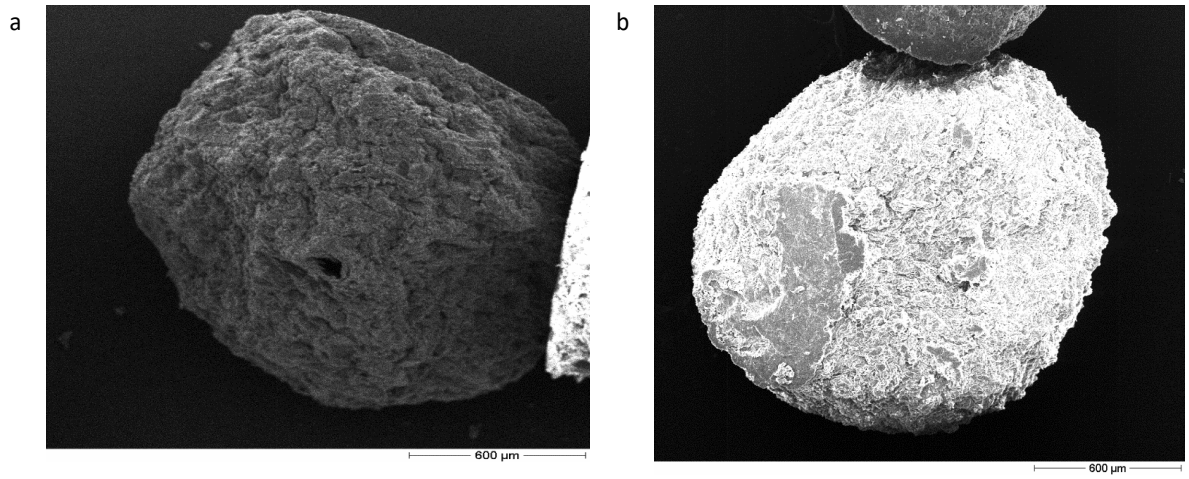

Fig. 2: SEM of Theophylline microbeads containing: a, pregelatinized breadfruit starch- alginate blend as polymer and b, sodium alginate alone

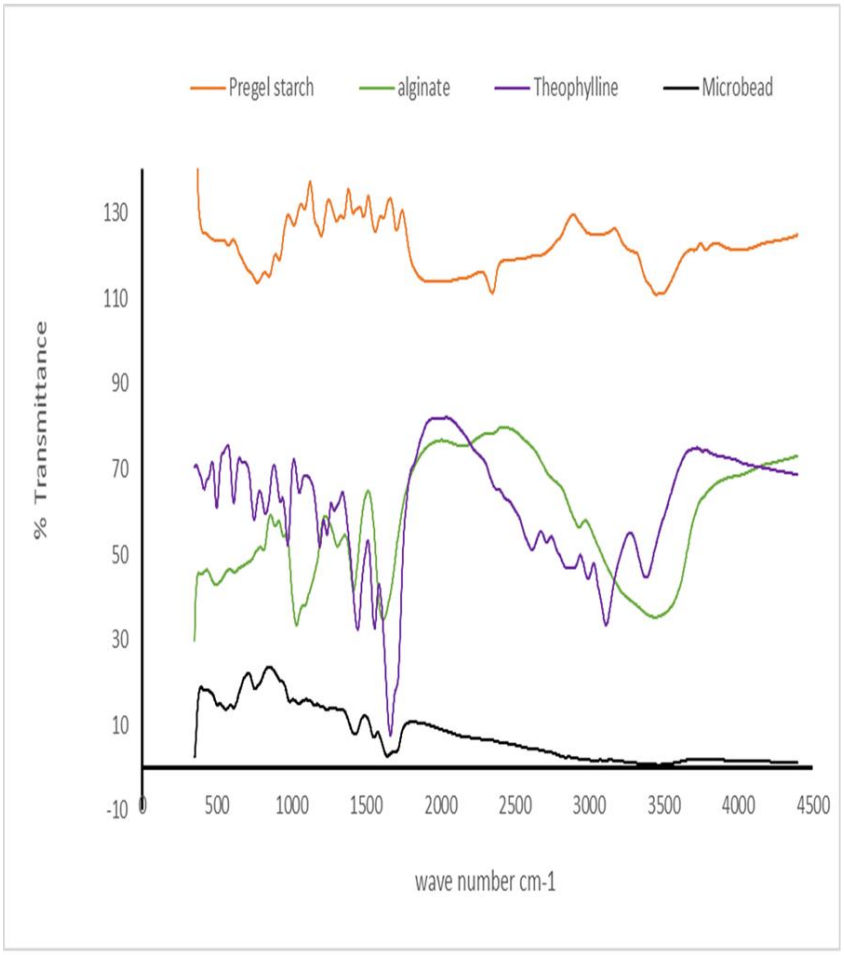

Fig. 3: FTIR spectra of Pregelatinized breadfruit starch, sodium alginate, theophylline and starch-alginate based microbeads of theophylline

Data analysis

The Box-Behnken experimental design was used in the study and the variables and their levels are presented in Table 1. The observed and predicted values with the residuals and percent error of responses are presented in Table 2.

Table 1: The variables and levels in Box-Behnken Design

Independent variables	Levels		
	Low	Medium	High
X_1 = polymer type (starch: alginate)	0:2	1:1	2:1
X_2 = polymer : drug ratio	1:1	2:1	3:1
X_3 = concentration of calcium chloride %w/v	5.0	7.5	10.0
Transformed values	-1	0	+1
Dependent values:			
Y_1 = entrapment efficiency			
Y_2 = quantity of drug released in 12 h (Q_{12})			

Table 2: Box-Behnken Experimental Design with measured responses

Batch	X_1	X_2	X_3	Y_1				Y_2			
				Observed entrapment efficiency %	Predicted entrapment efficiency %	Residuals	% Error	Observed Q_{12} %	Predicted Q_{12} %	Residuals	% Error
1.	-1	0	-1	38.00	33.12	4.88	12.84	73.94	74.24	-0.30	-0.41
2.	0	0	0	55.00	56.00	-1.00	-1.82	43.30	43.33	-0.03	-0.07
3.	0	1	-1	48.00	52.63	-4.63	-9.65	48.00	42.93	5.07	10.56
4.	0	0	0	57.00	56.00	1.00	1.75	44.00	43.43	0.57	1.30
5.	0	-1	-1	52.00	55.37	-3.37	-6.48	60.00	62.99	-2.99	-4.98
6.	-1	-1	0	35.00	36.50	-1.50	-4.29	88.00	84.71	3.29	3.74
7.	0	0	0	56.00	56.00	0.00	0.00	43.00	43.43	-0.43	-1.00
8.	-1	1	0	40.00	40.25	-0.25	-0.63	60.00	64.77	-4.77	-7.95
9.	1	1	0	65.00	63.50	1.50	2.31	38.75	42.03	-3.28	-8.46
10.	1	-1	0	60.00	59.75	0.25	0.42	50.00	45.23	4.77	9.54
11.	0	1	1	71.00	67.63	3.37	4.75	49.00	46.03	2.97	6.06
12.	0	-1	1	62.00	57.38	4.62	7.45	44.00	49.07	-5.07	-11.52
13.	-1	0	1	45.00	48.13	-3.13	-6.96	69.25	67.47	1.78	2.57
14.	1	0	-1	66.00	62.88	3.12	4.73	40.00	41.78	-1.78	-4.45
15.	1	0	1	60.00	64.88	-4.88	-8.13	38.00	37.70	0.30	0.79

**Q_{12} = quantity of drug released in 12 h*

Fifteen batches of theophylline microbeads were formulated and these were evaluated for entrapment efficiency and quantity released in 12 h. High entrapment efficiency values (≥ 50%) were found in Batches 2 ,4 , 5, 7, 9, 10, 11, 12, 14 and 15. Low values of quantity of drug released within 12 h ($Q_{12} \leq 50\%$), implying prolonged dissolution, were observed in Batches 2, 3, 4, 7, 9, 10, 11, 12, 14 and 15.

The dependent variables that were obtained at 3 levels of the independent variables were subjected to multiple regression to obtain second order polynomial equations (Zidan *et al*, 2007).:

Entrapment efficiency = $56.000 + 11.625X_1 + 1.8750X_2 + 4.250X_3 - 0.000X_1X_2 - 3.25X_1X_3 + 3.25X_2X_3 - 6.000\ X_1^2 + 0.000X_2^2 + 2.250X_3^2$ (1)

$Q_{12} = 43.430 - 15.550X_1 - 5.7813X_2 - 2.7113X_3 + 4.1875X_1X_2 + 0.6725X_1X_3 + 4.25X_2X_3 + 10.4008X_1^2 + 5.3533\ X_2^2 + 1.\ 7813X_2X_3^2$ (2)

The values of the correlation coefficient (r^2) of equations 1 and 2 were 0.9150 and 0.9528, respectively, indicating good fit. The values of entrapment efficiency measured for the batches showed a range between 35 and 71 %; this response is influenced by the three variables, X_1, X_2 and X_3. The positive values of all the three variables implies that increase from low to high level resulted in an increase in entrapment efficiency. Based on the magnitude of the values of the independent coefficient of the terms, the

ratio of starch: alginate, X_1, had the most significant influence on entrapment efficiency (p = 0.002). The entrapment efficiency obtained when the starch: alginate ratio was at low level was less than the value at high level. This is because higher amount of starch increased viscosity of the polymer-drug blend which in turn delayed the drug diffusion within the polymer droplets (Bodmeier and McGinity, 1988, Dhakar *et al*, 2010). Furthermore, when highly concentrated, the polymer precipitated faster on the surface of the dispersed phase and prevented drug diffusion across the boundary of the microbeads (Rafati *et al*, 1997). On the other hand, the values of the coefficients for interactive effects of the variables were negative for X_1X_2 and X_1X_3 but positive for X_2X_3. This implies that as the levels changed from low to high, the interaction between X_1 and X_2 as well as between X_1 and X_3 produced a decrease in the entrapment while interaction between X_2 and X_3 resulted in an increase. The ranking of the coefficients for the interactive effects was $X_1X_3 = X_2X_3 > X_1X_2$ with p values > 0.05, suggesting that the interaction between these variables were insignificant in predicting entrapment efficiency.

The quantity of drug released in 12 h (Q_{12}) from the theophylline microspheres was found to be in the range of 38 to 88 %. The negative value of variables X_1, X_2 and X_3 implies that increase from low to high level results in a decrease in Q_{12}, showing sustained release, a favorable effect. X_1 had the most significant influence (p = 0.0001). Increase in starch: alginate ratio enhanced the viscosity of the polymer solution which resulted in decrease in rate of drug release from the microbeads. On the other hand, the positive values of the coefficients of interaction for all the variables imply that increase from low to high level resulted in an increase in Q_{12}.

The analysis of variance (ANOVA) was applied and the results are presented in Table 3. The values of p > F < 0.05 indicate that the model terms were significant. The relationship between the dependent and independent variables was further established by constructing contour and response surface plots which are presented in Fig. 4. Fig. 4 a, b and c show the effects of X_1 and X_2, X_1 and X_3, X_2 and X_3, respectively on entrapment efficiency while Fig. 4 d, e and f show the effect of X_1 and X_2, X1 and X_3 and X_2 and X_3, respectively on Q_{12}. From the plots it was observed that high levels of X_1 and X_2 and medium level of level of X_3 favored high entrapment and low Q_{12}, both desirable effects.

Table 3: Results of ANOVA for entrapment efficiency and Q_{12}

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	9	1498.75	1498.75	166.53	5.98	0.032
Linear	3	1253.75	1253.75	417.92	15.01	0.006
X1	1	1081.13	1081.13	1081.13	38.82	0.002
X2	1	28.13	28.13	28.13	1.01	0.361
X3	1	144.50	144.50	144.50	5.19	0.072
Square	3	160.50	160.50	53.50	1.92	0.244
X1*X1	1	141.70	132.92	132.92	4.77	0.081
X2*X2	1	0.11	0.00	0.00	0.00	1.000
X3*X3	1	18.69	18.69	18.69	0.67	0.450
Interaction	3	84.50	84.50	28.17	1.01	0.461
X1*X2	1	0.00	0.00	0.00	0.00	1.000
X1*X3	1	42.25	42.25	42.25	1.52	0.273
X2*X3	1	42.25	42.25	42.25	1.52	0.273
Residual Error	5	139.25	139.25	27.85		
Lack-of-fit	3	137.25	137.25	45.75	45.75	0.021
Pure Error	2	2.00	2.00	1.00		
Total	14	1638.00				
Regression	9	2882.91	2882.91	320.32	11.16	0.008
Linear	3	2261.85	2261.85	753.92	26.26	0.002
X1	1	1935.66	1935.66	1935.66	67.41	0.000
X2	1	267.38	267.38	267.38	9.31	0.028
X3	1	58.81	58.81	58.81	2.05	0.212
Square	3	476.86	476.86	158.95	5.54	0.048
X1*X1	1	366.93	399.42	399.42	13.91	0.014
X2*X2	1	102.02	105.81	105.81	3.68	0.113
X3*X3	1	7.91	7.91	7.91	0.28	0.622
Interaction	3	144.20	144.20	48.07	1.67	0.286
X1*X2	1	70.14	70.14	70.14	2.44	0.`176
X1*X3	1	1.81	1.81	1.81	0.06	0.812
X2*X3	1	72.25	72.25	72.25	2.52	0.174
Residual Error	5	143.58	143.58	28.72		
Lack-of-fit	3	143.05	143.05	47.68	181.68	0.005
Pure Error	2	0.53	0.53	0.26		
Total	14	3026.49				

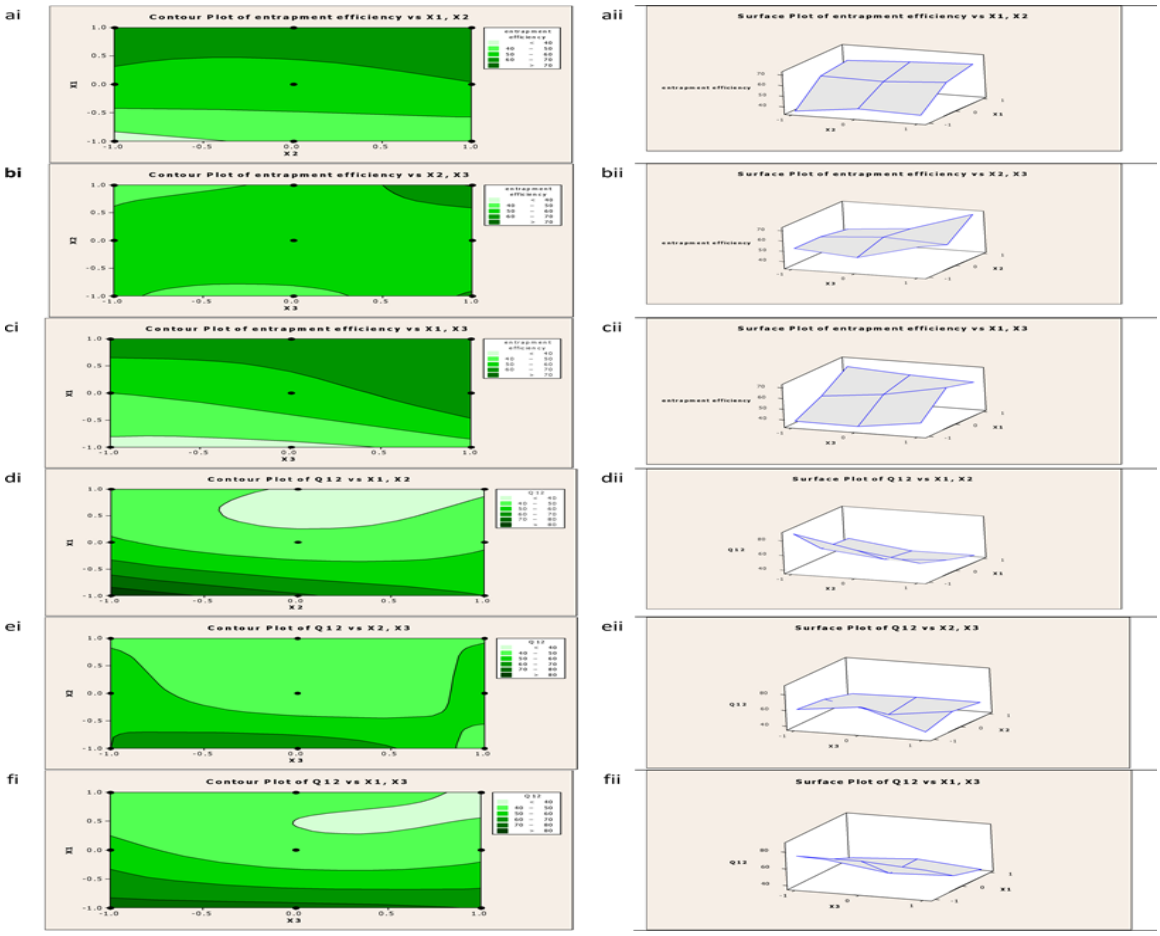

Fig. 4: Response and contour plots showing entrapment efficiency vs X1X2 (ai, aii), X2X3 (bi,bii),X1X3 (ci, cii) and Q12 vs, X1X2 (di,dii), X2X3 (ei,eii) and X2X3 (fi, fii)

The optimum formulation was that which gave a high value of entrapment efficiency but a low value of Q_{12}. Hence, the high level of X_1 and X_2 with the medium level of X_3 (Formulation 9) were selected as optimum. This formulation gave the desired properties of a good entrapment efficiency of 65% with sustained release of 38.75% in 12 hours.

Three checkpoint batches were prepared and evaluated for entrapment efficiency and Q_{12} (Table 4). The differences between the observed and predicted values were generally insignificant, thereby confirming the validity of the mathematical models for predicting the entrapment efficiency and Q_{12}.

Table 4: Checkpoint batches with their predicted and observed values of entrapment efficiency and Q_{12}

Batch code	X_1	X_2	X_3	Entrapment efficiency		Q_{12}	
				Observed	Predicted	Observed	Predicted
C_1	1	1	0	64.00	63.50	40.75	42.03
C_2	1	0	1	65.00	64.88	38.00	37.70
C_3	0	1	1	68.00	67.63	45.50	46.03

CONCLUSION

Microbead formulations of theophylline were successfully prepared using the ionic gelation method. Increase in pregelatinized breadfruit starch content of the polymer blend enhanced entrapment efficiency while reducing quantity of drug released. The Box-Behnken design was effective in predicting the values of independent variables that had significant influence

on preparation of optimized formulations of theophylline microbeads with desired properties. Pregelatinized starch was found to be a suitable polymer in the formulation of microbeads.

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