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Formulation Design and Optimization of Theophylline Microspheres Containing Akidi Beans (*Vigna Unguiculate*) Starch as Polymer Using Central Composite Design

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The aim of the study was to use central composite design in formulating theophylline microspheres containing Akidi beans (*Vigna unguiculata* L Warp) starch as a controlled-release polymer. Theophylline microspheres containing pregelatinized Akidi beans starch, alginate and chitosan were prepared using ionic gelation. A 2 factor, 2 Level central composite design was used with starch:alginate ratio (X_1) and polymer:drug ratio (X_2) as variables, and size, entrapment efficiency and quantity of drug released in 12 h, Q_{12}, as responses. Regression parameters and response surface plots were generated. The microspheres were spherical with size 1.68 00 ± 0.12 – 1.95 ± 0.03 mm. Optimized formulation containing 4:1 Akidi starch: alginate and 3:1 polymer: drug ratios, prepared according to levels determined by Minitab software using desirability function, showed significant increase in the responses in comparison to those containing alginate alone. Akidi beans starch demonstrated good potential as an alternative polymer for the controlled delivery of drugs.

Key words: Akidi beans starch, central composite design, controlled release, desirability function, sodium alginate, theophylline microspheres

INTRODUCTION

Efforts have been made to discover and develop starches from botanical sources different from the established official ones [1-3]. Akidi beans (*Vigna unguiculata* L Warp), family Fabaceae is an indigenous food crop with high starch content (60.57 % w/w on a dry weight basis) which makes it a cheaper source of starch that can be explored in the pharmaceutical industry as an alternative to imported polymers [4,5]. Akidi beans plant flourishes in hot and arid climates, with Nigeria and the Republic of Niger producing over 50% of the world's supply of the legume [4]. Modification of the starch by pregelatinization significantly improves swelling and viscosity, further enhancing its potential as a polymer in drug formulations. Oral theophylline has been one of the most prescribed drugs for the effective treatment of bronchial asthma for 70 years [6]. However, one of the problems associated with theophylline usage is its rapid and complete absorption after oral administration in solution or in immediate release solid oral dosage form. Furthermore, its high incidence of side effects has been a challenge. Inhaled theophylline has not been successful due to the lack of retention in the airways and irritation [6]. Hence a good approach to prolong its release, reduce the frequency of administration and the incidence of side effects, is to formulate theophylline in microspheres for oral delivery in a sustained release manner. The efficient carrying-capacity of microspheres make them valuable as controlled drug delivery systems and their drug release behaviour is often related to their polymer type [7-8].

Theophylline microspheres have been designed in previous studies [9-10]. In one of such studies, Sahoo and coworkers prepared theophylline microspheres with cellulose acetate using emulsion solvent evaporation technique [10]. The microspheres were free-flowing, spherical, with high entrapment and suitable controlled release of theophylline was obtained at drug: polymer ratio of 1:3.

Both sodium alginate and chitosan are well established natural polymers that are also

biodegradable and biocompatible [11]. The cross-linking of starch with alginate and chitosan in a hydrogel can be used to provide sustained release of the drug in which the resulting systems have enhanced stability compared to those obtained with a single polymer [12].

Several optimization studies have been carried out to determine the significant parameters required to develop some microsphere formulations [13-14]. The central composite design (CCD) with response surface methodology (RSM), principally consists of factorial, axial and centre points that provide complete knowledge of dependent variables with minimum experiments [15-16]. The adequacy and significance of the model can be justified by analysis of variance (ANOVA). The optimization of the Akidi beans starch-based microspheres of theophylline in order to determine the desired qualities in the design of this formulation is essential.

The aim of this research was to prepare microspheres of theophylline using pregelatinized starch obtained from Akidi in beans (white variety) different blend combinations with sodium alginate with a fixed amount of chitosan, at various polymer: drug ratios. The investigation was designed to prepare controlled release microspheres of theophylline using the ionic gelation method. The microspheres of combined polymers were designed according to 2^2 factorial central composite design (CCD), taking starch: alginate and polymer: drug ratios as the independent variables. A total of thirteen batches were prepared. The dependent variables were size, entrapment efficiency and quantity of drug released in 12 h (Q_{12}). Desirability function analysis was then applied to determine optimal formulation parameters for the formulation of theophylline microspheres.

EXPERIMENTAL

Materials

Akidi beans were purchased from a local market in Owerri, Imo State. Theophylline was obtained from Wuhan Hezhong Bio-Chemical Manufacture Co., Ltd., Wuhan, China. Sodium alginate was obtained from S.D. Fine Chem, Mumbia, India while Chitosan was obtained from Sigma-Aldrich Chemie, St Louis, MO, USA. Acetone, light liquid paraffin and isopropyl alcohol were obtained from BDH Chemicals, Poole, England.

Methods

Extraction and pregelatinization of Akidi starch

Akidi beans starch was extracted using a previously reported method [17]. To obtain pregelatinized Akidi beans starch, an aqueous slurry was prepared by dispersing 200 g of native starch in 1 L of distilled water and heated at 80 °C with stirring for 45 minutes. The resulting paste was dried in hot air oven at 50 °C for 48 hours.

Solid state characterization of pregelatinized Akidi beans starches

The X-ray diffraction (XRD) pattern of the starch powder was obtained using wide-angle X-ray diffraction (ARL X'TRA ThermoFisher Scientific, Landsmeer, The Netherlands), with copper- cobalt radiation (λ = 1.540562 Å) at 40 kV and 150 mA at 25 °C. The scan steps size of 0.030 were used with a dwell time of 0.150 s. The scanning region of the diffraction angle (2^{θ}) was from 5° to 70° at a scanning speed of 12 °/min. Thermal characteristics of the starch were studied using a differential scanning calorimeter, DSC **(**DSC 2 Mettler Toledo, Colombus OH, USA) heated from 60 to 300 °C at a heating rate of 10 °C /min.

Thermal transitions were characterized by onset temperature of gelatinization (T_o), peak temperature (T_p), gelatinization temperature (T_c) and the gelatinization enthalpy (ΔH). Fourier Transform Infrared (FT-IR) spectroscopy studies were carried out using FT-IR Spectrum BX II (Perkin Elmer, Waltham, MA, USA) recorded from 4000 to 400 cm^{-1} using 64 scans with resolution of 8 cm^{-1}.

Micromeritic properties of pregelatinized Akidi beans starches

The size of the starch granules was determined using a light microscope (Olympus Research microscope CH20i, Olympus Optical Co, Shinjuku, Japan). The shape of the starch granules was analysed using a scanning electron microscope (Phenom Prox, Phenomworld, Eindhoven, The Netherlands). Images of samples were taken at 15.0 kV accelerating voltage and magnification of 500.

The bulk and tapped densities of starch were determined as previously reported [3]. The solvent pycnometer method was used to determine the density of the starches using xylene as the non-solvent. The flow property of the starch was determined by calculating the Hausner's ratio and Carr's index using the values of bulk and tapped densities.

pH determination

The pH value of a 1% w/v aqueous solution of pregelatinized Akidi starch was determined using a pH meter (Model 720 A, Thermo Electron Corporation, Waltham, MA, USA).

Solubility and swelling power

Fifty milliliters of a 2% w/w aqueous starch suspension was prepared and incubated in a water bath at a constant temperature of 75 °C for 30 min. Subsequently, the samples were cooled to room temperature and centrifuged at 3000 rpm for 20 min. The supernatant was dried in an oven at 50 °C, and the sediment weight and solid content of the supernatant were determined [18]. The percent solubility and swelling power were determined according to equations 1 and 2:

$$\text{Solubility (\%)} = \frac{X}{W} \times 100 \quad (1)$$

$$\text{Swelling power} = \frac{Ws \times 100}{W\,(100 - \text{Solubility \%})} \quad (2)$$

where *X* is the solid content of the supernatant; *W* is the dry weight of starch sample and Ws is the sediment weight.

Viscosity

The viscosity of a 2 %w/v slurry of native and pregelatinized starches was determined on a Brookfield rheometer (DV-III model, Brookfield Engineering, Middleborough, MA, USA) operated at 50 and 100 rpm using CPE 40.

Preparation of theophylline microspheres

A 2 %w/w aqueous slurry of polymer consisting of sodium alginate (1g) and pregelatinized Akidi beans starch (1g) blended in 100 ml of distilled water was prepared and mixed thoroughly to form a homogeneous mixture of starch: alginate (1:1). To the alginate-starch polymer blend, 2 g of theophylline was added with continuous stirring for 20 min using a magnetic stirrer to achieve a homogeneous polymer-drug blend (1:1). The drug-loaded polymer solution was manually extruded into 200 ml of a 10% w/v calcium chloride solution using a 10-ml syringe with a 21G needle. The calcium chloride solution contained chitosan (0.2% w/v solution in 1% v/v dilute acetic acid) and was maintained at room temperature (27±2 °C). After 15 min, the microspheres formed were collected, washed with distilled water and dried overnight at 40 °C. Other batches of theophylline microspheres were prepared by varying the composition of the formulations using starch: alginate ratios of 2:1, 3:1, 4:1 and alginate alone with polymer: drug ratios of 1:2., 2:1, 3:1; 4:1.

Characterization of theophylline microspheres

Microencapsulation yield

The microencapsulation yield was determined by the ratio of the dry weight of the microspheres that were obtained to the total weight of solid raw materials (drug and polymers) used in the preparation of the microspheres.

Morphology

The shape and surface characteristics of the microspheres were determined using a scanning electron microscope (Hitachi SU8030 FE-SEM, Tokyo, Japan) using the gold sputter technique

[17]. The working distance was 20 nm at a zero-degree tilt and an accelerating voltage of 15 kv.

Differential Scanning calorimetry (DSC) analysis

The DSC analysis of pregelatinized Akidi beans starch, sodium alginate, chitosan, pure drug and drug-loaded microbeads was carried out using a differential scanning calorimeter (DSC2, Mettler Toledo, Colombus, OH, USA) to evaluate any possible drug polymer interaction.

X-ray diffractometry

X-ray diffraction peaks were obtained using an X-ray diffractometer (ARL X'TRA, Thermo Fisher Scientific, Landsmeer, The Netherlands).

Swelling

The swelling properties of the drug loaded microspheres were determined in simulated gastric fluid. Thirty microspheres were placed in a small beaker to which 200 ml of acidic buffer solution was added and then stirred with a magnetic stirrer at a speed of 50 rpm. After 1 hour, the swollen microspheres were observed and measured by optical microscopy. The magnitude of swelling was presented by the ratio of the mean diameter of swelling microspheres to the mean diameter of the dried microspheres before the test.

Entrapment efficiency

Accurately weighed amount of drug-loaded microspheres (50 mg) were crushed and suspended in 100 ml of phosphate buffer pH 6.8. After 24 hours, the solution was stirred for 15 min and filtered. The filtrate was appropriately diluted with the buffer and analyzed using a UV/VIS spectrophotometer (Spectrum Lab 752s, Changsha Hunan, China) at 270 nm. The drug entrapment efficiency (E) was determined according to equation 3:

$$E(\%) = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad (3)$$

Drug release study

The amount of microspheres containing 50 mg of theophylline were accurately weighed and suspended in 900 ml of phosphate buffer (pH 6.8) maintained at 37 ± 0.5˚C. The *in vitro* dissolution studies were carried out using the basket method, rotated at 50 rpm. Ten millilitres of dissolution medium were withdrawn at time intervals and replaced with equal amounts of fresh medium. The amount of theophylline released at each time interval was determined in triplicate at 270 nm, using a UV spectrophotometer (Spectrum lab 752s, Changsha Hunan, China).

Experimental design

The experimental design was carried out using Minitab statistical software (Minitab 16, USA). A 2 factor, 2 Level central composite design was done with starch:alginate ratio (X_1) and polymer:drug ratio (X_2), as variables and size, entrapment efficiency and quantity of drug released in 12 h (Q_{12}) as responses. The quadratic model was obtained for the responses. Multiple regression analysis was used to correlate the responses with the two variables studied using a second order polynomial equation. The quadratic regression model for the responses is represented by equation 4:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 \quad (4)$$

where Y is the level of the measured response, β_0 is the intercept, β_1 to β_5 are the regression coefficients, X_1 and X_2 refer to the main effects while X_1^2 and X_2^2 are the quadratic terms of the independent variables. Optimization of theophylline formulations was carried out by numerical optimization technique using the desirability function approach. This is a useful method for optimizing multiple response problems [19]. The estimated response was transformed into desirability (d), a scale-free value between 0 and 1, which increases as the corresponding response value becomes more desirable [20, 21]. D, the overall desirability, is obtained by combining the individual desirability values and also varies between 0 and 1. A desirability value approaching 1 is desired in order to determine the optimal setting.

RESULTS AND DISCUSSION

Characterization of pregelatinized Akidi beans starch

The XRD, DSC and FTIR spectra of the starch are presented in figures 1a, 1b and 1c, respectively. The XRD spectrum showed the amorphous granule structure of the pregelatinized starch, confirming the disruption of the internal order of the starch granules. DSC results showed endothermic peaks with the onset, peak and conclusion temperatures and enthalpy for the starch found to be 59.86 °C, 134.34 °C, 300.02 °C and 1986.25 J/g respectively. The FTIR spectrum showed four peaks at 3300, 1610, 1350 and 1000 cm^{-1}, corresponding to O–H stretching vibration, bound water, bending vibrational modes of O C-H, C C-H, and C-O-H as well as strong absorption peaks assigned to C-C and C-O stretching modes, respectively.

The SEM image (figure 2) revealed that the granules of pregelatinized Akidi beans starch were irregular in shape with size of 11.50±1.41µm. The micromeritic and material properties of the starch are presented in Table 1. The value of Carr's index and Hausner's ratio (obtained from bulk and tapped densities) revealed good flowability of pregelatinized Akidi beans starch [22]. The starch is acidic with good swelling power and solubility of < 10%. The results also revealed that as the shear speed increased from 50 to 100 rpm, the viscosity of the modified starch increased significantly.

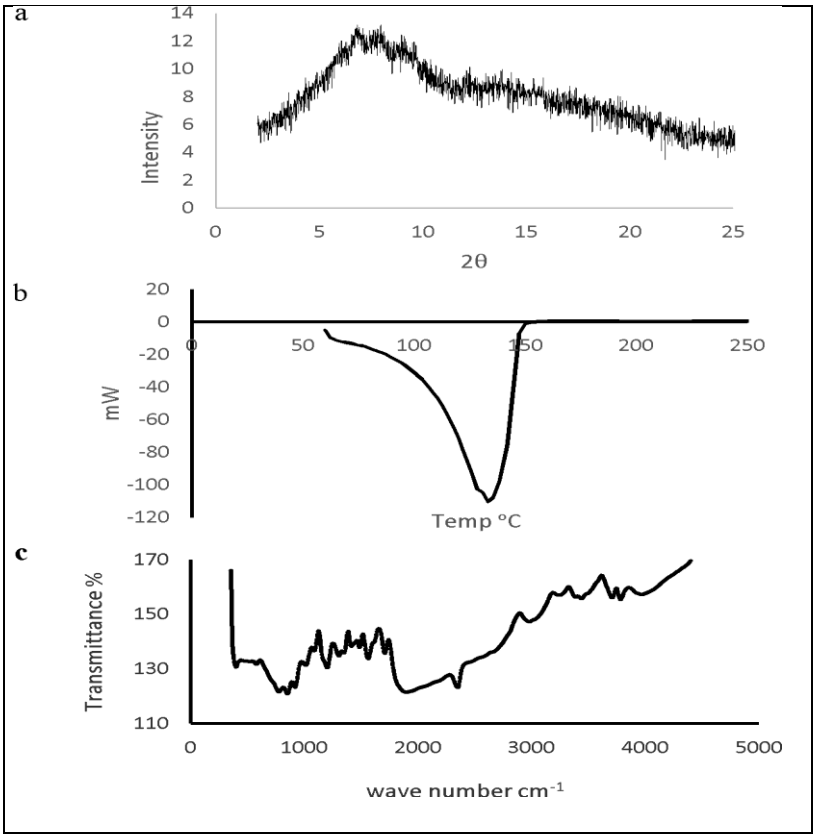

Figure 1: (a), Xray Diffraction (XRD), (b), Differential Scanning Calorimetry and (c), Fourier Transform Infrared (FTIR) spectra of pregelatinized Akidi beans starch

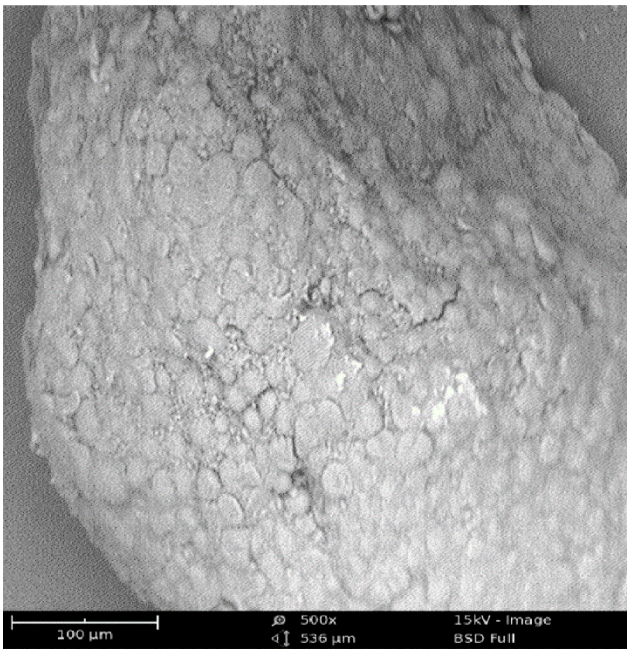

Figure 2: Scanning electron micrographs (SEM) of pregelatinized Akidi beans starch.

Table 1: Micromeritic and material properties of pregelatinized Akidi beans starch

Property	Value
Particle size µm	11.50±1.41
Particle density gcm^{-3}	1.49 ± 0.01
Bulk density gcm^{-3}	0.71±0.04
Tapped density gcm^{-3}	0.91±0.02
Carr's index %	22.00 ± 0.02
Hausner's ratio	1.28±0.00
pH	3.84 ± 0.01
Swelling power	12.64 ± 1.40
Solubility %	8.84± 0.11
Viscosity at 50 rpm cp	0.65± 0.10
Viscosity at 100 rpm cp	2.25± 0.40

Characterization of theophylline microspheres

In this study, theophylline microspheres were prepared without organic solvents. Polymer blend-drug mixtures were extruded drop-wise into calcium chloride solution containing chitosan. The alginate formed a polymeric backbone that aided the formulation of the microspheres [23].

The yield of the microspheres was within the range of 89.00 ± 3.00 to 97.55 ± 1.50 %, indicating that only low amounts of feed materials were lost during the formulation procedure. The SEM image of theophylline microspheres is shown in Fig. 3. Theophylline-loaded microspheres were near spherical with diameter ranging from 1.68 ± 0.13 to 1.95 ± 0.05 mm. The size increased with starch: alginate and polymer: drug ratio. The presence of greater amount of starch and total polymer produced dispersions of higher viscosity, forming larger droplets that contributed to the increased size of the microspheres.

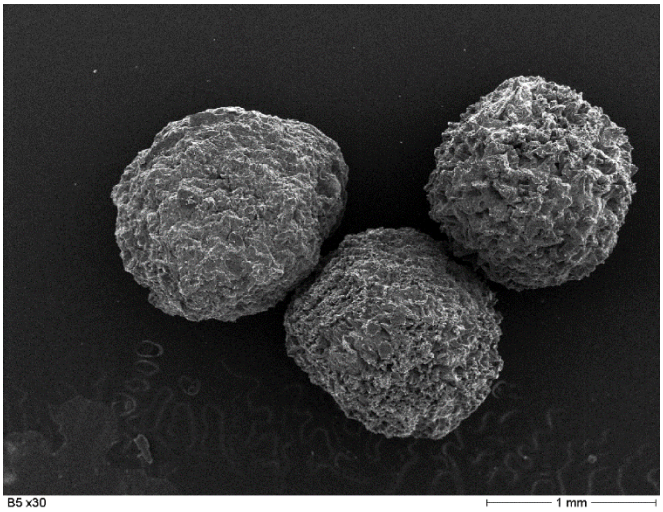

Figure 3: Scanning electron micrographs (SEM) of theophylline microspheres containing Akidi beans starch.

The XRD and DSC spectra of sodium alginate, chitosan, starch, theophylline and the theophylline microspheres are shown in Fig. 4. The X-ray diffraction (XRD) spectra of (i) pregelatinized Akidi beans starch, chitosan, sodium alginate and (ii) theophylline and theophylline microspheres are presented in Fig. 4(a) and Differential Scanning Calorimetry (DSC) of (i) pregelatinized Akidi beans starch, chitosan, (ii) sodium alginate, theophylline and theophylline microspheres are presented in Fig 4 (b). Theophylline showed the typical diffractogram of the crystalline drug. The X-ray diffraction profile of the three polymers indicated their presence as more amorphous than crystalline materials. XRD patterns showed that

the amorphous polymeric network did not alter the integrity of theophylline dispersed in the microspheres and confirmed the results obtained from DSC analysis. The DSC thermogram of theophylline exhibited a sharp endothermic peak at 91.73 °C which did not appear in the DSC thermogram of the microspheres, indicating that the drug was uniformly dispersed at the molecular level within the microspheres.

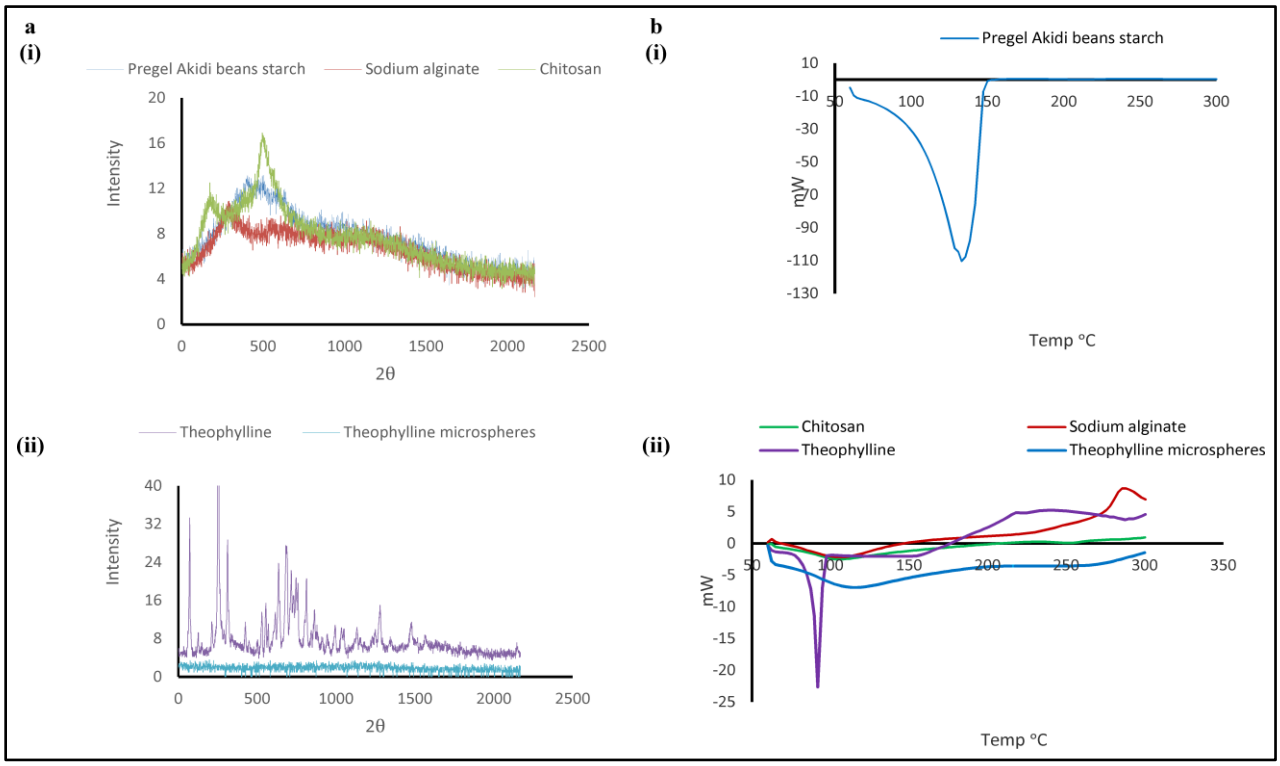

Figure 4: (a) X-ray diffraction (XRD) spectra of (i) pregelatinized Akidi beans starch, chitosan, sodium alginate, (ii) theophylline and theophylline microspheres, (b) Differential Scanning Calorimetry (DSC) of (i) pregelatinized Akidi beans starch, chitosan, (ii) sodium alginate, theophylline and theophylline microspheres

Drug entrapment for the microspheres was within the range of 41.00% ± 3.10 to 85.00% ± 6.16. Increasing the starch: alginate ratio and polymer: drug ratio enhanced entrapment efficiency probably owing to formation of a rigid network that restricted leaching of the drug molecules during their preparation [24]. The plots of percentage drug release versus time for the batches of theophylline microspheres are shown in figure 5. Drug dissolution was prolonged and Q_{12} values ranged from 40.00% ± 2.20 to 88.90% ± 4.35. The microspheres absorbed fluid in the dissolution medium and became noticeably swollen. Initial burst release was observed in some batches owing to initial release of drugs present on their surfaces, followed by diffusion.

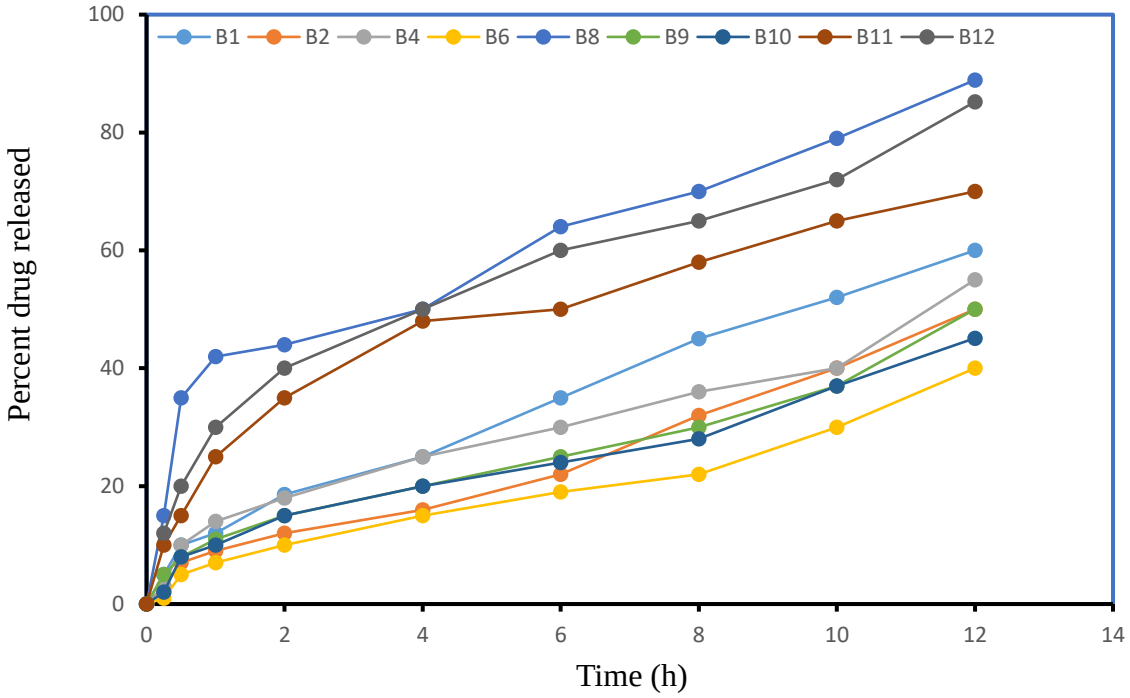

Figure 5: Dissolution profile of theophylline microspheres.

Experimental design

The quadratic model was selected by Minitab 16 software for the responses. Multiple regression analysis was used to correlate the responses of size, entrapment and Q_{12} with the two variables studied (starch: alginate and polymer: drug ratios) using a second order polynomial equation.

The quadratic regression models for size (Y_1), entrapment (Y_2) and Q_{12} (Y_3) can be represented by equations (5), (6) and (7), respectively. The values of the variables and codes of the formulations are presented in Table 2 while the responses are presented in Table 3.

$$Y_1 = 1.884 + 0.082X_1 + 0.044X_2 - 0.023X_1^2 - 0.006X_2^2 - 0.038X \quad (5)$$

$$Y_2 = 69.552 + 8.751X_1 + 4.563X_2 - 0.669X_1^2 - 1.707X_2^2 - 1.395X_1X_2 \quad (6)$$

$$Y_3 = 59.920 - 9.036\ X_1 - 12.064X_2 - 2.222X_1^2 + 2.828X_2^2 + 8.450\ X_1X_2 \quad (7)$$

Table 2: Formulation variables and codes for theophylline microspheres designed by 2 factorial central composite design

Variables	Code	Level of variable				
		-α	-1	0	+1	+α
Starch:alginate	X_1	0:2	1:1	2:1	3:1	4:1
Polymer:drug ratio	X_2	1:2	1:1	2:1	3:1	4:1

Table 3: Formulation code, variables and responses of theophylline microspheres

Formulation code	Coded variables		Independent variables		Responses		
	X_1	X_2	S:A ratio	P:D ratio	Size (mm)	Entrapment %	Q_{12} %
B_1	0	0	2:1	2:1	1.88	69.16	60.00
B_2	+1.414	0	4:1	4:1	1.95	85.00	50.00
B_3	0	0	2:1	2:1	1.89	70.00	60.00
B_4	0	+1.414	2:1	4:1	1.90	75.50	55.00
B_5	0	0	2:1	2:1	1.89	70.00	60.00
B_6	+1	+1	3:1	3:1	1.96	80.00	40.00
B_7	0	0	2:1	2:1	1.88	69.50	59.50
B_8	-1	-1	1:1	1:1	1.72	68.82	88.90
B_9	+1	-1	3:1	1:1	1.93	75.50	50.00
B_{10}	-1	+1	1:1	3:1	1.90	78.90	45.10
B_{11}	-1.414	0	0:2	2:1	1.68	41.00	70.00
B_{12}	0	-1.414	2:1	1:2	1.80	60.00	85.20
B_{13}	0	0	2:1	2:1	1.88	69.10	60.10

S:A = starch:alginate, P:D = polymer:drug

Effect of formulation variables on size (Y_1), entrapment (Y_2) and Q_{12} (Y_3)

The influence of starch:alginate ratio (X_1) and polymer:drug ratio (X_2) on size and entrapment were positive, indicating that increase from low to high level produced an increase in the responses. The values of individual coefficients on size and entrapment showed that starch:alginate ratio had greater influence ($p = 0.0001$) on the two response. However, the coefficient of interaction X_1X_2 was negative indicating an antagonistic effect that resulted in decrease in the drug size and drug entrapment efficiency. The coefficient values of X_1 and X_2 on quantity of drug released within 12 h (Q_{12}) were negative indicating the increase in the two variables gave microspheres with reduced amount of drug release or prolonged dissolution time. The values of the individual coefficients on Q_{12} showed that polymer:drug ratio had greater influence ($p = 0.0001$) on Q_{12}. The coefficient of interaction for Q_{12} was positive suggesting the two factors interacted synergistically to increase the quantity of drug released in 12 h.

The adequacy and significance of the model was justified by analysis of variance (ANOVA). Analysis of the data on effect of variables on size showed that the F value of this model was 17.27 ($p = 0.001$), suggesting that the overall model had significant capacity to explain variation in size of microspheres. The linear (effects of X_1 and X_2) and interaction effect (X_1X_2) were also significant ($F= 58.81$, 17.09 and 6.23, respectively). However, quadratic effects (effects of X_1^2 and X_2^2) were not significant. The R^2 value was 92.50 % implying that the model can determine 92.50 % variation in size. The analysis of variance of the regression model for entrapment indicated that the model was not significant, as obtained from the F-value 1.91 with p value of 0.211. While the linear effects of X_1 was significant ($F = 7.20$ with p-value 0.031), the linear effect of X_2, interaction effect (X_1X_2) as well as the quadratic effects of X_1^2 and X_2^2 were not significant. The R^2 value was 57.71%. ANOVA data for Q_{12} showed that the F-value of the model was 14.69 ($p = 0.001$), indicating a significant level. Linear effects of X_1 and X_2 were significant ($F = 21.74$ and 38.76, respectively) but quadratic effects of X_1^2 and X_2^2) were not. Interaction effect of X_1X_2 was also significant ($F = 9.51$, $p = 0.018$). The R^2 value was 91.30 %.

The response surface plots are shown in Fig. 6. The response surface plot in Fig. 6(a) revealed that the smallest size of (Y_1) was obtained when X_1 (starch:alginate) and X_2 (polymer:drug ratio)

levels were increased from microspheres 1:1 to 2:1. However, the size increased as the variables increased from 2:1 to 3:1. The surface plot (Fig. 6b) showed that highest entrapment (Y_2) was obtained when X_1 and X_2 levels were high. On the other hand, Fig. 6(c) revealed that smallest quantity of drug was released after 12 h when X_1 and X_2 levels were high.

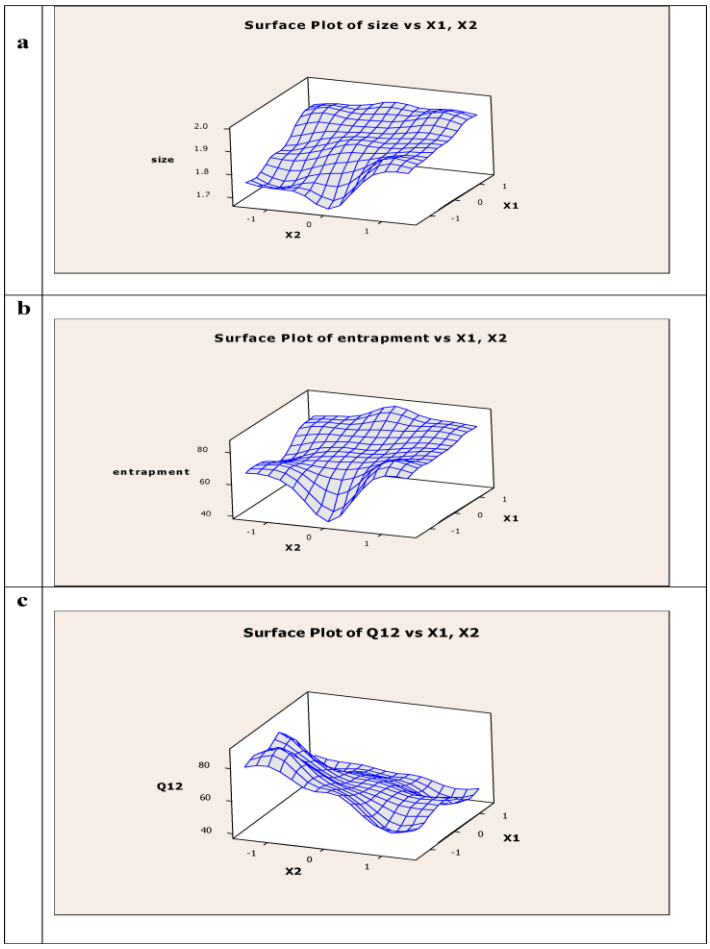

Figure 6: Response surface plots showing interactive effects of X_1 and X_2 on: (a) size, (b) entrapment and (c) Q_{12}

Response optimization

After generating the polynomial equations relating the dependent and independent variables, numerical optimization technique using desirability approach was employed to develop a new formulation with the desired response [21]. An optimized formulation was developed using Akidi beans starch at a starch: alginate ratio of 4:1 and polymer:drug ratio of 3:1. The optimized formulation was evaluated for size, entrapment and quantity of drug released at 12 h. For each response considered, individual desirability function was calculated and formulation variables were selected to maximize the overall desirability (d = 0. Thus, the estimated models were validated and their usefulness for predicting the responses for optimal formulations was confirmed. The observed response and the predicted response obtained by mathematical models are presented in Table 4. The low value of the percentage prediction error for the response confirmed the accuracy of the method.

Table 4: Comparison of experimentally observed responses to the predicted responses for the optimized theophylline microspheres

Response	Constraints sets	Observed value	Predicted value	% error
Y_1 (size mm)	1.70 - 1.98	1.94	1.95	0.513
Y_2 (entrapment %)	80.00 – 99.00	84.46	84.50	0.048
Y_3 (Q_{12} %)	40.00 – 50.00	45.03	45.00	-0.067

CONCLUSION

Controlled - release microspheres of theophylline were prepared using pregelatinized Akidi beans starch in different blend combinations with sodium alginate, by the ionic gelation method. The microspheres were designed according to 2^2 factorial central composite design (CCD), taking starch: alginate and polymer: drug ratios as the independent variables. Starch: alginate ratio and polymer: drug ratio were found to be important factors required to achieve good size, high encapsulation efficiency and prolonged release of theophylline from microspheres. The results established the reliability of the central composite design in determining optimal formulation parameters for the formulation of theophylline microspheres containing Akidi beans starch. It can be concluded from the above investigation that proper selection of formulation factors for a robust preparation technique can lead to the formulation of reproducible products with the desired properties.

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