



Use of coarse ethylcellulose and PEO in beads produced by extrusion–spheronization

Rama Mallipeddi, Kalyan K. Saripella, Steven H. Neau*

University of the Sciences in Philadelphia, Philadelphia College of Pharmacy, 600 S 43rd Street, Philadelphia, PA 19104, USA

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ABSTRACT

This study evaluated the potential of coarse ethylcellulose (CPEC) and high molecular weight polyethylene oxide (PEO) as excipients in the production of beads by extrusion–spheronization. CPEC was investigated as a diluent and PEO as an extrusion aid and a binder. Beads were manufactured with caffeine as a model drug. Release studies were conducted, and the bead size, shape, yield, and friability were determined. The effects of formulation and process variables and their interactions were studied by a sequential experimental design based on a response surface method. In the initial stage, a two level half fractional factorial design was employed as a screening design, which was subsequently augmented to a central composite design. Statistical analysis indicated that formulation variables including PEO content, microcrystalline cellulose (MCC) content, and water content, and two process variables, namely spheronizer speed and spheronization time, significantly affected the properties of the beads. Interactions between two factors have significant effects on several of the measured responses. Simultaneous optimization of the responses was conducted and validated by performing experiments at the optimal conditions. Overall, the results confirmed that immediate release, spherical beads with low friability and narrow size distribution could be produced with minimal amounts of MCC.

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1. Introduction

Extrusion–spheronization is becoming the most popular method for the production of beads due to advantages such as production of relatively dense and homogeneous beads with low surface porosity, as well as short processing times and the resultant operator and time savings (Vervaet et al., 1995). Microcrystalline cellulose (MCC) has long been considered crucial for bead production by extrusion–spheronization (Dukic-Ott et al., 2009; Vervaet et al., 1995; Barrau et al., 1993; Ku et al., 1993). However, there are disadvantages encountered with the use of MCC, including batch-to-batch variability in the commercial material, trace microbial contamination, generation of heat during the extrusion process, and failure of the beads to disintegrate that often results in incomplete drug release (Tho et al., 2002). Several drugs have been reported to be unstable in the presence of MCC (Brandl et al., 1995; George et al., 1994; Torres and Camacho, 1994; Patel et al., 1988; Signoretti et al., 1986; Carstensen et al., 1969). Specifically, the highly water soluble drug, ranitidine, has been shown to undergo chemical degradation by a complex three way interaction with MCC

and water at MCC levels greater than 60% (Basit et al., 1999). Reducing or completely removing MCC from the formulation should be a means to eliminate this problem. Nevertheless, there are few studies that address this issue using this approach (Charoenthai et al., 2007; Newton et al., 2007; Thommes and Kleinebudde, 2006; Howard et al., 2006; Agrawal et al., 2004; Tho et al., 2002; Basit et al., 1999).

MCC typically constitutes greater than 20% (w/w) of the bead formulation (Jover et al., 1996; Hileman et al., 1993). According to Kleinebudde et al. (1999), the minimal amount of MCC needed to form a continuous network is about 14%. In order to confirm that excipients other than MCC are suitable for beads produced by extrusion–spheronization, the amount of MCC in the formulation should therefore be less than 14%. In the present study, the use of two excipients in the preparation of beads with little MCC in them was investigated.

Ethylcellulose ethers are a family of inert hydrophobic polymers obtained by reacting ethyl chloride with alkali cellulose. The alkaline conditions are likely to reduce microbial contamination in comparison to that observed with MCC. Ethylcellulose manufactured by the Dow Chemical Company is available in two different size ranges. The standard form of ethylcellulose, coarse particle ethylcellulose (CPEC), is granular with an average particle size greater than 250 μm . Fine particle ethylcellulose (FPEC) is the finely milled version with an average particle size range of 6–50 μm . In addition, there is likely a lower batch-to-batch variability

* Corresponding author at: University of the Sciences in Philadelphia, Philadelphia College of Pharmacy, Box 80, 600 S 43rd Street, Philadelphia, PA 19104, USA. Tel.: +1 215 596 8825; fax: +1 215 895 1161.

E-mail addresses: s.neau@usp.edu, stevenneau@yahoo.com (S.H. Neau).

Table 1
Levels of variables in the experimental design.

Levels	Factors				
	A PEO (% w/w)	B MCC (% w/w)	C Water ^a (ml)	D Spheronizer speed (rpm)	E Spheronization time (min)
Alpha (−1.5)	2.5	7.0	147.5	450.0	7.0
Low (−1.0)	3.0	8.0	150.0	510.0	8.0
Base (0.0)	4.0	10.0	155.0	630.0	10.0
High (+1.0)	5.0	12.0	160.0	750.0	12.0
Alpha (+1.5)	5.5	13.0	162.5	810.0	13.0

^a Water content is for a 300 g powder blend.

than observed with MCC since the ethylcellulose products from Dow Chemical Company are available at specific viscosity levels that should minimize molecular weight variability, and the ethoxy level is specified and of a narrow range (e.g., an ethoxy content of 48–49.5% is specified for the product used in the present studies).

The level of polymer and the particle size of ethylcellulose in direct compression tablets have been shown to dramatically affect the drug release rates (Dabbagh et al., 1996; Katikaneni et al., 1995a,b). Smaller particle sizes of ethylcellulose were shown to produce direct compression tablets of lower porosity and increased hardness due to differences in compactibility and compressibility. Similar studies are lacking regarding the application of ethylcellulose in extrusion–spheronization.

Polyethylene oxide (PEO) is a nonionic, synthetic, linear polymer of ethylene oxide. It is highly water soluble and rapidly swells upon exposure to an aqueous environment to form a strong gel. The major pharmaceutical applications of PEO have been in the production of dry blends, direct compression tablets (Hong and Oh, 2008; Kojima et al., 2008; Yang et al., 1996) and in hot melt extrusion (Prodduturi et al., 2007; Repka and McGinity, 2000). Maggi et al. (2000) investigated the use of high molecular weight PEO as an alternative to HPMC as a binder in direct compression tablets. The influence of the molecular weight of PEO on study of the drug release from direct compression tablets revealed that swelling was the primary mechanism for drug release with very high molecular weight PEO while low molecular weight PEO released the drug by both erosion and swelling (Maggi et al., 2002; Kim, 1998; Apicella et al., 1993).

Pinto et al. (2004) investigated the use of high molecular weight PEO in extrusion. Different PEO levels were tested for their ability to produce an extrudate, but they do not describe the preparation of beads by a subsequent spheronization process. They report that the affinity of PEO for water is so high that the hydrogel formed dramatically affects the extrudability of a granulation or wetted mass. Low molecular weight PEO (MW 300,000) was used along with methoxy polyethylene glycol by Howard et al. (2006) in the production of extruded and spheronized beads containing pseudoephedrine HCl. In their study, MPEG reduced the tackiness of PEO and improved the lubricity of the wetted mass.

The first objective of the present study was to investigate the application of CPEC as an excipient in the production of beads with little or no MCC. High molecular weight PEO was chosen as a binder and an extrusion aid in the process. The second objective was to identify important formulation and process variables that affect the properties of the beads and to optimize those effects by using statistical experimental design.

2. Materials and methods

2.1. Materials

CPEC (EthocelTM Standard Premium 7 cps viscosity grade with ethoxy content of 48–49.5%) and high molecular weight PEO (HMW

PEO, PolyOxTM WSR N-12K) were gifts from the Dow Chemical Company (Midland, MI). Microcrystalline cellulose (Avicel PH-101, 36,450 average molecular weight, 51.5 μm average particle size, and 1.57 g/cm³ powder density) was a gift from FMC Corporation (Philadelphia, PA). Caffeine from Sigma–Aldrich (St. Louis, MO) served as a model drug. Distilled de-ionized water was used as the wet massing fluid.

2.2. Bead manufacture

Preweighed quantities of CPEC, HMW PEO, MCC, and caffeine were mixed in a KitchenAid[®] planetary mixer for 5 min. The batch size was 300 g. De-ionized water was added and wet massing was carried out for 10 min. The wetted mass was passed through an EXD60 twin screw extruder (Fuji Paudal Co., Osaka, Japan) equipped with a 1.2 mm axial screen. The extruder speed was set at 38 rpm. The extrudate was introduced immediately into a Q230 spheronizer (Fuji-Paudal Co.) fitted with a cross-hatched plate. The beads obtained were tray dried in an oven at 50 °C for 8 h.

The effects of formulation variables, namely the HMW PEO content, the MCC content and the amount of water required in the wet massing step, and the effects of the process variables spheronizer speed and spheronization time on the characteristics of the beads were investigated. Significant formulation and processing factors, as well as interactions between pairs of them, that influence the bead characteristics were identified by using a two level, half fractional factorial (2^{5-1}) design (resolution V) as a screening design. Replicated center points (with each factor at their middle values) were used to add additional degrees of freedom to allow the estimation of pure error and of curvature in the responses upon variation in the factor levels. Additional batches based on a central composite design with alpha level 1.5 were performed to model the response surfaces and optimize the responses. The range for each factor was determined in preliminary experiments. The levels for each factor are presented in Table 1. In the statistical design, the factor levels were coded for negative alpha, low, medium, high, and positive alpha settings using −1.5, −1.0, 0.0, +1.0 and +1.5. The 0.0 coded level represents the value midway between the high and low factor levels. Responses were not coded.

2.3. Bead characterization

2.3.1. Shape, size and yield

Sieve analyses were conducted by screening 35 g of beads at a time through a nest of U.S standard sieves with a $2^{1/2}$ progression of the aperture using a Retsch Vibrotronic VE1 sieve shaker (Brinkmann Instrument Co., Westbury, NY) for 5 min. The entire mass of dried beads for each batch was measured in this way. The mass of the beads retained on each sieve was recorded and the average bead size was calculated based on the equation:

$$d_{\text{avg}} = \frac{\sum (\% \text{ retained}) (\text{average sieve aperture})}{100\%}$$

The cumulative mass of beads in the 12/20-mesh cut (1.68–0.84 mm) for each batch, expressed as a percentage of the total mass of beads, was reported as the yield. Further characterization was performed only on the beads from the 12/20-mesh cut.

Bead shape was evaluated by the QICPIC Dynamic Image Analysis System (Sympatec Inc., Clausthal-Zellerfeld, Germany) equipped with the RODOS/L dry dispersing unit. Beads were fed into the high-speed dry disperser where they were accelerated to a speed of up to 100 m/s via a Venturi tube located in the dispersing line. During this process, the beads were dispersed and aerosolized by centrifugal forces caused by velocity gradients. Images of the particles were captured by a high-speed digital camera with a synchronized light source. Motion blur during image acquisition was minimized by using a pulsed light source with an exposure time of approximately 1 ns. The images captured were analyzed using Windox 5.0 software. Sphericity of the beads was calculated as the ratio of the perimeter of a circle with an area equivalent to that of the bead image (P_{EQPC}) to the actual perimeter (P_{real}) of the bead image.

$$\text{Sphericity} = \frac{P_{EQPC}}{P_{real}} = \frac{2\sqrt{\pi A}}{P_{real}}$$

where A is the area of the bead image. The Feret diameter of a bead was measured from several different orientations and the ratio of the maximum and minimum values was defined as the aspect ratio (AR). Both sphericity and AR values will be in the range 0–1. The higher the value, the more regular is the shape of the bead.

2.3.2. Microscopy

Surfaces and cross-sectional areas of beads were evaluated for texture and shape. Bead samples mounted on a metal disc with silicon adhesive were sputtercoated with gold using a Denton Desk II Vacuum (Moorestown, NJ). The samples were then examined with a Hitachi S-530 Scanning Electron Microscope (Hitachi High Technologies America, Inc., Pleasanton, CA) at an accelerating voltage of 15 kV. Digital images were taken using Orion software.

2.3.3. Friability

Beads weighing 3 g, along with 25 glass beads (3 mm in diameter), were placed in a Model 1805 Roche friabilator (Vankel Industries, Inc., Edison, NJ) that was then operated for 100 revolutions at 25 rpm. Glass beads were separated by screening with a 12-mesh sieve and the beads collected on a 20-mesh sieve with its 0.84-mm aperture, after smaller particles were allowed to pass through, were weighed. The friability was determined as the percentage loss of mass of the beads. Each batch was assessed in duplicate.

2.3.4. Release studies

Drug release from 200 mg bead samples in 900 ml of 0.05 M, pH 6.8, phosphate buffer solution at 37 °C was studied in triplicate using a USP type I Model No. 2100 C dissolution apparatus (Distek Inc., North Brunswick, NJ) with a 100 rpm basket stirring rate. Samples were withdrawn at specified intervals and the drug concentration was measured at 273 nm using a Shimadzu UV 1601 UV/Vis spectrophotometer (Shimadzu Scientific Instruments, Inc., Columbia, MD).

2.4. Statistical experimental design

Response surface methodology was used to characterize the effects of multiple variables on the amount of product obtained (yield), bead size (average bead diameter), bead shape (spheric-

ity, aspect ratio) and their ruggedness (friability). This method was carried out in sequential stages as described below.

2.4.1. Fractional factorial design

A two level half fractional factorial (2^{5-1}) design with three center points was employed to identify the significant formulation and process variables that affect bead properties, including size, shape, yield, and friability. The fractional design was chosen because it provides sufficient degrees of freedom to statistically discriminate the effects of main factors and binary interactions in about one-half the experiments required for a full factorial design. The detection of curvature in the model was facilitated by adding center points that were replicated to ensure the proper estimation of pure error. This analysis is based on the assumption of a linear response to increases in the factor levels, as given in this model equation:

$$Y = B_0 + \sum_{i=1}^5 B_i X_i + \sum_{i=1}^4 \sum_{j=i+1}^5 B_{ij} X_{ij}$$

2.4.2. Response surface method

The factorial design was augmented to a central composite design (CCD) to investigate curvature in the responses and to optimize the effects. Additional experiments comprising the CCD were performed as an axial block with an alpha level of 1.5. A second order polynomial equation was fitted to the CCD results data based on the following equation:

$$Y = B_0 + \sum_{i=1}^5 B_i X_i + \sum_{i=1}^4 \sum_{j=i+1}^5 B_{ij} X_{ij} + \sum_{i=1}^5 B_{ii} X_i^2$$

where Y is the predicted response, X_i are the factors, X_{ij} are the two-factor interactions, B_0 is the y -intercept, B_i are the coefficients for linear effects, B_{ii} are the coefficients for quadratic effects, and B_{ij} are the coefficients for interaction effects. The terms that appear in the equations presented below were determined by reverse hierarchical regression analysis. Analysis of variance (ANOVA) was performed for each response at an error probability of 0.05.

The simultaneous optimization technique popularized by Derringer and Suich (1980) was chosen for optimization of the responses. This method is based on the utilization of desirability functions. Each response is converted into an individual desirability function d_i that can be varied over the range $0 < d_i < 1$. The design variables are then selected to maximize the overall desirability:

$$D = (d_1 d_2 d_3 \dots d_m)^{1/m}$$

where D is the overall desirability, d_i is the individual desirability and m is the number of responses (Montgomery, 2001). The design and statistical data of the response surface methodology were analyzed and optimized using Design-Expert 7.0.3 (Stat-Ease Inc., Minneapolis, MN) software.

3. Results

3.1. Preliminary studies

The appropriate use and level of each excipient was determined by conducting preliminary studies. Preliminary studies in our lab indicated that CPEC can be used in the production of spherical beads, although these beads, produced using a radial extruder, could be obtained only at a particular water level. However, it is desirable to have a range over which water could be varied and still be able to produce characterizable product. In the present study, conducted with an axial extruder, the model drug and CPEC either

alone or in combination were investigated for their bead forming properties with de-ionized water as the wet massing fluid, but no extrudate was produced. Under the influence of the forces of extrusion, the material was compressed into a hard slug in the extrusion zone resulting in reverse load on the motor. Water levels were increased, hoping to improve the lubricity of the mass in the extruder, but water was squeezed out of CPEC on compression, evidenced by droplets on the surface of the screen. In order to enhance the extrudability of the mass, HMW PEO was chosen. PEO forms a strong gel upon contact with water. The strength of the gel decreases as water content is increased (Howard, 2004). In comparison to lower molecular weight versions of PEO, HMW PEO has higher cohesive strength, holds the extrudate together better, and also prevents it from sticking to the extruder. The addition of HMW PEO to the formulation dramatically improved the extrudability of the wetted mass. The generation of heat, observed when extruding an MCC-containing wetted mass, was dramatically reduced when PEO was included in the formulation.

The water content required to form a sufficiently wetted mass was reduced by the addition of HMW PEO, as predicted by Hileman et al. (1997). Spherical beads could be produced at appropriate water levels, although the water range over which desirable beads could be produced was narrow. MCC was included in the formulation at low levels to improve the water tolerance of the formulation. Spherical beads with good yield and low friability were obtained at MCC levels as low as 8% in the formulation. CPEC formulations with MCC at levels even up to 20% did not result in any extrudate in the absence of HMW PEO, confirming that HMW PEO is indeed acting as an extrusion aid.

As PEO is water soluble, the amount of water needed to form a wetted mass decreased as the PEO level in the formulation was increased (Hileman et al., 1997). At PEO levels above 20%, the cohesiveness of the formulation increased and the wetted mass resisted flow through the extruder die even at appropriately wetted levels. If the water levels were reduced, it made it even more difficult for the wetted mass to be extruded. Higher water levels eased the flow of the wetted mass through the die, but the resulting extrudate was too tacky for further processing. Extrudate suitable for further processing was obtained only when PEO levels in the formulation were below 20%. However, at PEO levels above 7%, the resistance of the extrudate pieces to round up in the spheronizer was increased with increasing levels of PEO. Based on these preliminary studies, the PEO levels were chosen to be below 7% in the formulation. Variables such as dry blending time, wet massing time, and extrusion speed determined in preliminary studies were kept constant for further studies.

3.2. Release studies

Release profiles for CPEC beads from the screening design and the CCD are shown in Figs. 1–3, revealing that greater than 80% of the drug was released within 30 min. Although a definition of an immediate release pellet product has yet to be established (Krause et al., 2009), the results of the release study indicate that the formulation and process variables in the studied ranges do not slow drug release to a profound extent. CPEC was expected to slow the drug release rate due to its hydrophobic nature, but, in pragmatic terms, there are no differences in the release profiles. High molecular weight PEO is known to sustain drug release from direct compression tablets by the formation of a swollen and gelled matrix. However, in the studies by Maggi et al. (2000), PEO was shown to be less effective than HPMC at diminishing the release rate of a water soluble drug, diltiazem hydrochloride. This was attributed to the formation of a softer gel by PEO. In the present study, the softer gel and high surface area of the beads led to faster dissolution of this polymer in the release medium, leaving pores through

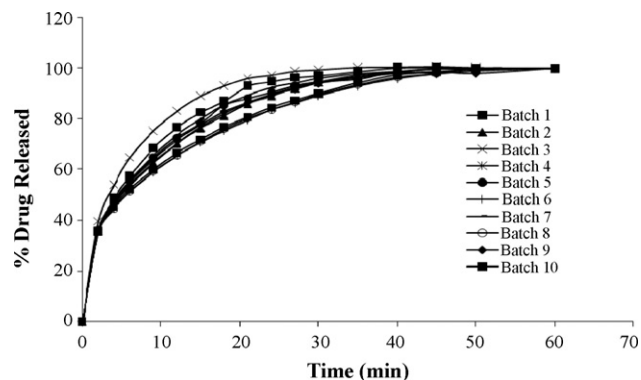


Fig. 1. Cumulative drug release profiles for beads of screening design (batches 1–10).

which drug can be released. These pores were probably the reason why 100% of the drug was released, as might not be the case with MCC beads. Also, the shorter diffusion path lengths of beads compared to those of tablets make any small differences in the release rate as a function of PEO content even less apparent. Overall, the release study indicated that neither CPEC nor high molecular weight PEO sustained the release of the drug. Beads in each case retained their shape even to the end of the release study, but then disintegrated immediately upon touch. Beads with higher MCC levels were more likely to retain their shape whereas beads with higher PEO levels were slightly swollen and disintegrated very easily.

Data for each of the responses that were studied by statistical analysis are presented in Tables 2 and 3. The independent variables were initially screened by the fractional factorial design. Since each

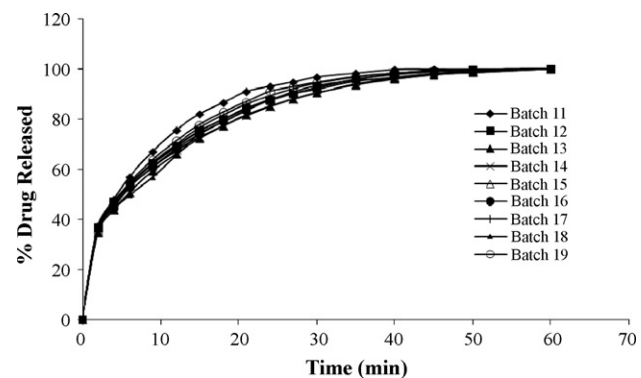


Fig. 2. Cumulative drug release profiles for beads of screening design (batches 11–19).

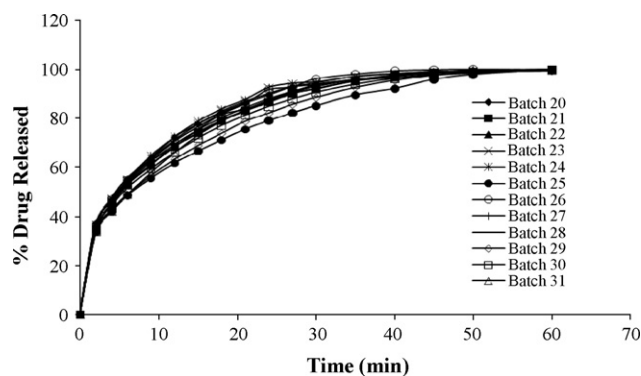


Fig. 3. Cumulative drug release profiles for beads of the axial block (batches 20–31).

Table 2
Half fractional factorial (2^{5-1}) block (screening design).

Standard run	Factors					Mean responses ^a				
	A	B	C	D	E	Yield (%)	Bead size (mm)	Bead shape		Friability (%)
	PEO	MCC	Water	Spheronizer speed	Spheronization time			PS ^b	AR ^c	
1	-1	-1	-1	-1	+1	78.21	0.91	0.94	0.90	1.53
2	+1	-1	-1	-1	-1	63.19	1.44	0.94	0.91	0.55
3	-1	+1	-1	-1	-1	71.21	0.86	0.93	0.88	1.62
4	+1	+1	-1	-1	+1	82.54	1.30	0.94	0.91	0.79
5	-1	-1	+1	-1	-1	84.69	1.04	0.94	0.90	1.29
6	+1	-1	+1	-1	+1	1.10	2.34	0.94	0.89	0.06
7	-1	+1	+1	-1	+1	86.20	1.13	0.94	0.91	1.54
8	+1	+1	+1	-1	-1	16.07	1.85	0.94	0.89	0.21
9	-1	-1	-1	+1	-1	86.40	1.06	0.94	0.93	1.41
10	+1	-1	-1	+1	+1	10.07	1.96	0.94	0.92	0.13
11	-1	+1	-1	+1	+1	83.67	0.95	0.95	0.94	1.47
12	+1	+1	-1	+1	-1	37.71	1.62	0.94	0.91	0.41
13	-1	-1	+1	+1	+1	87.91	1.15	0.95	0.95	1.29
14	+1	-1	+1	+1	-1	2.57	2.19	0.93	0.89	0.07
15	-1	+1	+1	+1	-1	89.50	1.06	0.95	0.94	1.35
16	+1	+1	+1	+1	+1	46.95	1.54	0.94	0.91	0.50
17	0	0	0	0	0	90.69	1.15	0.95	0.94	0.46
18	0	0	0	0	0	89.50	1.19	0.95	0.93	0.42
19	0	0	0	0	0	86.50	1.28	0.94	0.93	0.35

^a Averaged from two determinations.^b Projection sphericity.^c Aspect ratio.**Table 3**
Runs to augment the screening design to a central composite design for five variables: axial block with alpha = 1.5.

Standard run	Factors					Mean responses ^a				
	A	B	C	D	E	Yield (%)	Bead size (mm)	Bead shape		Friability (%)
	PEO	MCC	Water	Spheronizer speed	Spheronization time			PS ^b	AR ^c	
20	-1.5	0	0	0	0	80.07	0.93	0.94	0.92	1.71
21	+1.5	0	0	0	0	5.66	2.07	0.94	0.90	0.10
22	0	-1.5	0	0	0	72.85	1.38	0.94	0.93	0.73
23	0	+1.5	0	0	0	90.38	1.22	0.94	0.93	1.07
24	0	0	-1.5	0	0	83.12	1.13	0.94	0.92	0.90
25	0	0	+1.5	0	0	51.18	1.60	0.94	0.92	0.41
26	0	0	0	-1.5	0	82.80	1.29	0.93	0.91	0.87
27	0	0	0	+1.5	0	77.02	1.32	0.94	0.95	0.77
28	0	0	0	0	-1.5	70.46	1.37	0.94	0.92	0.64
29	0	0	0	0	+1.5	65.90	1.42	0.94	0.93	0.59
30	0	0	0	0	0	90.26	1.21	0.95	0.94	0.43
31	0	0	0	0	0	84.86	1.24	0.94	0.93	0.45

^a Averaged from two determinations.^b Projection sphericity.^c Aspect ratio.

of the independent variables exhibited a significant effect on the dependent variables, and each of the responses studied revealed significant curvature, a higher order model with all of the independent variables retained was pursued. The following discussion centers on significant main factor effects and those of binary interactions on the dependent variables as discovered by statistical analysis of the data. The appropriateness of the selected mathematical model was ensured by a high correlation coefficient, the absence of a lack of fit of the model equation to the data, and the randomness of the residuals.

3.3. Yield

One determinant of the success of an extrusion–spheronization process is the percentage yield in the desired size range. A high yield can ensure a cost-effective production. The yield in the targeted 12/20-mesh fraction was 1.10–90.69%, indicating a strong influence of formulation and process variables and ultimately the success of the process. ANOVA of the screening design data suggested that the

fit of the model to the data was significant ($p < 0.05$) and resulted in a good correlation ($R^2_{\text{adjusted}} = 96.47\%$). Lack of fit was not significant ($p > 0.05$), indicating that the data can be described adequately by the mathematical model (Table 4). Residuals were randomly distributed, ensuring the appropriateness of the mathematical model.

Table 4
Analysis of variance: fractional factorial design.

Source	Response			
	Yield	Bead size	Bead shape	Friability
<i>p</i> -Value				
Model	<0.0001	<0.0001	<0.0001	<0.0001
Lack of fit	0.0915	0.9047	0.7760	0.8835
Curvature	<0.0001	0.0012	<0.0001	<0.0001
<i>R</i> ² value				
<i>R</i> ²	0.9854	0.9967	0.9693	0.9979
Adjusted for degrees of freedom	0.9647	0.9889	0.9420	0.9949
Predicted	0.8554	0.9747	0.8713	0.9881

The linear regression equation for the yield in terms of the coded factors is:

$$\text{Yield} = 58.00 - 25.47A + 6.23B - 6.13C - 2.40D + 1.58E \\ + 7.06AB - 9.73AC - 5.80AD + 9.03BE + 7.26CD$$

Backward hierarchical regression analysis of variance for the reduced quadratic model suggested a better fit to the data ($R^2_{\text{adjusted}} = 97.53\%$) and lack of fit was not statistically significant ($p > 0.05$, Table 5). Normal plots for residuals and outliers were unremarkable. The second order polynomial regression equation

Table 5
ANOVA for the response surface reduced quadratic model: yield.

Source	p-Value	Source	p-Value
Model	<0.0001	BE	<0.0001
A-PEO content	<0.0001	CD	<0.0001
B-MCC content	<0.0001	A ²	<0.0001
C-Water content	<0.0001	C ²	0.0002
D-Spheronizer speed	0.0410	E ²	0.0004
E-Spheronization time	0.3943	Lack of fit	0.1876
AB	<0.0001	R ²	0.9872
AC	<0.0001	Adj R ²	0.9753
AD	0.0002	Pred R ²	0.9209
BD	0.0390		

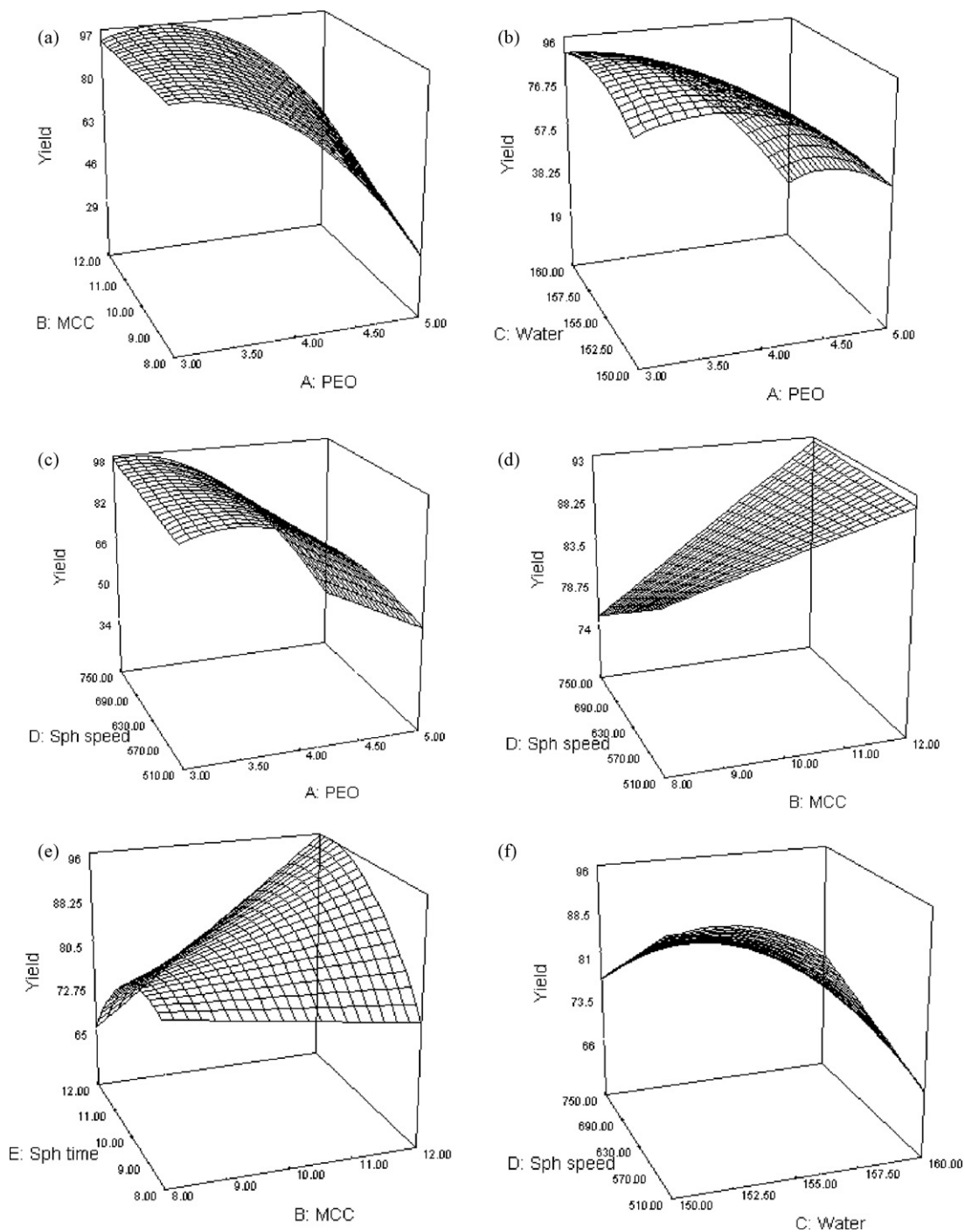


Fig. 4. Response surface plots for yield as a function of PEO content and MCC content (a), PEO content and water content (b), PEO content and spheronizer speed (c), MCC content and spheronizer speed (d), MCC content and spheronization time (e), and water content and spheronizer speed (f). The other variables were at their base level.

for the yield in terms of coded factors is:

$$\begin{aligned} \text{Yield} = & 86.00 - 25.33A + 6.15B - 7.12C - 2.30D + 0.90E \\ & + 7.06AB - 9.73AC - 5.80AD + 2.63BD + 9.03BE \\ & + 7.26CD - 17.73A^2 - 6.94C^2 - 6.48E^2 \end{aligned}$$

Because the effects from a number of two-factor interactions are statistically supported, the influence of the main effects on the yield cannot be considered independently. The effect of the formulation and process variables on a response can be evaluated by studying the response plots. From Fig. 4a–c, the response plots for yield as a function of PEO content, it can be seen that the yield is affected the most by the PEO content and the lowest yield values are obtained at the highest PEO levels. Fig. 4b indicates that a greater reduction in the yield with PEO was observed at higher water levels. At the highest PEO and water levels, the extrudate becomes sticky and likely overwetted due to excessive binder and fluid present, respectively, which results in agglomeration into larger than desired beads, and the yield decreases. This can be observed with batches 6, 8, 14, and 16. At the highest PEO levels, the extruded wetted mass will possess higher than desired binding strength, confirmed by the observation that increasing the spheronization speed does not result in fracturing of the extruded cylinders (Fig. 4c). These results are in agreement with results from earlier studies by Agrawal et al. (2004) with HPMC as a binder in extruded and spheronized beads, confirming that the results are due to PEO binding properties.

At the highest PEO levels, increasing the MCC content results in an improvement in the yield (Fig. 4a), likely due to the high water absorbing capacity of MCC. When water is taken up by MCC, there is a reduction in the tack of the wetted mass. The yield reaches a maximum as the PEO levels are decreased. Further reduction in the PEO content results in moderate reduction of the yield. As the PEO content is decreased, the extrudate displayed substantial shark skinning and results in the production of fines or undersized beads, thus decreasing the percentage of beads in the desired size range.

Fig. 4d and e shows the interaction of MCC with the process variables. When MCC levels are decreased, higher spheronization speeds and longer spheronization times tend to decrease the yield. This can be attributed to the better water holding capacity of MCC in comparison to CPEC. When MCC levels are low, excess water is expressed to the surface of the extruded cylinders at higher spheronization speeds. Longer spheronization times increase the particle to particle interactions in the spheronizer and encourage the formation of agglomerates and oversized beads, resulting in a reduction in the yield. Increasing the water level in the formulation increases the yield up to a certain extent by imparting necessary plasticity and lubricity to the wetted mass. After the optimum, increasing the water levels results in a decrease in the yield due to overwetting and agglomeration that leads to oversized beads.

3.4. Bead size

The screening experiments (Table 2) indicate that the mean bead size varied between 0.86 and 2.34 mm, indicating a profound influence of formulation and process variables. Statistical analysis of the bead size supported the significance ($p < 0.05$) of four of the five variables, PEO content, MCC content, water content, and spheronizer speed, and a number of two-factor interactions. ANOVA suggested that the mathematical model is significant ($p < 0.05$) and has a good fit to the data ($R^2_{\text{adjusted}} = 98.89\%$). Lack of fit was not statistically significant ($p > 0.05$, Table 4), and the residuals were randomly distributed. The regression equation for the

Table 6

ANOVA for the response surface reduced quadratic model: bead size.

Source	p-Value	Source	p-Value
Model	<0.0001	BE	0.0001
A-PEO content	<0.0001	CD	<0.0001
B-MCC content	<0.0001	DE	0.0011
C-Water content	<0.0001	A ²	<0.0001
D-Spheronizer speed	0.0081	C ²	0.0205
E-Spheronization time	0.3104	E ²	0.0038
AB	<0.0001	Lack of fit	0.6593
AC	0.0002	R ²	0.9916
BC	0.0305	Adj R ²	0.9827
BD	0.0118	Pred R ²	0.9673

bead size in terms of the coded factors during screening is:

$$\begin{aligned} \text{Bead size} = & 1.40 + 0.38A - 0.11B + 0.14C + 0.042D + 0.011E \\ & - 0.092AB + 0.062AC - 0.031BC - 0.037BD \\ & - 0.068BE - 0.093CD - 0.052DE \end{aligned}$$

Although the fifth factor, spheronization time, was not statistically significant, it is retained in the model equation for hierarchical reasons.

When augmented to the CCD, ANOVA suggests that the reduced quadratic model had a good fit to the data ($R^2_{\text{adjusted}} = 98.27\%$) and lack of fit was not significant ($p > 0.05$, Table 6). The residuals were randomly distributed. The second order polynomial regression equation for the bead size in terms of coded factors is:

$$\begin{aligned} \text{Bead size} = & 1.24 + 0.38A - 0.098B + 0.14C + 0.035D + 0.012E \\ & - 0.092AB + 0.062AC - 0.031BC - 0.037BD - 0.068BE \\ & - 0.093CD - 0.052DE + 0.100A^2 + 0.040C^2 + 0.054E^2 \end{aligned}$$

Statistical analysis of the CCD (Table 6) is in reasonable agreement with the screening design in terms of the significance of the effect of main factors on the bead size. Each of the variables except spheronization time had a statistically significant influence ($p < 0.05$) on the size of the beads. However, spheronization time was involved in significant binary interactions with MCC and spheronizer speed. The effect of the formulation and process variables on this response can be evaluated by studying Figs. 5 and 6.

From the regression equation, bead size is most sensitive to PEO and water levels. The average bead diameter is at a minimum when PEO and water levels are both low and maximizes when both are high. The change in the bead size is more pronounced at higher PEO levels. This is because the amount of water required to wet the mass is reduced with an increase in the PEO levels and water is in excess.

MCC interacts with each of the other factors in the model (Fig. 6a–d). From the regression equation and the response plots, it can be seen that an increase in MCC causes a reduction in bead size. As MCC is increased, the wetted mass can accommodate more water and the tendency to overwet is reduced. Consequently, at higher MCC levels, the increase in bead size due to agglomeration is profoundly limited. As previously reported by Kleinebudde (1997), MCC beads tend to shrink on drying, leading to a further reduction in the bead size in the present study. Supporting this, the response plots show that this effect is more pronounced at higher water and PEO levels. When PEO is high, there is an excess of moisture in the formulation due to the hydrophilicity of PEO and the wetted mass tends to be overwet. Higher speeds and longer spheronization times at low MCC levels tend to increase the bead size by agglomeration as more water is expressed to the surface of the beads due to higher speeds. Agglomeration due to further parti-

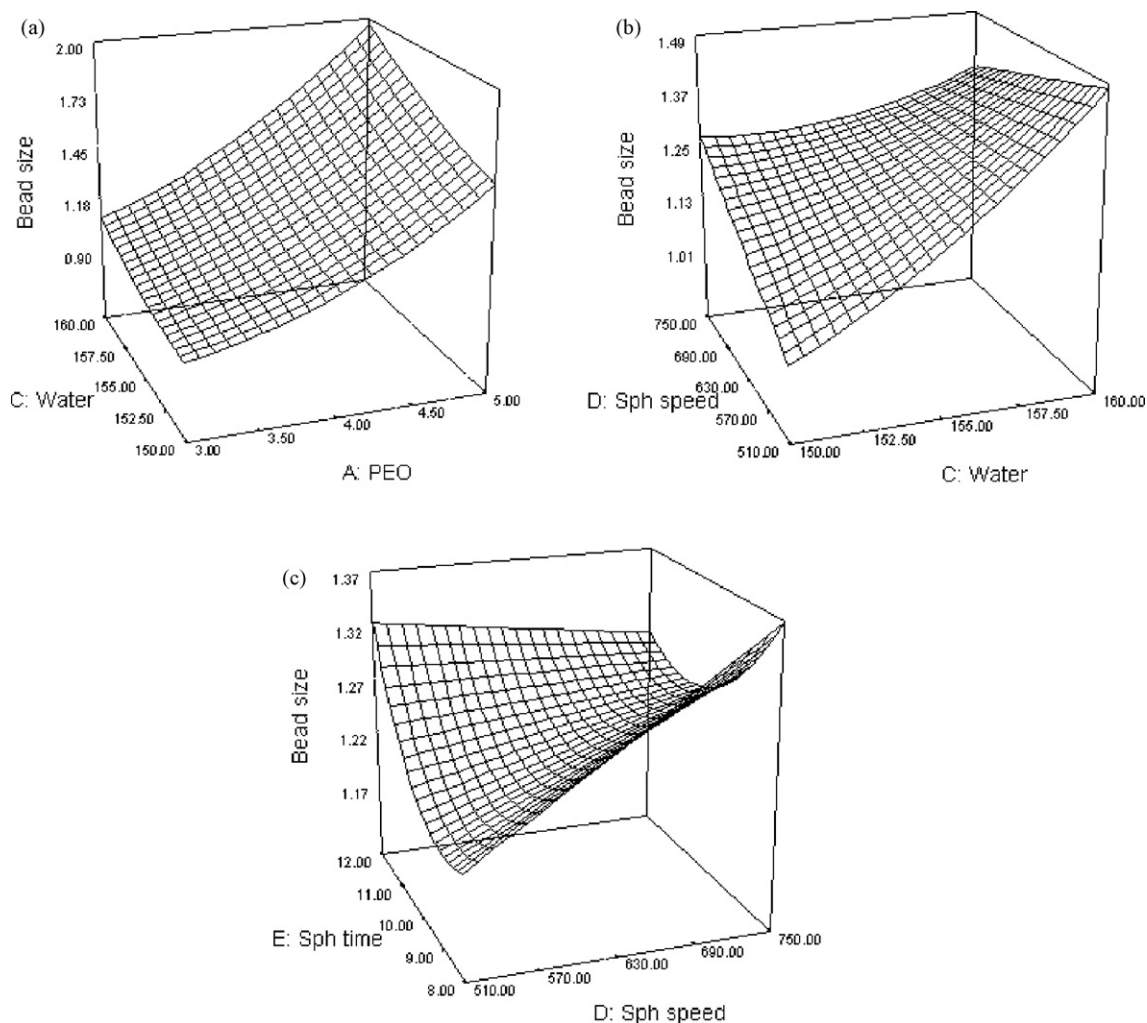


Fig. 5. Response surface plots for bead size as a function of PEO content and water content (a), water content and spheronizer speed (b), and spheronizer speed and spheronization time (c). The other variables were at their base level.

cle to particle interactions occurs with longer times. Spheronizer speed and spheronization time interact with each other. At lower spheronizer speeds, the bead size is found to increase with longer spheronization times. This is because, at low speeds, the greater number of particle to particle interactions facilitates the agglomeration of fines and smaller sized beads, resulting in an increase in the average bead size. At higher spheronization speeds, the curvature in the response is likely due to the aggressive particle to spheronizer plate interactions that break the extrudates into shorter strands causing bead size reduction, although increased particle to particle interactions can still cause an increase in the bead size due to agglomeration.

3.5. Bead shape

While it is desirable to obtain high usable yields of durable beads, it is ultimately the shape that is critical for a number of processing advantages of beads, such as flowability and uniformity in coating. Bead shape was evaluated based on two parameters – projection sphericity (PS) and aspect ratio (AR). Both PS and AR values were high (>0.88) for all the beads in the design. The excipient CPEC is therefore a good diluent for the manufacture of beads by the extrusion–spheronization process. The PS values were in a short range of 0.93–0.95, indicating that each of the batches provided beads that were nearly spherical. AR seemed to be a more sensitive

parameter and showed a relatively wider variation of 0.88–0.95, indicating that bead shape was influenced by the factors in the design. When these changes were modeled during the screening, ANOVA suggested that the model was significant ($p < 0.05$) with a reasonably good fit ($R^2_{\text{adjusted}} = 94.20\%$) to the data. Lack of fit was not significant ($p > 0.05$), indicating that the model could mathematically explain the changes in bead shape when the factor levels were changed. The linear regression equation for bead shape in terms of coded factors is:

$$\text{Bead shape} = 0.91 - 0.0075A - 0.0013C + 0.012D + 0.005E \\ - 0.0075AC - 0.0088AD + 0.0025BC$$

Ultimately, it is the spheronization process that causes the fragmentation of the extrudate through interactions with the frictional plate, and subsequently rounds and smoothes the fragments into beads through particle to spheronizer wall and particle to particle interactions. Consequently, it is not surprising that the process variables influenced the bead shape more than the formulation variables. Spheronizer speed and the spheronization time both influenced bead shape significantly ($p < 0.05$). Among the formulation variables, PEO content revealed a significant effect ($p < 0.05$) on the bead shape in terms of AR. Statistically significant curvature ($p < 0.05$) indicated that a higher order model could describe the response surface better.

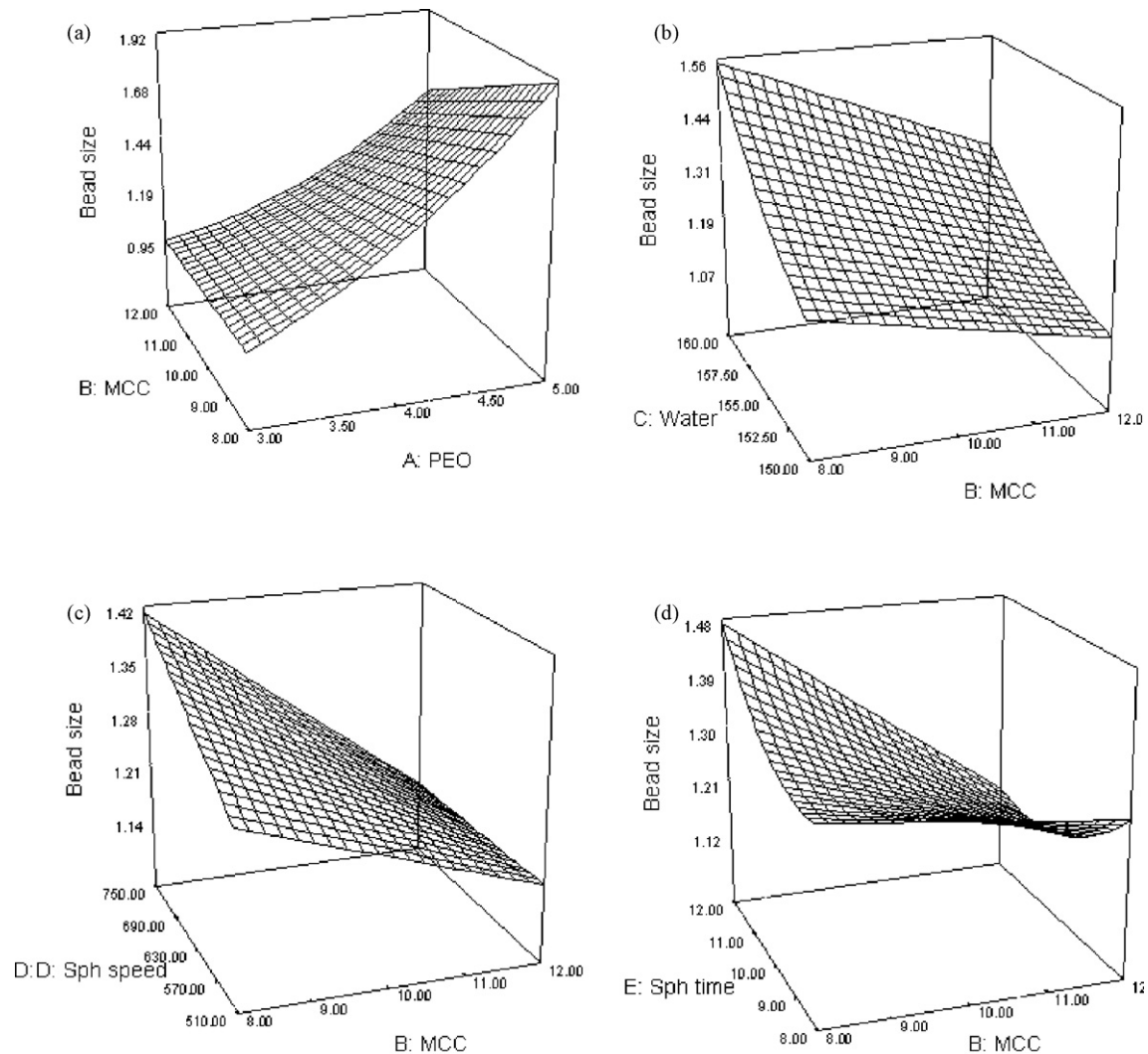


Fig. 6. Response surface plots for bead size as a function of MCC content and PEO content (a), water content (b), spheronizer speed (c), and spheronization time (d). The other variables were at their base level.

Analysis of variance suggested that the reduced quadratic model was a good fit ($R^2_{\text{adjusted}} = 94.61\%$) and lack of fit was not statistically significant ($p > 0.05$, Table 7). The plots for residuals and outliers were unremarkable. The second order polynomial regression equation for bead shape in terms of AR and the coded factors is:

$$\begin{aligned} \text{Bead shape} = & 0.93 - 0.0073A - 0.001C + 0.013D + 0.0046E \\ & - 0.0075AC - 0.0088AD + 0.0025BC - 0.010A^2 \\ & - 0.0060C^2 - 0.0038E^2 \end{aligned}$$

Table 7
ANOVA for the response surface reduced quadratic model: bead shape.

Source	p-Value	Source	p-Value
Model	<0.0001	BC	0.0277
A-PEO content	<0.0001	A ²	<0.0001
B-MCC content	1.0000	C ²	0.0002
C-Water content	0.3041	E ²	0.0074
D-Spheronizer speed	<0.0001	Lack of fit	0.9339
E-Spheronization time	<0.0001	R ²	0.9665
AC	<0.0001	Adj R ²	0.9461
AD	<0.0001	Pred R ²	0.9093

Both of the process variables again had an effect on the bead shape while PEO is the only formulation variable affecting the bead shape. PEO content was involved in binary interactions with water and spheronizer speed. The response surface for PEO and water (Fig. 7a) shows an optimal region close to the center points (batches 17, 18, 19, 30, and 31). The bead shape deviates from the optimum at extreme values. This is because, when PEO and water are both low, the extrudate produced under these conditions is rough and irregular, exhibiting shark skinning due to the lower lubricity. This causes the extrudate to break unevenly in the spheronizer and, due to insufficient plasticity, to resist rounding up in the spheronizer. When both PEO and water are high, the wetted mass is overplasticized due to the formation of a soft PEO hydrogel, resulting in an extrudate that flattens on subjection to the mechanical forces in the spheronizer. The beads produced are also flatter and the surfaces are rougher due to the evaporation of water from the PEO hydrogel during drying.

Water content exhibited a significant ($p < 0.05$) interaction with MCC content (Fig. 7c). Sphericity of the beads was increased with MCC content at higher water level while it was decreased at low water levels. At higher water levels, increasing the MCC content leads to a reduction in the overwetting of the extrudate and, thus, increases sphericity. At lower water levels, reducing the MCC content makes more water available, thus enhancing the

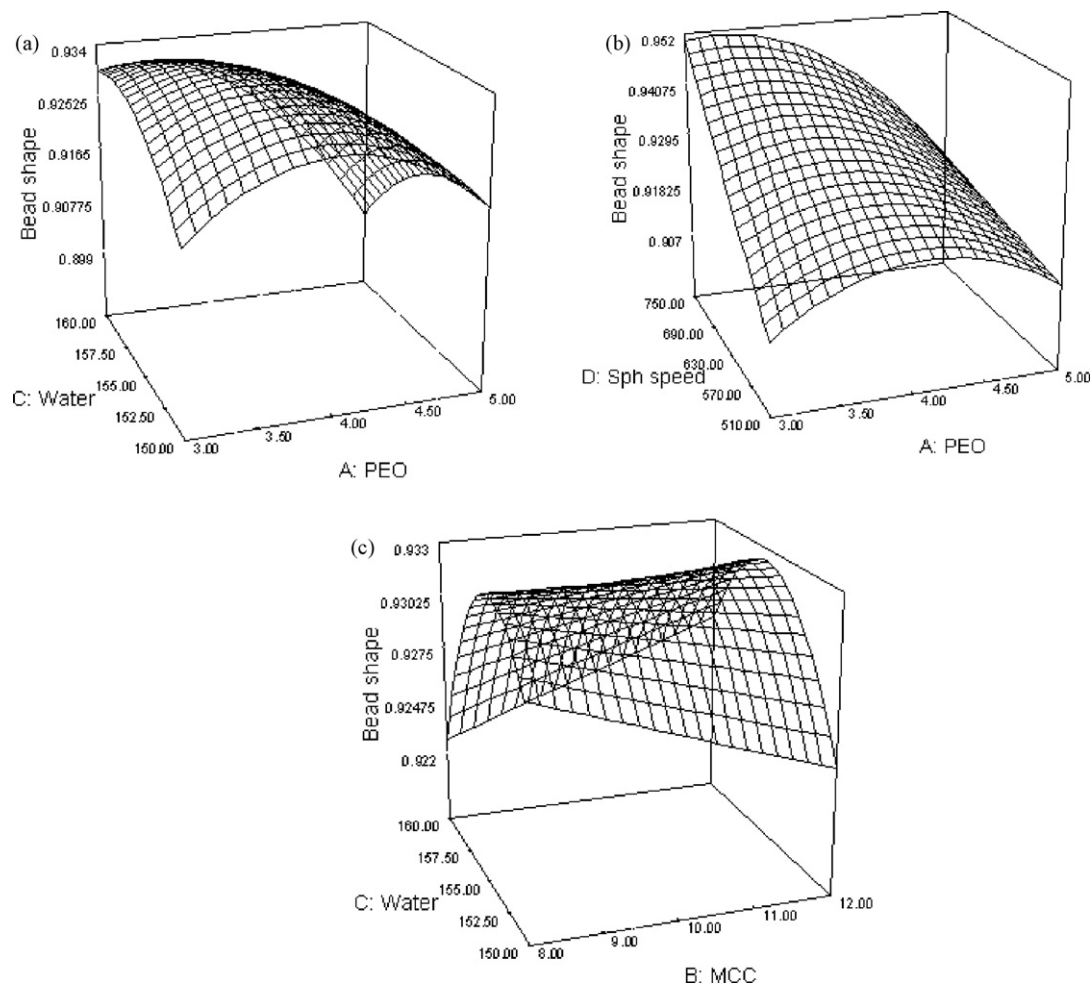


Fig. 7. Response surface plots for bead shape as a function of PEO content and water content (a), PEO content and spheronizer speed (b), and MCC content and water content (c). The other variables were at their base level.

plasticity of the wetted mass and resulting in more spherical beads. Spheronizer speed was involved in a binary interaction with PEO content (Fig. 7b). In general, higher spheronizer speeds resulted in more spherical beads. The coefficient for PEO indicates that higher PEO content impacts the bead shape negatively. These findings are

in agreement with the earlier discussion of yield where higher PEO content imparts more than the desired binding strength to the extruded wetted mass, such that, even upon increasing the spheronization speed, the mechanical forces are not sufficient to cause fracturing and eventual rounding up of the extrudate.

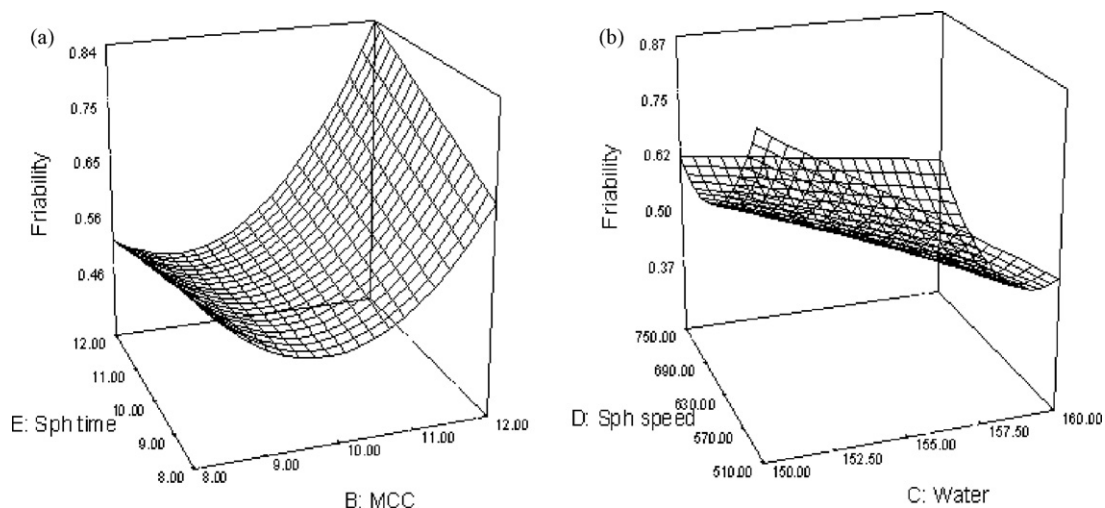


Fig. 8. Response surface plots for friability as a function of MCC content and spheronization time (a), and water content and spheronizer speed (b). The other variables were at their base level.

Table 8
ANOVA for the response surface reduced quadratic model: friability.

Source	p-Value	Source	p-Value
Model	<0.0001	A ²	<0.0001
A-PEO content	<0.0001	B ²	<0.0001
B-MCC content	<0.0001	D ²	0.0002
C-Water content	<0.0001	Lack of fit	0.1393
D-Spheronizer speed	0.0138	R ²	0.9807
E-Spheronization time	0.4473	Adj R ²	0.9706
BE	0.0098	Pred R ²	0.9547
CD	0.0038		

3.6. Friability

Beads with low friability are more rugged and thus more likely to maintain their integrity upon subsequent handling and coating processes. Each of the batches produced beads that exhibited low friability (<2%). Nevertheless, friability exhibited a wide variation in the range 0.04–1.71%. The screening design indicated that each of the variables except spheronization time significantly influenced the friability. The effects of several two-factor interactions were also observed. The model was significant ($p < 0.05$) with good fit ($R^2_{\text{adjusted}} = 99.49\%$) to the data. Lack of fit was insignificant, but there was significant curvature in the model ($p < 0.05$). The linear regression equation for the model in terms of coded factors is:

$$\text{Friability} = 0.89 - 0.55A + 0.098B - 0.099C - 0.059D + 0.024E \\ + 0.040AB - 0.030AC + 0.064BE + 0.074CD + 0.034CE$$

On analysis of the CCD responses, PEO, MCC and water contents have significant effects on the friability of the beads; spheronizer speed also has a significant effect on the friability ($p < 0.05$, Table 8). ANOVA shows that the model is significant with a good fit ($R^2_{\text{adjusted}} = 97.06\%$) to the data. Lack of fit is not significant ($p > 0.05$), suggesting that the model equation adequately describes

the response surface. The second order polynomial regression equation for friability in terms of coded factors is:

$$\text{Friability} = 0.49 - 0.55A + 0.10B - 0.11C - 0.053D + 0.015E \\ + 0.064BE + 0.074CD + 0.16A^2 + 0.16B^2 + 0.13D^2$$

PEO content is the factor that has the strongest influence on friability. The negative coefficient suggests that increasing the amount of PEO in the formulation improves the ruggedness of the beads by decreasing the friability. This is in agreement with the previous report by Maggi et al. (2000) where PEO was shown to impart binding properties to direct compression tablets. The response to this effect of PEO, however, is not linear. Low PEO levels result in high friability due to insufficient binding. At high PEO levels, even though the binding capability is higher, the surface is rough due to drying of the hydrogel, and these rougher surfaces tend to chip, contributing to the higher friability. MCC content is involved in an interaction with spheronization time (Fig. 8a). MCC also demonstrates a quadratic effect on the friability of the beads. Friability initially decreases with increasing MCC. However, a further increase in the MCC content leads to unavailability of water to the wetted mass leading to reduced plasticity of the wetted mass and an increased friability as the components in the formulation are not bonded well. Under these conditions, subjecting the underwetted beads to the abusive forces of spheronization for longer times results in higher friability of the beads. This can also be seen from the interaction plot between spheronizer speed and water content (Fig. 8b). At high spheronizer speeds, where abusive forces are high, increasing the water content does not reduce the friability of the beads. When spheronization speed is lowered along with an increase in the water, ruggedness of the beads is improved as depicted by the lower friability.

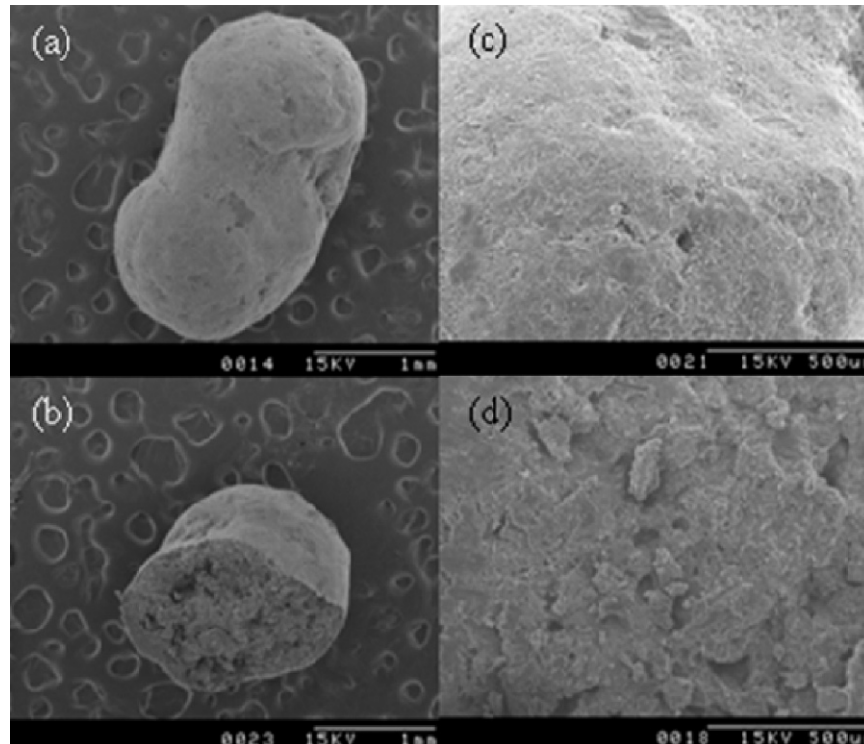


Fig. 9. SEM micrographs of a central composite design batch number 3 bead (a and c) and its cross-section (b and d) at different magnifications of 30× (a and b) and 80× (c and d).

Table 9
Comparison between predicted and experimental values for the optimal formulation.

	Yield (%)	Bead size (mm)	Bead shape (AR)	Friability (%)
Predicted ^a	90.19 ± 2.57	1.24 ± 0.03	0.94 ± 0.002	0.89 ± 0.04
Experimental	89.12, 88.26	1.21, 1.23	0.94, 0.94	0.93, 0.91

^a Mean ± standard error.

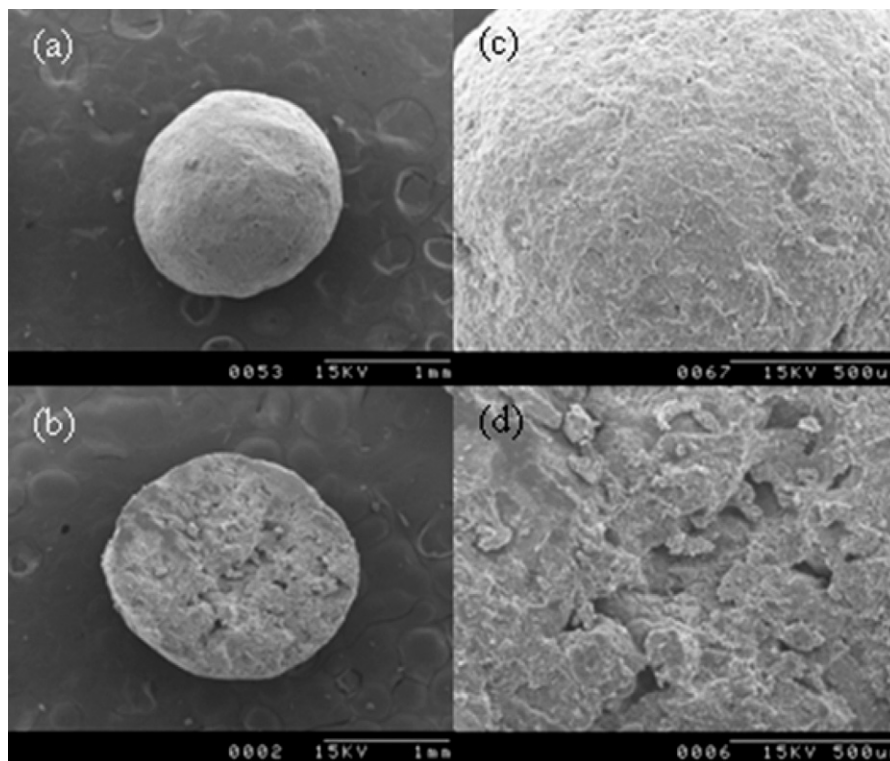


Fig. 10. SEM micrographs of an optimum batch bead (a and c) and its cross-section (b and d) at different magnifications of 30× (a and b) and 80× (c and d).

3.7. Optimization

After generating the polynomial equations relating the dependent and independent variables, the formulation was optimized for the four responses: yield, bead size, bead shape, and friability. The optimum values of the variables were obtained by graphical and numerical analyses based on the criterion of desirability functions. The optimized factor values were arrived at by minimizing MCC content and friability, maximizing yield and bead shape, and targeting an average bead diameter of 1.2 mm. Constraints were placed on the dependent variables to avoid over-predicting by venturing out of the design space. The bead size was constrained to a more conservative 1.0–1.4 mm with a target of 1.2 mm average bead diameter. The optimum factor levels were 3.6% PEO, 8% MCC, 155.6 ml water, 750 rpm spheronizer speed and 9 min spheronization time. To confirm the reliability of the response surface model, two batches of beads with the optimized factor levels were prepared and evaluated for the responses. The experimental results were in agreement with the predicted values (Table 9), which confirmed the predictability and validity of the model.

SEM analysis revealed the changes in the characteristics of the beads such as shape and texture with changing the conditions of experimental variables. Fig. 9 presents beads from batch 3 which has the combination of extreme conditions such as low PEO and water contents and high spheronization speed. Fig. 9a reveals the failure of the beads to round up under these conditions. The texture of the bead at higher magnification in Fig. 9c shows that the surface of the bead is rough and marked with irregularities. Beads from the

optimal batch, presented in Fig. 10, are relatively spherical with a smooth surface, demonstrating the success of the optimization procedure.

4. Conclusions

The results from a central composite design (alpha equal to 1.5) demonstrated the feasibility of producing high quality extruded and spheronized beads with minimal amounts of MCC by using CPEC and high molecular weight PEO. High molecular weight PEO was used as an extrusion aid and a binder. Each of the batches in the study produced beads that were highly spherical irrespective of the formulation and process variables, suggesting that CPEC is a good excipient for the production of beads by extrusion–spheronization. The beads exhibit the necessary physical and mechanical characteristics for further pharmaceutical processing such as capsule filling and coating. A statistical approach was used for simultaneous evaluation of the different formulation and process variables to allow optimization of the variables. Observed responses for the optimized product were in close agreement with the predicted values, thereby demonstrating the feasibility of the optimization procedure.

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