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PEO and MPEG in high drug load extruded and spheronized beads that are devoid of MCC

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Abstract

A means to produce extruded–spheronized beads, devoid of microcrystalline cellulose (MCC) and with a high drug load (greater than 80%, w/w), is presented. Immediate release bead product with a high yield (greater than 60% of 1 mm diameter beads) and low friability (mass loss less than 4.0%) that were spherical to the naked eye (roundness score less than 1.20) were obtained. The formulation consists only of water-soluble components, taking advantage of the properties of soluble polyethylene oxide (PEO) and methoxypolyethylene glycol (MPEG). This approach incorporates minimal processing aids, with wetted PEO providing the apparent plasticity and cohesiveness, and MPEG550 providing the apparent self-lubricating characteristics necessary for successful extrusion and subsequent spheronization into beads. The success of this approach has important implications in cases where high drug load beads are desired, but where MCC cannot be used due to chemical incompatibility or where complete release cannot be achieved with MCC-containing beads.

Keywords: Extrusion–spheronization; Pellets; Polyethylene oxide; Polyoxyethylene; Statistical design

1. Introduction

Beads are a popular multiparticulate pharmaceutical dosage form that are utilized for both immediate release and a number of different controlled or specialty release applications (Umprayn et al., 1999; Law and Deasy, 1998; Vervaet et al., 1995). Although there are numerous production methods whereby beads can be manufactured, extrusion–spheronization has rapidly grown in favor in the pharmaceutical industry. However, the manufacture of beads by extrusion–spheronization is a poorly understood process and typically the formulations rely heavily on microcrystalline cellulose for successful production of a high integrity, spherical product (Vervaet et al., 1995; Barrau et al., 1993; Ku et al., 1993). Indeed, publications on the preparation of acceptable beads without microcrystalline cellulose are rare (Agrawal et al., 2004; Tho et al., 2002; Basit et al., 1999).

The extrusion and spheronization process and equipment offer many advantages over other wet granulation techniques, including the ease of equipment set-up, a shorter duration of processing time, the resulting reduction of operator time, and ultimately cost savings (Ghebre-Sellassie, 1995, 1989). Extruded and spheronized beads are usually immediate release products, but then film coating of the beads is often an additional step to modify the release rate of the active from the bead core or to enhance its stability (Wu and McGinity, 2003; Song et al., 2002; Vervarcke et al., 2002).

The minimal components necessary for the successful development of a bead usually include a diluent, a binder, a lubricant and the active component. The binder is utilized to maintain the bead integrity and minimize friability. Typically, water is selected for its ability to act as both a binder in the wet-massing step and a lubricant in the extrusion and spheronization steps (Ghebre-Sellassie, 1995; Thoma and Ziegler, 1998). In most bead formulations, microcrystalline cellulose (MCC), commercially available as Avicel® and Emcocel® products, is regarded as a crucial diluent and spheronizing aid for successful extrusion and spheronization (Alvarez et al., 2002; Heng and Koo, 2001;

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Koo and Heng, 2001; Kleinebudde et al., 1999). It is believed that MCC acts as a molecular sponge by holding water applied during the wet massing step until pressure is applied (by extrusion or spheronization forces) that causes the held water to be expressed to the particle surface (Ek and Newton, 1998). The water present at the surface of the particles acts as a lubricant, reducing the shear forces of extrusion and thus assisting in the formation of cylindrical extrudate from the wetted mass. The water remaining inside the extrudate acts as a plasticizer in that it allows the MCC to be less structurally rigid during spheronization.

Since MCC is considered essential in bead development, it typically constitutes greater than 20% (w/w) of the final formulation for successful bead production (Hileman et al., 1993; Jover et al., 1996). Unfortunately, this limits the active load in the final bead.

Often bead formulations with higher drug loads require the addition of a lubricant in addition to water, or addition of a plasticizer to improve the sphericity of the final product (Wheatley, 2000; Mesiha and Valles, 1993; Chien and Nuessle, 1985).

Since MCC is a natural product derived from wood, it will exhibit lot to lot variability, as well as trace microbial contamination. It is not surprising then, that MCC also exhibits chemical incompatibility with a number of drugs (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, Basit et al. (1999) determined that the production of a ranitidine hydrochloride bead with the use of MCC was possible, but the drug was not chemically stable due to a complex three-way interaction between water, ranitidine hydrochloride, and MCC. Consequently, less conventional excipients were used to replace MCC, viz., barium sulfate with glycerol monostearate. Nevertheless, they could only achieve acceptable bead production by limiting the active load to 50%.

Tho et al. (2002) stated that the need to identify alternative extrusion–spheronization aids was important since bead formulations based upon MCC do not disintegrate. The intact beads often result in incomplete release of poorly water-soluble actives from the core beads. They proposed that pectinic acid, with a higher aqueous solubility than MCC, would be capable of producing beads that could disintegrate and fully release a poorly water-soluble compound, riboflavin, from its core. Unfortunately, the release after 60 min for beads containing 20 and 80% pectinic acid was 90 and 60% of the drug, respectively.

Polyethylene oxide (PEO) is a highly water-soluble, nonionic, synthetic polymer with known binding properties that is generally regarded as safe (GRAS status) for use in solid oral human dosage forms (Dow Product Info, 2004; Kim, 1998, 1995). PEO has been previously studied as a wet granulation binder for immediate and sustained release tablets (Dow Product Info, 2004); as an aid in hot melt extrusion (Repka and McGinity, 2000); as a bioadhesive for oral (Deshmukh et al., 2003; Betageri et al., 2001; Moroni and Ghebre-Sellassie, 1995), buccal (Tiwari et al., 1999), and ocular (DiColo and Zambito, 2002) products; and for coarse extrusion for tableting (Pinto et al., 2004), but not as an aid in the production of beads by extrusion–spheronization. Pinto et al. (2004) acknowledged that the affinity of PEO for water is so high that the hydrogel formed dramatically affects the extrudability of a granulation or wetted mass. As expected, by decreasing the diameter of the extrusion die, greater extrusion forces were required to produce extrudate, imposing greater stresses on the extruded mass (Pinto et al., 2004). Based upon the principles of spheronization established by Conine and Hadley (1970), the diameter of the extrusion orifice is critical to the dimensions of the final bead.

For many years, it has been known that the successful production of spherical beads by extrusion and spheronization is dependent upon the production of a wetted mass that is cohesive, plastic, and self-lubricating (Ghebre-Sellassie, 1989). Due to its chemical nature, PEO forms a strong hydrogel in the presence of water and, if this PEO hydrogel is subjected to the shear forces of extrusion, the water is not readily released (Pinto et al., 2004), unlike the "sponge" behavior of wetted MCC (Ek and Newton, 1998). Thus, a wetted PEO mass should be cohesive and plastic, but not self-lubricating.

The purpose of the research presented herein was to characterize the effects of formulation and processing conditions on pelletization using a high drug concentration. The formulations are devoid of MCC and the bead production method employs low pressure extrusion and subsequent spheronization.

2. Materials and methods

2.1. Materials

Polyethylene oxide (PEO, PolyOx® WSR-N80) [MW approximately 200k amu], to be used as an extrusion and spheronization aid, was purchased from Dow Chemical Company (Midland, MI). Triethyl citrate (TEC) and acetyltributyl citrate (ATBC), obtained from Morflex (Greensboro, NC), and polyethylene glycol 400 (PEG400) and methoxypolyethylene glycol 550 (MPEG550, Carbowax Sentry®) from Dow Chemical Company were each evaluated as lubricants/plasticizers. Pseudoephedrine hydrochloride (PSE) from Gaines Chemical (Carlstadt, NJ) was used as the model drug. Drug load in the formulation ranged from 82 to 88% (w/w). Water was distilled and deionized in-house for use as the wet massing fluid.

2.2. Bead manufacture

PSE and PEO were dry-mixed in a Hobart Model N-50 planetary mixer (Hobart Corporation, Troy, OH) for 5 min. MPEG550, PEG400, TEC, or ATBC was added to the dry mix as a lubricant/plasticizer prior to the addition of water as the wet massing fluid. Water was then added to form a wetted mass for extrusion. The wetted mass was further mixed for 1 min, and then passed through a radial-basket Nica E-140 extruder (Niro Pharma Systems, Columbia, MD) equipped with a 0.8 mm screen. The extruder feed rate was varied from 25 to 75 rpm, and the extruder rate from 75 to 125 rpm. The extrudate was collected on butcher paper. The extrudate was spheronized for up to 4.5 min in a Nica S-320 spheronizer (Niro Pharma Systems) fitted with a cross-hatched plate. The spheronizer rate was varied from 650 to 950 rpm. The contents emptied from the spheronizer

were dried in a Strea-1 fluidized bed dryer (Niro Pharma Systems) at 50 °C for 20 min.

2.3. Bead characterization

The usable yield (UY) was determined by sieve analysis of the entire dried spheronization product from each batch using a U.S. Standard Sieve series. The 16/25 mesh fraction (approximately a 1-mm diameter bead) was considered the usable yield.

Friability testing was performed in triplicate using a Model 10805 Roche friabilator (VanKel Industries, Inc., Edison, NJ). Specifically, a pre-weighed bead sample (approximately 6 g) taken from the 16/25 mesh cut was placed in the friabilator along with 25 steel spheres, each 2-mm in diameter. After 100 revolutions at 25 rpm, the mass retained on the 25-mesh screen was weighed and the friability was calculated as the percentage loss of mass between the initial and final weights of each bead sample.

Individual bead measurements (breadth, length, and roundness) were assessed using a computerized video-tracking system with a digital CCTV camera (Javelin Ultrachip) mounted onto a viewing plate, connected to a Pentium III personal computer. Digital measurements were evaluated by the computer using Leica Quantimet 5000+ software, which reports a roundness score, the length (defined as the longest dimension) and the breadth (defined as the shortest dimension) data. Care was taken prior to imaging to ensure that all beads were counted as individual entities and calibration was performed with steel spheres (roundness score 1.05, Fig. 1a). One pixel was calibrated to a width of 28.6 μm (Podczeck et al., 1999). Individual bead values (from 1000 ± 50 beads per batch) were pooled to calculate population statistics for each batch (Eriksson et al., 1997). The roundness score is calculated using the perimeter of the individual bead image, p, and the area covered by that image, A, as defined in Eq. (1):

$$\text{Roundness score} = \frac{p^2}{4\pi A} \quad (1)$$

Thus, the two-dimensional image of a spherical bead would have a roundness score of 1, and any other shape would result in a roundness score greater than 1.

Even though immediate and complete release was expected, because the formulation included only water-soluble components (Nesbitt, 1994), release studies were carried out to ensure complete release. The testing conditions consisted of 900 mL of 1 mM hydrochloric acid at 37 ± 0.5 °C in a USP dissolution apparatus 2, with a 50 rpm paddle stirring rate. Each sample was a size 3 hard gelatin capsule filled with a sufficient quantity of beads to deliver 100 mg of PSE, i.e., approximately 122 and 114 mg for 82 and 88% drug loading, respectively. A placebo consisting of a size 3 hard gelatin capsule filled with approximately 16 mg PEO and 8 mg MPEG550 was used to confirm method specificity. Drug release was studied using a reverse-phase HPLC method on a Whatman Partisil 10 SCX, 4.6 mm × 250 mm, column using a mobile phase of 50/50 (v/v) acetonitrile/phosphate buffer (0.024 M sodium phosphate containing 0.003 M sodium perchlorate, pH 2.0) with a flow rate of 1.5 mL/min. Each injection consisted of a 10 μL volume from a sample previously passed through a 45 μm filter tip. PSE was detected using UV analysis at 210 nm, with a relative retention time of 6 min.

Table 1
Empiric formulation and processing parameters

Material	% (w/w)
Pseudoephedrine hydrochloride	85.0
Polyethylene oxide (WSRN-80)	10.0
MPEG550	5.0
Purified water, USP*	5.0
Parameter	**Magnitude**
Feeder rate (rpm)	75
Extruder rate (rpm)	100
Spheronizer rate (rpm)	850
Spheronization residence time (min)	3

* Removed during processing, not present in final product.

2.4. Statistical design and analysis

After the empiric bead formulation and processing parameters were identified (Table 1), a five-factor, two-level, half fraction (2^{5-1}) screening design with three center points (Table 2) was employed to characterize the effect of formulation and process variables on the shape, friability, usable yield, and quantity of fines of the beads. The ranges of the formulation and process variables are given in Table 3. The screening design was established and the results collected were analyzed with the aid of Design-Expert, Version 6.0.6. (StatEase, Minneapolis, MN). The regression equation that is fitted to the data of the screening design is of the sort:

$$\begin{aligned} Y = {} & B_0 + B_1X_1 + B_2X_2 + B_3X_3 + B_4X_4 + B_5X_5 \\ & + B_{12}X_1X_2 + B_{13}X_1X_3 + B_{14}X_1X_4 + B_{15}X_1X_5 \\ & + B_{23}X_2X_3 + B_{24}X_2X_4 + B_{25}X_2X_5 + B_{34}X_3X_4 \\ & + B_{35}X_3X_5 + B_{45}X_4X_5 \end{aligned} \quad (2)$$

where Y is the modeled response, X_i the factors, X_iX_j the two-factor interactions, and B_i the coefficients characterizing the main (B_0–B_5) and the two-factor interaction (B_{12}, B_{13}, B_{14}, B_{15}, B_{23}, B_{24}, B_{25}, B_{34}, B_{35}, B_{45}) effects. Analysis of variance (ANOVA) was performed for each response employing an error probability of $p = 0.05$. The terms that appear in the equations were determined by reverse hierarchical regression analysis.

Due to the very low water requirement, only 5% (w/w) of the powder blend to produce an adequate wetted mass for extrusion, water level was not included as a factor in the statistical model for these PSE formulations. This particular design is attractive for five variables because it provides sufficient degrees of freedom to statistically discriminate between main factor and binary interactions in about one-half the experiments required for a full factorial design. The effects of interactions involving three or more factors are confounded and cannot be estimated. Center points were added to the design to provide additional

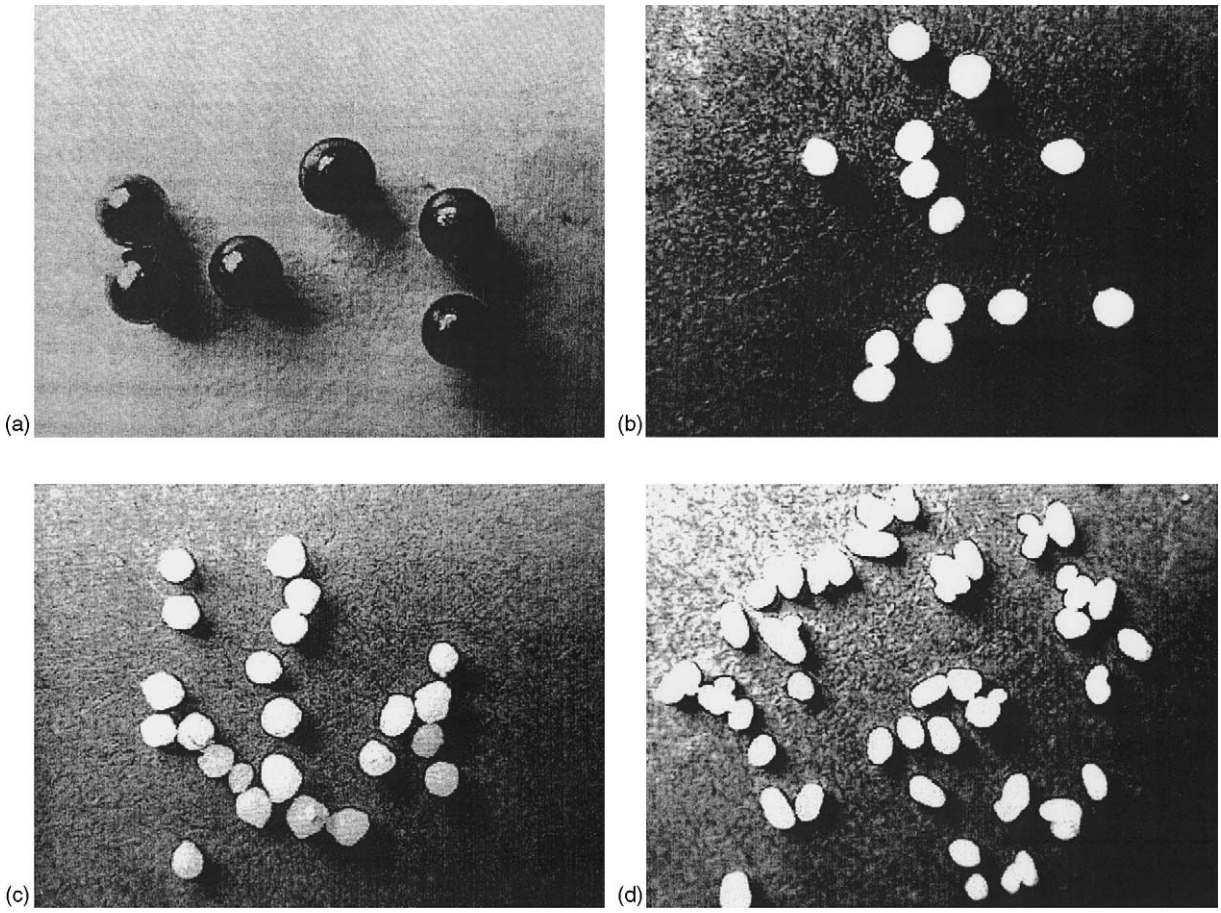

Fig. 1. Digital images of steel spheres and bead products: (a) steel spheres for image analysis calibration and for the friability studies, (b) beads from standard order batch 13 (average roundness score 1.15), (c) beads from standard order batch 10 (average roundness score 1.25), and (d) beads from standard order batch 1 (average roundness score 1.36).

degrees of freedom, to provide a measure of experimental error, and to provide for a statistical check for curvature in the responses (Montgomery, 2001). Analysis of variance was performed for each response employing an error probability of $p = 0.05$. Response variables measured included usable yield (expressed as the percentage of beads in the 16/25 mesh cut), friability (expressed as the percentage loss of mass of beads after the friability test), roundness score (as defined above),

Table 2
Statistical experimental design

Standard order	Feeder rate (*A*)	Extruder rate (*B*)	Spheronization rate (*C*)	Spheronization residence time (*D*)	Drug load (*E*)
1	−1	−1	−1	−1	+1
2	+1	−1	−1	−1	−1
3	−1	+1	−1	−1	−1
4	+1	+1	−1	−1	+1
5	−1	−1	+1	−1	−1
6	+1	−1	+1	−1	+1
7	−1	+1	+1	−1	+1
8	+1	+1	+1	−1	−1
9	−1	−1	−1	+1	−1
10	+1	−1	−1	+1	+1
11	−1	+1	−1	+1	+1
12	+1	+1	−1	+1	−1
13	−1	−1	+1	+1	+1
14	+1	−1	+1	+1	−1
15	−1	+1	+1	+1	−1
16	+1	+1	+1	+1	+1
17	0	0	0	0	0
18	0	0	0	0	0
19	0	0	0	0	0

Table 3
Factor level definition

Factor	Low level (−1)	High level (+1)
Feeder rate (rpm)	25	75
Extruder rate (rpm)	75	125
Spheronization rate (rpm)	650	950
Spheronization residence time (min)	1.5	4.5
Drug load[a] (%)	82	88

[a] The batch size was fixed at 600 g.

and "fines" (expressed as the percentage of material passing through the 25 mesh screen).

3. Results

3.1. Preliminary studies

Experiments were conducted to determine if the model drug, with deionized water as the wet massing binder, was able to exhibit the properties necessary to result in spherical beads. No cohesive extrudate was produced, let alone beads. Under the influence of the forces of extrusion, the wetted mass returned to a form consistent with the starting powder blend.

Mixtures of PSE and PEO (0–12%) were wetted with deionized water to determine if suitable extrudate and beads could be produced. Formulations containing PEO concentrations of less than 5% (w/w) were not able to form a wetted mass capable of producing extrudate, while successful production of reasonably spherical beads, with low friability, could be produced with as little as 10% (w/w) PEO. At the upper end of the PEO concentrations studied, the wetted mass was cohesive enough to withstand the shear forces of extrusion, and visibly bead-like material was discharged from the spheronizer.

The lubricants selected for this study were water-soluble PEG400, MPEG550, and TEC, as well as the poorly water-soluble ATBC. For formulations containing ATBC, the extrudate produced was highly viscous yet flexible, with a high retention of moisture, and formed large aggregates in the spheronizer. Reducing ATBC levels to as little as 2% (w/w) did not improve the quality of the product. Formulations incorporating TEC was slightly more promising, with the best batches still producing visibly irregular beads. While the addition of either citrate plasticizer appeared to reduce the quantity of material on the spheronizer walls, neither was capable of totally eliminating material collection.

Including PEG400 in the formulation not only reduced the mass of material collecting on the spheronizer walls, but it also allowed the successful production of beads. However, the PSE–PEO–PEG400 beads were noticeably soft. It could be confirmed visually that the bead geometry was negatively impacted upon fluid bed drying. Beads that were subjected to forced hot air tray drying experienced significant particle agglomeration.

3.2. Statistical design experiments

Beads were successfully produced with a PSE–PEO–MPEG550 formulation. Numerous formulations were prepared to empirically determine a wetted mass consisting of only PSE, PEO, MPEG550, and water that would yield a product with the following characteristics: (1) spherical beads; (2) usable bead yield (16/25 mesh cut) greater than 60%; (3) minimal bead friability, surviving fluid bed drying and experiencing less than 4% loss in the friability test; and (4) drug load greater than 80%. An empiric formulation and process were identified (Table 1). Results from preliminary experiments revealed that the key responses, usable yield, friability, and roundness score were sensitive to the mass ratio of 2:1:1 PEO/MPEG/water. The ranges for other variables that led to a bead product that could still be characterized were established in preliminary studies. The experimental design batches were then completed using the ranges about the center values (Tables 2 and 3).

Table 4
Mean responses from screening design

Standard order	Usable yield (% theoretical)	Friability (% weight loss)	Roundness score	Fines (% theoretical)
1	47.4	29.1	1.36	23.2
2	51.8	3.62	1.22	19.1
3	47.4	7.33	1.28	10.5
4	66.1	3.23	1.30	25.9
5	45.7	5.85	1.24	5.06
6	55.8	11.3	1.29	25.3
7	60.2	2.60	1.32	27.5
8	29.8	2.65	1.29	8.57
9	66.7	6.78	1.18	10.2
10	51.1	17.5	1.25	17.8
11	73.4	20.9	1.32	14.6
12	80.4	5.75	1.24	9.42
13	76.7	3.17	1.15	9.56
14	57.1	11.8	1.33	24.6
15	30.0	1.05	1.20	7.29
16	62.2	4.01	1.23	8.82
17	76.4	8.20	1.20	6.61
18	64.4	7.50	1.22	10.2
19	68.4	9.20	1.21	13.2

Usable yield values ranged from 56.5 to 78.0% theoretical, and friability values ranged from 1.1 to 29.1% mass loss, largely due to the harsh nature of the friability test. The quantity of fines ranged from 7.29 to 27.5%. Individual values for usable yield, friability, roundness score, and fines are provided in Table 4. The results of the statistical analysis on the usable yield and friability are presented in Tables 5 and 6, respectively. The results of the statistical analysis on the roundness score are in Table 7, and the results for fines are in Table 8.

Table 5
Analysis of variance: usable yield

Source	p-Value	Source	p-Value
Model	0.0018	*BC*	0.0016
A	0.7538	*BE*	0.0171
B	0.8926	*CE*	0.0019
C	0.0149	Lack-of-fit	0.7139
D	0.0028	Curvature	0.0047
E	0.0050	R^2	0.943
AB	0.0539	Adj R^2	0.862
AE	0.0417		

Table 6
Analysis of variance: friability

Source	*p*-Value	Source	*p*-Value
Model	0.0005	*AE*	0.0120
A	0.0341	*BD*	0.0062
B	0.0009	*BE*	0.0228
C	0.0003	*CE*	0.0005
D	0.4081	Lack-of-fit	0.1974
E	0.0005	Curvature	0.8082
AB	0.0449	R^2	0.988
AC	0.0003	Adj R^2	0.960
AD	0.0031		

Table 7
Analysis of variance: roundness score

Source	*p*-Value	Source	*p*-Value
Model	0.0012	*AD*	0.0042
A	0.1915	*AE*	0.0065
B	0.0510	*CE*	0.0013
C	0.1617	*DE*	0.0078
D	0.0007	Lack-of-fit	0.3143
E	0.0104	Curvature	0.0015
AB	0.0146	R^2	0.969
AC	0.0015	Adj R^2	0.913

Table 8
Analysis of variance: fines

Source	*p*-Value	Source	*p*-Value
Model	0.0009	*DE*	0.0022
A	0.0584	Lack-of-fit	0.4985
B	0.1656	Curvature	0.0409
D	0.0154	R^2	0.834
E	0.0026	Adj R^2	0.743
AB	0.0106		

4. Discussion

Pseudoephedrine hydrochloride was selected as the model drug for several reasons. It has a high solubility in water, which could be challenging in the wet massing step. In addition, there are currently multiple commercial bead formulations with a high pseudoephedrine hydrochloride load, indicating the need for such a product.

Consistent with technical reports from the manufacturer (Dow Product Info, 2004), PEO was capable of exhibiting binding properties in both the wetted mass and extrudate. After the PSE–PEO–water extrudate was charged into and subjected to the forces of spheronization, the product was only oval and bead-like, somewhere between smaller extrudate pieces and true spheres. Even with addition of citrate plasticizers, there was still substantial build-up of material on the spheronizer wall. Further experiments focused on the addition of a lubricant to reduce the collection of material on the spheronizer walls, improve the bead sphericity, and improve reproducibility.

An ideal extrusion–spheronization lubricant should possess the following properties. First, it should be readily available as a liquid at room temperature in order to achieve uniform distribution in all processing phases. Next, the lubricant should be of minimal molecular size, so as to be able to move about the polymer strands to impart flexibility. Last, the selected lubricant, regardless of its aqueous solubility, should be effective at concentrations low enough to not influence the rate of drug release from the bead. Chien and Nuessle (1985) commented on the potential use of polyethylene glycol as a lubricant for extrusion–spheronization. In later publications, authors discuss the use of common pharmaceutical plasticizers and surfactants as lubricants for extrusion and spheronization (Junnila et al., 1998; Blanque et al., 1995; Mesiha and Valles, 1993).

PEG400 was selected due to it structural similarity to PEO. It was hoped that this structural similarity would allow the PEG400 in the wetted mass to also act as a plasticizer during the extrusion and spheronization steps. Conceptually, with the applied forces of extrusion, the PEG400 would be capable of moving between the strands of PEO to be expressed to the surface. Then, at the surface, the waxy texture of PEG400 would act as an adjunct lubricant to water to reduce surface extrudate damage and dehydration.

Methoxypolyethylene glycol was identified as a potential plasticizer similar in chemical structure to PEG400, but less chemically reactive due to the methoxy end group. MPEG of higher molecular weight has been used in biopharmaceutical formulations to add stability, both chemical and biological, to liposomes (Zhang et al., 2004). Recently, Chen and Scott (2003) demonstrated that MPEG could be attached to allogenic tissues to provide “immunocamouflage”, thus reducing tissue rejection associated with transplants.

Statistical analysis of the results data indicates that the models for usable yield, friability, and roundness score are significant (Tables 5–7), with $R^2 > 0.94$. The R^2 for fines was only 0.83, although the model describing the data was statistically significant (Table 8). Lack-of-fit was not statistically significant ($p > 0.05$), and the plots for both normal residuals and outliers were unremarkable for each of the responses. Curvature is statistically significant for usable yield, roundness score, and fines, suggesting that three-dimensional plots for these responses are more curvilinear than linear in the design space.

The reported complexity of the extrusion–spheronization process is supported by the results of this study. While the greatest usable yield and lowest roundness scores occur under similar conditions, the lowest friability values do not. The lowest friability occurs under the highest extrusion conditions (feeder and extruder rates), while the usable yield is highest and roundness scores are lowest with the slowest extrusion conditions. Interestingly, the highest usable yield and lowest roundness scores occur with the most aggressive spheronization conditions (fastest spheronization rate and longest spheronization time), while the lowest friability values occur with the mildest spheronization conditions. Increasing drug load has a positive influence by increasing usable yield and decreasing roundness scores, while decreasing drug load reduces bead friability. Nevertheless, each of the four models for the responses predicts well the results from the study. In general, the complex nature and statistical significance of multiple two-factor interactions did not make it possible to independently evaluate the effects

of formulation or processing parameters on these responses. Since the effects of main factors and two-factor interactions varied depending on the response, discussion of the individual responses follows.

4.1. Usable yield

One measure of success for an extrusion–spheronization formulation and process is a high percentage of beads produced within a selected size range. For these studies, a 1-mm bead was desired and the 0.8–1.2 mm diameter range (the 16/25-mesh range) was studied. Percentage of theoretical was selected as a more conservative calculation, rather than the percentage based upon the total mass of beads following drying. The regression equation for yield in terms of actual factors is:

$$\begin{aligned}\text{Usable yield (\%)} = {} & 10.3 + 0.0321 \times A - 0.0345 \\ & \times B - 0.0104 \times C + 0.0389 \times D - 0.127 \\ & \times E + 4.82 \times 10^{-5} \times AB - 4.32 \\ & \times 10^{-4} \times AE - 1.72 \times 10^{-5} \times BC + 5.39 \\ & \times 10^{-4} \times BE + 1.40 \times 10^{-4} \times CE \qquad (3)\end{aligned}$$

Unfortunately, drawing conclusions from graphical interpretations of a single three-dimensional plot is incomplete and often deceptive. Fig. 2 demonstrates that imbedding multiple levels of additional factors can expand the possible graphical interpretation to up to five dimensions, thus providing a more complete evaluation of five factors for one response. Each of the imbedded graphs is plotted identically. The imbedded axes include usable yield ranges from zero to 80% on the *z*-axis, the feeder rate from 25 to 75 rpm on the *x*-axis, and extruder rate from 75 to 125 rpm on the *y*-axis. Within each graph, three diagonally arranged layers represent 1.5, 3.0, and 4.5 min of spheronization time. In each case, the 1.5 min time is the lower left portion and 4.5 min is the upper right portion of the plot, whereas the three plots on the diagonal represent 3.0 min of spheronization time. The positive coefficient for the main factor '*D*' and the absence of its involvement in any two-factor interactions in the model equation indicates that, irrespective of the level of any of the other factors, an increase in spheronization time will result in an increase in usable yield.

The major vertical axis represents the spheronization rate. The bottom row of all three imbedded graphs represents 650 rpm, the middle row represents 800 rpm, and the upper row represents 950 rpm spheronizer rate. It can be concluded that, under all combinations within the design space, as long as the drug load is greater than 82% (w/w), higher spheronization rates result in increases in the usable yield. For combinations containing the lowest drug load studied (82%, w/w), only a small difference in usable yield is observed with an increase in spheronization rate.

The major horizontal axis represents increasing drug load. The first column of graphs represents the low drug load (82%, w/w), the second column is the middle drug load (85%, w/w), and the third column is the highest drug load (88%, w/w). As long as the spheronization rate is greater than 650 rpm, increasing the drug load increases the usable yield. With the slowest spheronization rate, an increase in drug load can increase or decrease the usable yield, the direction being highly dependent on opposing feeder and extruder rates.

From this graphical interpretation, the greatest usable yield values appear in the uppermost right corner of the graph, specifically low feeder and extruder rates, with high spheronization rates, spheronization time, and drug load. Usable yield appears to be dominated by the influence of drug load. This could be because the content of PEO is inversely proportional to the drug load, and the production of extrudate is more sensitive to dehydration when the PEO content is higher. These conditions would represent the greatest opportunity for starving the extrusion zone with extrusion rates three times the rate of material fed into the extrusion zone. Any damage encountered is subsequently exposed to the friction, heat, and shear forces produced by the highest spheronization rates studied. The ultimate effect is milling of the spheronized material, which would produce a greater quantity of "fines" and reduce the usable yield. Substituting the optimal conditions into the usable yield equation above, a value of 81.0% is predicted. This value closely approximates the 76.7% observed value.

4.2. Friability

Bead friability is assessed because beads with low friability are more likely to retain their integrity on handling and during further processing, such as film coating. The regression equation for the friability in terms of actual factors is:

$$\begin{aligned}\text{Friability (\%)} = {} & -661.0 + 0.872 \times A + 1.19 \times B + 0.496 \\ & \times C - 6.80 \times D + 8.78 \times E - 1.56 \times 10^{-3} \\ & \times AB + 8.51 \times 10^{-4} \times AC + 0.0520 \times AD \\ & -0.0188 \times AE + 0.0442 \times BD - 0.0158 \\ & \times BE - 6.59 \times 10^{-3} \times CE \qquad (4)\end{aligned}$$

For Fig. 3, the imbedded axes include friability ranges from 0 to 30% on the *z*-axis, while all other axes remain in magnitude and orientation as stated previously. Graphical interpretation is complex with the lowest friability scores occurring under the fastest feeder and extruder rates, with the slowest spheronization rate, shortest spheronization time, and lowest drug load. In contrast to the results for usable yield, the optimum conditions for minimal friability appear to correlate with the conditions that would provide optimum extrudate production. Unfortunately, this was not a batch prepared within the study. Taking into account the high correlation coefficient for this model ($R^2 = 0.988$), high predictability would be expected.

4.3. Roundness score

While it is desirable to obtain high usable yields of durable beads, it is ultimately the shape of the collected material that is

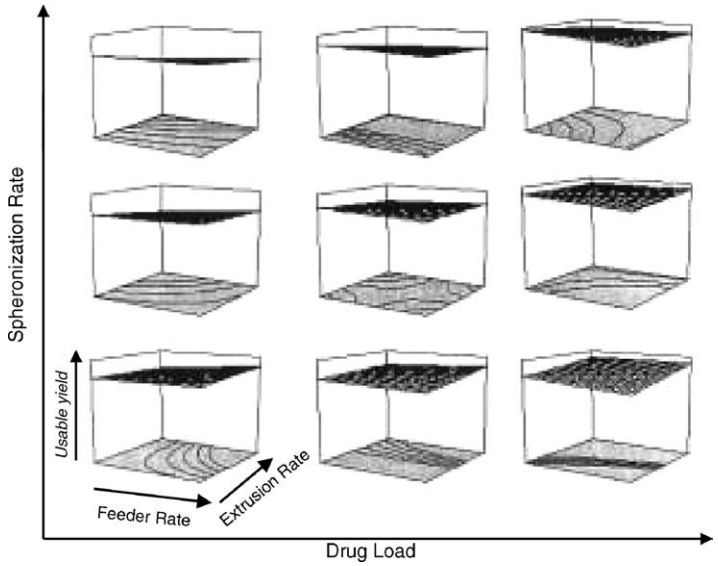

Fig. 2. Effect of feeder, extrusion and spheronization rates, spheronization time, and drug load on the usable yield.

critical for a number of processing advantages of beads (e.g., a free-flowing and uniformly coated product). It is ultimately the work of the spheronization process to fragment the extrudate through interactions with the frictional plate, and subsequently round and smooth the fragments into beads largely through particle to particle interactions. Roundness scores ranged from 1.15 to 1.36, with a roundness score of 1 representing a perfect sphere.

To illustrate the difference between roundness scores of 1.15 and 1.36, digital images of three selected batches representing average roundness scores of 1.15, 1.25, and 1.36 are provided in Fig. 1b–d. These images support the observation of Hileman et al. (1993) that beads with average roundness scores of 1.20 or less are spherical to the naked eye. Prior to, and at the conclusion of all bead measurements, the roundness score of steel spheres were measured as reference material (roundness score 1.05) to ensure the reliability of the reported values.

The regression equation for the roundness score in terms of actual factors is:

$$\begin{aligned}\text{Roundness} = {} & -4.20 + 0.0149 \times A + 1.49 \times 10^{-3} \times B + 3.97 \\ & \times 10^{-3} \times C + 0.258 \times D + 0.0670 \times E - 2.19 \\ & \times 10^{-5} \times AB + 5.95 \times 10^{-6} \times AC + 4.82 \\ & \times 10^{-4} \times AD - 2.19 \times 10^{-4} \times AE - 5.07 \\ & \times 10^{-5} \times CE - 3.51 \times 10^{-3} \times DE \end{aligned} \quad (5)$$

For Fig. 4, roundness scores ranging from 1.15 to 1.45 are on the z-axis, while all other axes remain in magnitude and orientation as stated previously. Graphical interpretation is complex with the lowest roundness scores appearing to occur in the uppermost right corner of the graph corresponding to low feeder and extruder rates, with all other factors at their high level. The optimum conditions for roundness scores correlate with the slowest feeder and extruder rates. Subsequently, the extrudate is subjected to the most aggressive spheronization conditions, to separate, round, and smooth the extrudate into spherical beads. Substituting these conditions into the roundness model equation, a value of 1.16 is predicted. This closely approximates the 1.15 observed value.

4.4. Fines

Due to the small quantity of water required to adequately produce beads for the center point of the design, 5% (w/w) as compared to typical MCC formulations requiring 20–30% (w/w), the quantity of fines was analyzed. The quantity of fines was defined as the mass of dried material that passes through a 25-mesh screen. For prolonged spheronization times, two mechanisms exist to decrease the usable yield. First, extrudate that is not sufficiently plastic or lubricated at the surface will experience greater damage through the forces of spheronization, ultimately fracturing the forming beads through attrition, and thus increasing the quantity of fine particles. Alternatively, if the extrudate is overwetted, excessive quantities of water are expressed to the surface leading to agglomeration. This agglomeration increases the quantity of abnormally large particles, while decreasing the usable yield. Analysis of variance (Table 8) suggests the mathematical model is more than an adequate fit to the data ($R = 0.834$). Lack-of-fit was not statistically significant ($p > 0.05$), and the plots for both normal residuals and outliers were unremarkable.

Table 9
Average (R.S.D.) dissolution values

Drug loading	15 min	30 min	45 min
82%	98.4 (1.1)	99.8 (1.0)	98.9 (1.3)
88%	99.8 (3.4)	100.0 (3.4)	99.8 (3.4)

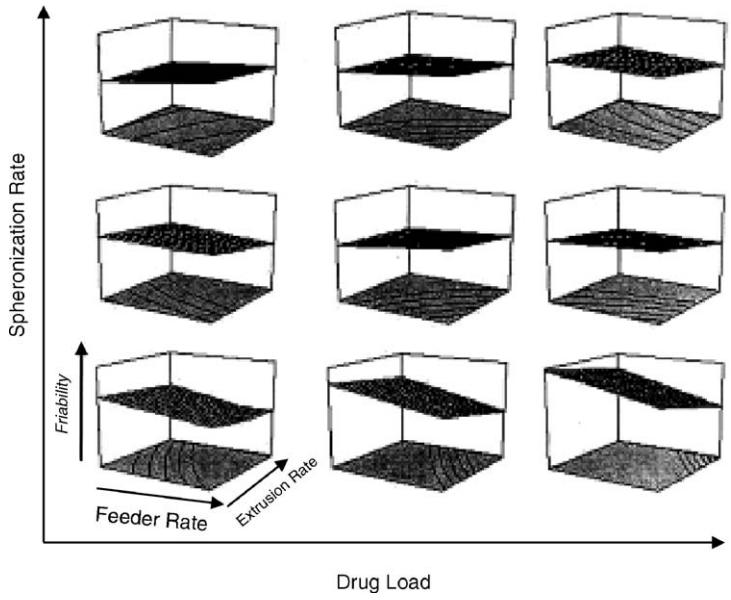

Fig. 3. Effect of feeder, extrusion and spheronization rates, spheronization time, and drug load on the friability.

The regression equation for the quantity of fines in terms of actual factors is:

$$\text{Fines} = -3.14 + 0.00539 \times A + 0.00174 \times B + 0.683 \times D + 0.0368 \times E - 4.60E - 005 \times AB - 0.00825 \times DE \quad (6)$$

For Fig. 5, fines quantities range from 0 to 30% on the vertical axis, while all other axes remain in magnitude and orientation as stated previously.

Graphical interpretation reveals that differences in the fines quantity are small, and this is reflected in the lower R^2, despite the fact that the model is significant. Since the factor C is not included in the model equation, spheronization rate has no influence on the quantity of fines. The lowest quantity of fines is obtained with the slowest feeder and extrusion rates, shortest spheronization time, and lowest drug load. Substituting these conditions into the fines model equation, a value of 6.6% is predicted. This value closely approximates the 5.05% observed value.

4.5. Drug release studies

One potential concern with beads produced with the aid of MCC is the inability to achieve complete release, which in turn would negatively impact bioavailability (Tho et al., 2002). While it was fully anticipated that 100% release would be achieved within 30 min, two batches with different drug loading (82 and 88%, w/w) were selected from the screening design to determine

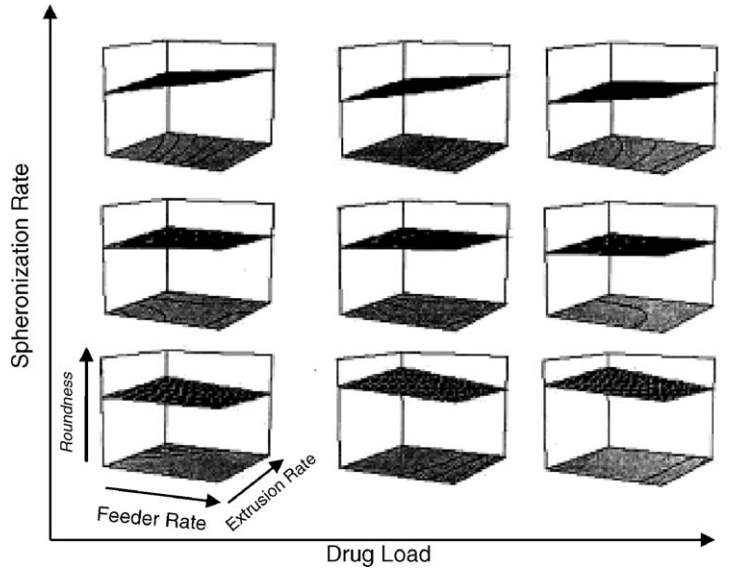

Fig. 4. Effect of feeder, extrusion and spheronization rates, spheronization time, and drug load on the roundness score.

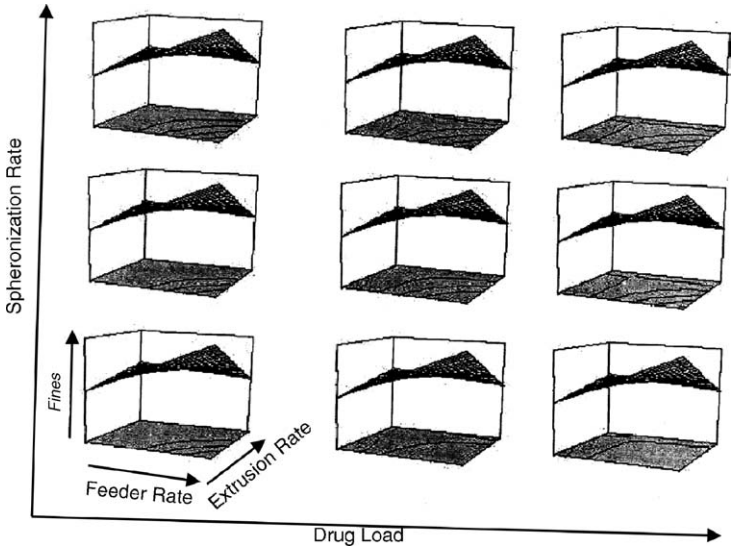

Fig. 5. Effect of feeder, extrusion and spheronization rates, spheronization time, and drug load on the fines.

the PSE release profile. The release of PSE was fast with complete release (greater than 95%) occurring at 15 min, regardless of the drug loading. The average release results are provided in Table 9.

5. Conclusions

The present study results demonstrated that PEO with MPEG550 provides a suitable alternative approach for using low pressure extrusion, and subsequent spheronization to produce beads that are devoid of MCC and that have a high drug load. The statistical analysis provided highly correlated linear models that included many two-factor interactions. Overall, the approach produced a high yield of immediate release, low friability beads that were visibly spherical.

The proposed formulation approach incorporates minimal processing aids, with wetted PEO providing the apparent plasticity and cohesiveness, and MPEG550 providing the apparent self-lubricating characteristics necessary for successful extrusion and subsequent spheronization into beads. These results have important implications in cases where high drug load (greater than 80%, w/w) beads are desired, but where MCC cannot be used due to chemical incompatibility or where complete release cannot be achieved with MCC-containing beads.

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