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Formulation and Characterization of a Compacted Multiparticulate System for Modified Release of Water-Soluble Drugs – Part 1 Acetaminophen

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The aim of this study was to characterize and evaluate a modified release, multiparticulate tablet formulation consisting of placebo beads and drug-loaded beads. Acetaminophen (APAP) bead formulations containing ethylcellulose (EC) from 40–60% and placebo beads containing 30% calcium silicate and prepared using 0–20% alcohol were developed using extrusion–spheronization and studied using a central composite experimental design. Particle size and true density of beads were measured. Segregation testing was performed using the novel ASTM D6940-04 method on a 50:50 blend of uncoated APAP beads (60%EC) : calcium silicate placebo beads (10% alcohol). Tablets were prepared using an instrumented Stokes-B2 rotary tablet press and evaluated for crushing strength and dissolution rate. Compared with drug beads (60%EC), placebo beads (10% alcohol) were smaller but had higher true densities: 864.8 μm and 1.27 g/cm^3, and 787.1 μm and 1.73 g/cm^3, respectively. Segregation testing revealed that there was approximately a 20% difference in drug content (as measured by the coefficient of variation) between initial and final blend samples. Although calcium silicate-based placebo beads were shown to be ineffective cushioning agents in blends with Sure-lease®-coated APAP beads, they were found to be very compactibile when used alone and gave tablet crushing strength values between 14 and 17 kP. The EC in the APAP bead matrix minimally suppressed the drug release from uncoated beads ($t_{100\%}$ = 2 h). However, while tablets containing placebo beads reformulated with glycerol monostearate (GMS) showed a slower release rate ($t_{60\%}$= 5 h) compared with calcium silicate-based placebos, some coating damage (~30%) still occurred on compression as release was faster than coated APAP beads alone. While tablets containing coated drug beads can be produced with practical crushing strengths (>8 kP) and low compression pressures (10–35 MPa), dissolution studies revealed that calcium silicate-based placebos are ineffective as cushioning agents. Blend segregation was likely observed due to the particle size and the density differences between APAP beads and calcium silicate-based placebo beads; placebo bead percolation can perhaps be minimized by increasing their size during the extrusion–spheronization process. The GMS-based placebos offer greater promise as cushioning agents for compacted, coated drug beads; however, this requires an optimized compression pressure range and drug bead : placebo bead ratio (i.e., 50:50).

Keywords multiparticulate delivery systems; modified release; matrix tablets; ethylcellulose; extrusion–spheronization; segregation

INTRODUCTION

The development of coated, modified release beads produced by extrusion–spheronization is currently an important and popular research topic in the pharmaceutical industry. Traditionally, these beads were filled into gelatin capsules, and this process was gentle enough to avoid damaging the bead coating; however, capsule filling is generally more time-consuming and costlier than tableting. If the technological challenges related to protecting the bead coating during tablet compaction can be overcome through a thorough understanding of material science and the physical/mechanical properties of the beads themselves, then tablet manufacturing would be the preferred method of production.

Acetaminophen (APAP) is a well-known analgesic and was chosen as a model drug for this study because of its relatively short plasma half-life of between 1 and 3 h (Parfitt, 1999), and this would make it an ideal candidate for extended release, and it has high aqueous solubility of approximately 13 mg/mL (Fairbrother, 1974). APAP is classified as biopharmaceutics classification system (BCS) class I drug (Amidon, Lennernas, Shah, & Crison, 1995). It is a weak acid with a pK_a of 9.0 (Fairbrother, 1974). The ultimate goal of this research was to make a water-soluble drug formulation containing APAP dissolution rate limited through the use of two release-controlling features, namely, a hydrophobic bead matrix and bead film coating. To achieve this aim, a modified release, multiparticulate system consisting of film-coated drug beads and cushioning placebo beads were blended in an optimum ratio and compressed into tablets.

Modified release matrix formulations used to delay drug release are relatively inexpensive to produce and have been studied extensively with other swellable hydrophilic polymers such as

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hydroxypropylmethylcellulose (HPMC) (Ford, Rubinstein, & Hogan, 1985; Li, Martini, Ford, & Roberts, 2005; Merchant, Shoaib, Tazeen, & Yousuf, 2006; Williams, Reynolds, Cabelka, Sykora, & Mahaguna, 2002) and to some degree with combinations of HPMC and ethylcellulose (EC) (Makhija and Vavia, 2002; Tiwari, Murthy, Pai, Mehta, & Chowdary, 2003; Vatsaraj, Zia, & Needham, 2002). Although HPMC is known to provide zero-order drug release with profiles spanning 24 h or more (Ford et al., 1985; Merchant et al., 2006), it is also known to form relatively tacky solutions (Ritala, Holm, Schaefer, & Kristensen, 1988). This polymer would not be the preferred choice for extrusion–spheronization as it would form a tacky, cohesive, and swelling mass that would be difficult to extrude and spheronize, and therefore, the properties of EC are ideal for this application.

EC is available in a number of viscosity grades (7, 10, and 100 cP) that differ in their degree of substitution and average molecular weight. It was hypothesized that the elevated levels of a high surface area, nonswellable, and micronized grade (7 cP) of EC could act as a hydrophobic matrix in the beads to effectively delay drug release. EC can produce hard tablets with low friability, and while the tablets will usually disintegrate readily, the hydrophobic nature of EC acts to retard drug release. In fact, it has been shown that the lower viscosity grade of EC (7 cP) allows for the production of harder tablets under similar compression forces (Katikaneni, Upadrashta, Neau, & Mitra, 1995a; Katikaneni, Upadrashta, Rowlings, Neau, & Hileman, 1995b; Upadrashta, Katikaneni, Hileman, Neau, & Rowlings, 1994). This grade also displayed an improved compactibility and reduced elastic recovery. In fact, the tablets prepared using low-viscosity EC have been shown to have lower porosity values; and this resulted in slower dissolution rates as compared with the tablets prepared using higher viscosity EC grades (Khan & Meidan, 2007; Shlieout & Zessin, 1996). Although these unique properties of low-viscosity, micronized EC warrant its further study in beads prepared via extrusion–spheronization, no work to date has examined the role that EC alone plays in modifying the release of water-soluble drugs from multiparticulate systems.

An excipient believed to play an important role in placebo bead formulations would be calcium silicate. The presence of high levels of calcium silicate (~40%) has been shown to give substantially higher mechanical strength to tablets (Yuasa, Akutagawa, Hashizume, & Kanaya, 1996). These authors explained that this highly porous excipient deformed plastically and underwent brittle fracture at low compression pressures. This fracturing could increase the contact points and contact area among particles, which increases interparticle bonding and tablet crushing strength. Moreover, because of its highly porous nature and the ease with which the calcium silicate deforms and fractures, it should be able to adequately protect the drug bead film-coat from rupturing by widely distributing the compressive stress along the surface of the drug particles and preventing stress concentration at contact points that could lead to fracturing of the film coating (Asano et al., 1997; Yuasa, Takashima, Omata, & Kanaya, 2001).

Water plays an important role in the extrusion–spheronization process as it acts as a lubricant in helping ease the passage of extrudates through the die wall. However, the presence of too much moisture in the wet mass can cause stickiness and excessive aggregation of the extrudate strands; conversely, material that is too dry can generate a wider particle size distribution with substantial amounts of fines during extrusion–spheronization (Rough, Bridgwater, & Wilson, 2000). Moreover, the type of granulating liquid can have a profound impact on the bead characteristics.

Microcrystalline cellulose (MCC) is well known to be an important moisture modulator during extrusion–spheronization (Ek & Newton, 1998; Kleinebudde, 1997), and recent research has shown that MCC swells significantly less in the presence of alcoholic solvents (e.g., ethanol and isopropanol) (El Seoud, Fidale, Ruiz, D'Almeida, & Frollini, 2008). Beads prepared from alcohol tend to be weak, friable, irregular in shape (Elbers, Bakkenes, & Fokkens, 1992; Millili & Schwartz, 1990), and porous (Berggren & Alderborn, 2001). Johansson, Wickberg, Ek, and Alderborn (1995) showed that bead porosity was inversely proportional to the tensile strength of compacts formed at a certain compression pressure. However, increasing the water content of the granulation liquid led to an increase in bead crushing strength (Millili & Schwartz, 1990). Beads prepared with MCC and higher water levels between 35 and 45% (wt/wt) were shown to be less friable and have larger particle sizes (Heng & Koo, 2001). The behavior of MCC in the presence of moisture will affect its ability to be an extrusion–spheronization aid and can ultimately impact the bead quality. There have been a number of articles dating back to more than a decade that have tried to address the problem of producing tablets from controlled release-coated beads. Because the topic is very complex and there are several potential problems such as the properties and levels of the coated drug beads and placebo beads themselves, mechanical properties of the polymer films used to coat the drug beads, segregation during tableting, and drug release during dissolution, the earlier research has met with varying levels of success (Aulton, Dyer, & Khan, 1994; Dyer, Khan, & Aulton, 1995). More recently, however, authors have achieved success in tableting-coated drug beads by the careful selection of the film-coating material, cushioning placebo bead formulation, ratio of placebo beads to coated drug beads, and compression force (Lundqvist, Podczeck, & Newton, 1998; Vergote, Kiekens, Vervaet, & Remon, 2002).

Although the aim of this study was to first characterize the physical properties of the APAP beads and placebo beads, the overall objective of this research was to develop prototype modified release APAP tablet formulations with in vitro release profiles greater than 8 h. Moreover, it was also desired to study (a) the compactibility of the placebo beads themselves and their protective cushioning effect when compacted with coated drug beads, (b) the individual effectiveness that both the

EC matrix and the Surelease® bead coating had on the suppression of APAP release, and (c) the segregation tendency of a mixture of placebo beads and uncoated, drug-loaded beads.

MATERIALS AND METHODS

Materials

APAP USP and polyvinylpyrrolidone (PVP NF) K29/32 were supplied by ISP (Wayne, NJ, USA) and Mallinckrodt (St. Louis, MO, USA), respectively. Fine particle EC NF 7 cP viscosity grade (Ethocel 7-FP Premium), with an ethoxyl content of 48.0–49.5%, was a gift from Dow Chemical Company (Midland, MI, USA). MCC NF (Avicel® PH-101) was supplied by FMC Corp. (Princeton, NJ, USA). Calcium Silicate NF (FM 1000) was donated by J.M. Huber Corp. (Havre de Grace, MD, USA). Glycerol monostearate (GMS) NF flakes were purchased from Spectrum Chemicals (New Brunswick, NJ, USA). Sodium Starch Glycolate NF (Explotab®) was supplied by JRS Pharma (Patterson, NY, USA). Magnesium Stearate NF was obtained from Mutchler, Inc. (Harrington Park, NJ, USA). Denatured Alcohol formula 3A was purchased from VWR Scientific (Bridgeport, NJ, USA). Heavy white mineral oil (density 0.88 g/mL) was purchased from ICN Biomedicals, Inc. (Aurora, OH, USA). Surelease® dispersion (Lot# IN509318) and Starch 1500 NF were supplied by Colorcon (West Point, PA, USA).

Bead Manufacture: APAP Beads and Calcium Silicate-Based Placebos

Batches of 400 g were mixed in a planetary mixer (Model KU-1; Erweka, Heusenstamm, Germany). The drug formulations were prepared by combining all dry powders including PVP K29/32 in the mixing bowl, granulating with distilled water, and mixing for 5 min. The placebo formulations containing calcium silicate were prepared in the same way except that a 10% (wt/wt) aqueous binder solution of PVP K29/32 was used to deliver between 3 and 6% (wt/wt) solids on a dry weight basis. Furthermore, the effect of the alcohol added to batches at three levels of 0, 10, and 20% (wt/wt) was also studied (Table 1). After the wet mass was prepared, it was extruded at 37 rpm using a single-screw Fuji Paudal Co. Extruder (Osaka, Japan), Model# EXKS-7 fitted with a screen of 1-mm aperture size. The extrudates were then immediately spheronized at 500 rpm for approximately 30 seconds using a Caleva Model 15 Spheronizer (GB Caleva Ltd., Ascot, UK) equipped with a 375-mm diameter crosshatched plate. The beads were air-dried at ambient temperature for 48 h. All subsequent tests were determined using a #18/30 sieve cut of beads to eliminate any oversize and fines.

GMS Placebo Bead Manufacture

The lipid-based placebo beads consisted of the following ingredients (wt/wt): 50% GMS (m.p. 53ºC), 42% Starch 1500, and 8% sodium starch glycolate. Beads were produced using a high-shear homogenizer (Model PT 10/35, Polytron® Kinematica AG; Brinkmann Instruments, Westbury, NY, USA) at 22,000 rpm. Batches of 1,300 g were prepared by first heating the GMS to 80°C in a stainless steel beaker on a double boiler. The powders were weighed, blended together, and slowly added into the GMS while the mixture was being continuously stirred with a metal spatula. Once all powders were added, the mixture was subsequently homogenized for an additional 10 min. An ice bath was used to cool the mixture to 50°C, and then the material was hand sieved through a #12 screen, and the beads were immediately spheronized at 550 rpm for 25 s. The material was again sieved on a #30 screen and the fines discarded.

TABLE 1
Generalized APAP Bead and Calcium Silicate-Based Placebo Bead Formulations

Component[a]	Drug	Placebo
Acetaminophen (15 mg)	7.1	0
Avicel® PH-101	25–40	20–30
Lactose, anhydrous	qs	qs
PVP K 29/32	2–6	3–6
Ethylcellulose, 7 cP	40–60	0
Calcium silicate	0	30
AcDiSol®	0	20
Granulating liquid	Water	Alcohol (0–20%, wt/wt)

[a]All quantities are in % (wt/wt).

Experimental Design

Separate fractional factorial central composite designs were done for both calcium silicate-based placebo beads and APAP beads, and batches were generated and analyzed using Statgraphics Plus® 5.0 (Herndon, VA, USA). A triplicate run of the center point was performed to check for precision. For drug-loaded beads, each independent variable was studied at three levels: (a) EC : MCC ratio (1:1 to 2.4:1) and (b) dry binder level (PVP K29/32) (2–6%, wt/wt). For placebo beads, each independent variable was also examined at three levels: (a) MCC level (20–30%, wt/wt); (b) PVP K29/32 binder solution (36%, wt/wt on a dry weight basis); and (c) alcohol level (binary mixture of denatured alcohol and distilled water from 0–20%, wt/wt).

Particle Size and Shape Analysis

The bead particle size was determined in triplicate by sieve analysis (ATM Model L3P Sonic Sifter®, Milwaukee, WI, USA). The tests were run for 5 min at an amplitude setting of 6 and a pulse setting of 5. Preliminary tests that compared the weight retained on the sieves at 5, 8, and 10 min showed no difference so a 5-min time was adopted for sieving.

The percentage of beads by weight retained on each sieve was determined and the geometric mean diameter, labeled as GMD, D_{50}, or d_g, and geometric *SD*, σ_g, of the distributions were calculated using the following equations (Sinko, 2006):

$$\log d_g = \frac{\sum(n_i \times \log d_i)}{\sum n_i}, \quad (1)$$

where n_i is the weight percent of particles in the *i*th interval, for all n_i; and d_i is equal to the midpoint of the diameter of the size interval in the *i*th interval, for all d_i.

$$\log \sigma_g = \frac{\sum n_i (\log d_g - \log d_i)^2}{\sum n_i} \quad (2)$$

A two-dimensional shape factor was measured using a Nikon Eclipse ME600 optical microscope coupled with SPOT v. 3.5.6 image analysis software (Diagnostic Instruments, Inc., Sterling Heights, MI, USA). Transmission illumination was used with a 5× objective. The calculation used the following equation with a value of 1 indicating a perfect sphere, and any value less than 1 reflecting a deviation from perfect sphericity (Debunne, Vervaet, Mangelings, & Remon, 2004):

$$\text{Sphericity} = \frac{4\pi \times \text{projected area}}{\text{perimeter}^2} \quad (3)$$

True Density

True density was measured using a helium displacement pycnometer (Accupyc 1330, Micromeritics, Norcross, GA, USA) according to the USP 29 general chapter <699> on density of solids. The true densities reported are the average of five determinations.

Flow Properties and Moisture

Bulk densities of batches were determined by using a powder funnel to gently fill beads up to the 60-mL mark on a 100-mL graduated cylinder. The tap densities of the 18/30 mesh cut of beads were determined by using a Jel Stampf® Volumeter Model 2003 (Ludwigshafen, Germany) and calculated after an additional 750 taps according to USP 24 method <616>. Densities were determined in duplicate. The Carr Compressibility Index (CI%) is a measure of flowability and is calculated from the bulk (ρ_b) and tapped densities (ρ_t) as follows:

$$\text{CI\%} = \frac{\rho_t - \rho_b}{\rho_t} \times 100 \quad (4)$$

Loss on drying (LOD) was determined on dried batches using a Computrac Max 2000XL Moisture Analyzer (Arizona Instruments, Tempe, AZ, USA). All batches were dried to a LOD < 1.0% with an endpoint rate set at < 0.01%/min.

Porosity of APAP Beads and Calcium Silicate-Based Placebos

Porosity was determined by first using a helium displacement pycnometer to measure the true density of the beads and from this to calculate their true volume (V_t). Determinations were based on five replicates. The same weight of beads used for the true density determination was put into a 25-mL graduated cylinder filled with a known volume of heavy white mineral oil. The volume of oil displaced by the beads is taken to be V_g, or the apparent granular volume, and represents the true volume of the solid plus the volume of the pores >10 mm. The percent porosity is calculated by the equation:

$$\varepsilon = \frac{V_g - V_t}{V_g} \times 100 \quad (5)$$

This method is a reasonable calculated estimate of the actual intraparticle porosity and is also environmentally safe, as no mercury is used during the test. Determinations were based on three replicates.

For comparison purposes, a sample of the 20% ETOH placebo beads was analyzed using a Quantachrome® Autoscan 60 Mercury Intrusion Porosimeter (Particle Technology Labs Ltd., Downers Grove, IL, USA). The sample was analyzed according to the procedures outlined by the USP 29/NF 24 using method <846>. A 10-point B.E.T. isotherm analysis was used during the high pressure intrusion to analyze intraparticle pores in the range of ~8–0.004 μm.

Coating of APAP Beads

The coating of APAP beads with Surelease® diluted to 15% (wt/wt) solids was performed at Colorcon. Drug beads (50 g) were mixed with qs sugar spheres 20/25 NF (990–1,400 μm) from Chr. Hansen, Inc. (Milwaukee, WI, USA) for a batch size of 300 g and coated using a Fluid Air lab scale model #0002 (Aurora, IL, USA) equipped with a 0.8-mm nozzle. Inlet air temperature was approximately 75°C, product temperature was 40°C, exhaust air temperature was 35°C, and atomizing air pressure was 1.2 bar. Beads were coated to three different theoretical weight gains of 10, 15, and 20%. Bottom spray was used until the desired theoretical weight gain was achieved; the sugar spheres were then sieved out and discarded.

Tableting and Tablet Evaluation

For manual tableting studies, 10 g of a combination of drug and placebo beads in various ratios were added to a plastic bag

and mixed for 3 min. Blends of APAP beads and calcium silicate-based placebos required the addition of 0.5% magnesium stearate (passed through a #30 screen) and bead ratios of 50:50 and 60:40 resulted in APAP tablet dosages of 12.30 mg and 14.79 mg, respectively. A single-station instrumented Stokes B2 rotary tablet press (operating at 30 rpm) equipped with an instrumented eye bolt for compression force and an ejection cam for ejection force was used with 8.7 mm round, concave punches. Beads were accurately weighed and manually filled into the die to achieve target tablet weights of 350 ± 5 mg. Tablet crushing strength (hardness) was determined by diametric compression and measured from a range of compression forces using a hardness tester (Model HT-300; Key International Inc., Englishtown, NJ, USA). All tablets were kept at ambient temperature for 24 h before crushing strength testing for elastic recovery.

Dissolution Testing

Dissolution testing of different tablets and beads was performed in 900 mL of distilled water at 37°C ± 0.5°C using USP apparatus II at 50 rpm (Vankel VK 7000; VanKel Industries, Inc., Cary, NC, USA) in conjunction with a dissolution bath heater (Model VK 750D, VanKel, Edison, NJ, USA). Samples (1.5 mL) were manually withdrawn at specified time intervals and replaced by new media. The samples were placed in Eppendorf® centrifuge tubes and spun using an Eppendorf® 5415C centrifuge (Brinkmann Instruments Inc.) at 13,000 rpm for 2 min. This was found to be more effective than filtration and led to more stable spectrophotometric readings. APAP was spectrophotometrically analyzed at 254 nm using a Spectronic Genesys 2 UV/VIS spectrophotometer (Thermo Electron Corp., Waltham, MA, USA) with quartz cuvettes of 1-cm pathlength. All dissolution profiles are the mean of six dissolution runs and all tests were performed under sink conditions. Absorbance values were converted to amount of the dissolved drug, and a standard curve ($R^2 \geq .999$) was generated. The amount of the drug dissolved in milligrams was then normalized for all time points based on the amount originally present in the tablet or bead.

Scanning Electron Microscopy

Surface morphology of beads were observed with a Jeol T-200 SEM (Tokyo, Japan) using a 25-kV accelerating voltage and a working distance of 20 mm. Beads were adhered to standard aluminum mounts using a glue stick, and the samples were then sputter coated with gold/palladium at 10 mA for 3 min (Hummer IV, Annandale, VA, USA).

Segregation Testing: APAP Beads and Placebo Beads

Calcium silicate-based placebo beads (10% alcohol) and uncoated APAP beads (60% EC) (prepared with 0.03% gentian violet) were mixed together in a 50:50 vol/vol ratio in a 2-qt. V-blender for 5 min. Dyeing of the APAP beads was performed to give a good visual examination of any segregation occurring during the particle flow. A segregation tester was assembled and used according to the ASTM D6940-04 procedure (Xie et al., 2007). Fourteen bags were collected with approximately 40–45 g of the blend in each bag (Figure 1). Concentrations of APAP in the first, middle, and last samples were obtained by UV spectroscopy at 254 nm and the coefficient of variation (CV) of APAP content calculated between the first and middle samples, middle and last samples, and first and last samples.

Statistical Analysis

Statistical analysis of the data was performed using SPSS software v. 12 (Chicago, IL, USA) and one-way analysis of variance (ANOVA) with least significant difference (LSD) was selected as the post hoc test. The LSD is the least conservative post hoc test and is therefore more likely to find differences within a treatment. Statistical differences within either the drug or the placebo bead groups were determined, and a *p*-value less than .05 was considered significant.

RESULTS AND DISCUSSION

Preparation of APAP Beads and Calcium Silicate-Based Placebo Beads

The type of granulating liquid can have a profound impact on the bead characteristics, affecting porosity, density, crushing strength, friability, and shape. The percentage of water added (dry basis) for granulation was higher for all placebo batches as compared with drug batches; approximately 200 versus

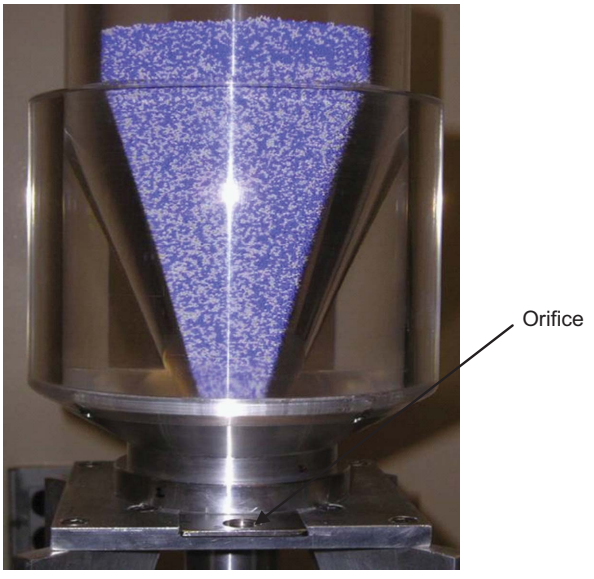

FIGURE 1. Segregation tester for the blend of APAP beads and calcium silicate-based placebo beads.

80–90% (wt/wt), respectively. This reflects the fact that the placebo batches required much greater levels of liquid (roughly 2.5 times more) to obtain a uniform wet mass of the correct plastic consistency that would prevent generation of excess fines during processing. It was also observed that the placebos prepared with the highest alcohol content (20%) required the addition of the most granulating liquid; however, it is known that solvents generally suppress the hydration and swelling of MCC (El Seoud et al., 2008) and may have an impact on the hydration of other excipients as well. The amount of water required for granulation has been shown to have a direct effect on the bead porosity, with higher water levels leading to increased porosity (Agrawal, Howard, & Neau, 2004). While these results show only a minor effect on porosity using levels of alcohol from 0 to 10%, 20% alcohol produced placebo beads with significantly higher porosities. Although previous work demonstrated that beads prepared from alcohol tended to be weak, friable, and irregular in shape (Elbers et al., 1992; Millili & Schwartz, 1990), increasing the water content of the granulation liquid can also lead to increased bead crushing strength (Millili & Schwartz, 1990). However, such placebo beads with mechanical strengths greater than the admixed-coated drug beads would be ineffective as cushioning agents (Aulton et al., 1994). It is essential to have a thorough knowledge of excipient properties so that optimal formulations can be prepared. For example, it is known that MCC is hydrophilic and also has some swelling ability. Although its use was required to obtain the correct plasticity of the extruded mass, the MCC level needed to be kept low at around 15% to prevent internal bead swelling. Such swelling would produce cracks in the outer bead film coating and thus, destroy the controlled release effect. Also, other hydrophilic excipients such as the PVP binder and lactose should also be closely examined to see whether they can be replaced by other ingredients such as dibasic calcium phosphate, which is insoluble in water and can also assist in delaying release of water-soluble drugs.

Batch yields varied and were in the range of 60–80%. Typical scanning electron micrographs of placebo beads (20% ETOH) and APAP beads are shown in Figure 2. It is evident that while drug beads exhibit a smooth surface and fairly round shape, the surfaces of the placebo beads are rougher and covered with pores of varying sizes, and the bead shapes are more irregular.

Characterization: APAP Beads and Calcium Silicate-Based Placebo Beads

Calcium silicate-based placebo beads and APAP beads were characterized according to bulk and tap densities, CI, geometric mean particle size ($d_g \pm \sigma_g$), and intraparticle porosity. While the summary of the results is presented in Table 2, all results from the Statgraphics® central composite designs are given in Tables 3 and 4 with the center point batches shaded gray. CI values were all less than 15, indicating very good flowability of beads (Wells, 1988). The APAP beads had consistently lower bulk and tap densities with lower *SD*s as compared with placebo beads. Iyer, Augsburger, Pope, and Shah (1996) observed that beads prepared with higher water levels have higher tap densities as moisture assists in densifying and deforming the extrudates during spheronization. Placebo beads were shown to have consistently higher tap densities compared to drug beads. However, although the mean particle sizes were generally somewhat higher for the APAP beads, the 40% EC level showed beads that were significantly smaller than beads prepared with higher EC levels. Perhaps, the higher quantity of the micronized EC powder can act to increase the bead particle size through a layering effect while the beads are in contact with each other spinning around in the spheronizer. The particle size distributions were found to be log-normal.

The Pareto Charts for APAP beads and calcium silicate-based placebo beads are shown in Figures 3 and 4, respectively. The intersection of a horizontal bar with the vertical line indicates that a parameter is statistically significantly different ($p < .05$) from the rest of the group.

For APAP beads, the EC : MCC ratio had a significant effect on both particle size and bulk density ($p < .05$) with *p*-values of .023 and .001, respectively; whereas the PVP level had no

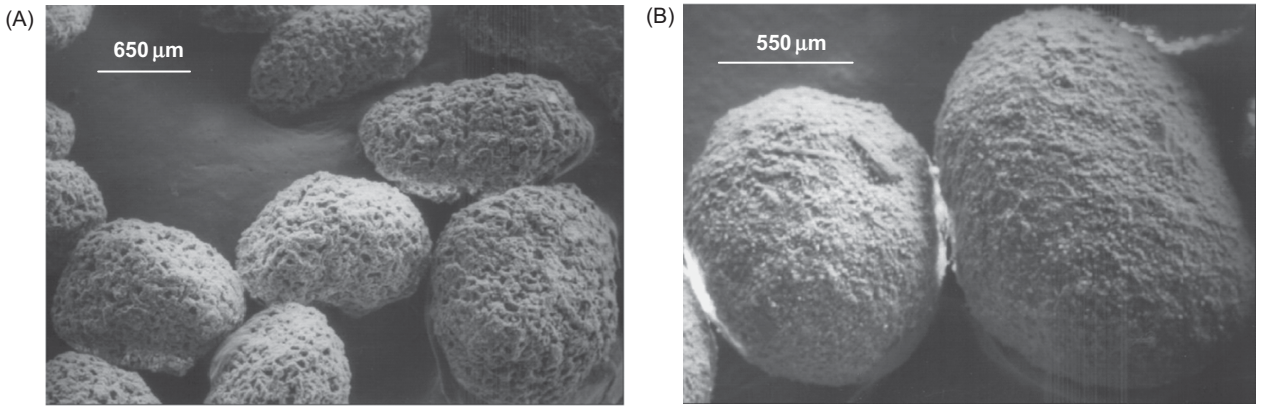

FIGURE 2. Scanning electron micrographs of (A) calcium silicate-based placebo beads (20% ETOH), 53× and (B) APAP beads, 70×.

TABLE 2
Densities, CI, Particle Size, and Intraparticle Porosity of APAP Beads and Calcium Silicate-Based Placebo Beads

Sample	Bulk density (g/cm^3)[b]	Tap density (g/cm^3)[b]	CI (%)	$d_g \pm \sigma_g$[c]	Intraparticle Porosity[b] (%)
Drug					
40% EC	0.56 ± 0.01	0.64 ± 0.00[a]	10.7 ± 0.9[a]	838.1 ± 1.11[a]	19.8 ± 0.9
51% EC	0.54 ± 0.01	0.58 ± 0.01[a]	7.1 ± 1.1	868.3 ± 1.13	21.2 ± 0.4
60% EC	0.51 ± 0.01[a]	0.53 ± 0.00[a]	7.0 ± .9	864.8 ± 1.08	20.1 ± 0.7
Placebo					
0% ETOH	0.76 ± 0.03	0.83 ± 0.02	9.0 ± 1.0	789.6 ± 1.15	22.8 ± 0.4
10% ETOH	0.75 ± 0.02	0.82 ± 0.02	8.1 ± 0.8	787.1 ± 1.14	23.4 ± 1.1
20% ETOH	0.66 ± 0.02[a]	0.74 ± 0.03[a]	9.1 ± 1.1	800.9 ± 1.14	34.0 ± 0.3[a]

[a]Values within drug or placebo column are significantly different from each other by LSD ($p < .05$).
[b]Mean ± *SEM*; $n = 3$.
[c]Geometric mean ± geometric *SD*; $n = 3$.

TABLE 3
Statgraphics® Central Composite Experimental Design and Results for APAP Drug Beads Containing EC

	Block	EC : MCC ratio	PVP level (%)	Bulk density (g/cm^3)	Mean Particle size (μm)
1	1	2.4	4	0.49	860.1
2	1	1.7	6	0.54	854.1
3	1	1.7	4	0.55	878.2
4	1	1.7	2	0.53	865.5
5	1	1	2	0.57	831.1
6	1	1	6	0.56	853.3
7	1	2.4	6	0.51	869.5
8	1	1.7	4	0.53	879.4
9	1	1.7	4	0.53	871.1
10	1	1	4	0.57	845.1
11	1	2.4	2	0.51	890.5

significant effect. The data variability for APAP bead particle size and bulk density was also reasonably well explained with R^2 values of .773 and .909, respectively. However, for placebos, no independent variables showed any significant effects for either particle size or bulk density. Moreover, R^2 values for placebo particle size and bulk density were only .749 and .545, respectively. The correlation matrix for either particle size or bulk density found no statistically significant confounding interactions between variables for either drug or placebo beads. These lower R^2-values indicate that there are additional variables contributing to either bulk density or particle size effects, which are not yet accounted for. The highest EC : MCC ratio of 2.4 would be used if the goal was to maximize particle size (885 μm), whereas the lowest EC : MCC ratio of 1.0 would be used if bulk density was to be maximized (.57 g/cm^3).

A one-way ANOVA with least-squared difference (LSD) post hoc test was performed using SPSS® and used to check for differences between true density as well as sphericity means among APAP beads and calcium silicate-based placebo bead batches. The drug beads were less dense than the placebo beads and all samples within either the drug or the placebo group were significantly different from each other. It was hypothesized that the placebo beads should have been less dense than the drug beads because they were prepared with 10–20% (wt/wt) alcohol and a highly porous excipient, calcium silicate. The reason may be that while drug beads were prepared with about 80–90% (wt/wt) water, placebo beads required 185–215% (wt/wt) water on a dry weight basis to achieve a plastic mass for extrusion. As mentioned earlier, a higher quantity of water used for granulation can lead to harder and therefore, denser beads (Millili & Schwartz, 1990).

On the other hand, the drug beads exhibited significantly higher sphericity values (Equation 3) when compared with placebo beads. The highest sphericity values were with the 40% EC drug beads, and these were significantly

TABLE 4
Statgraphics® Central Composite Experimental Design and Results for Calcium Silicate-Based Placebo Beads

		Mean				
	Block	MCC level (%)	PVP level (%)	Ethanol level (%)	Bulk density (g/cm^3)	Particle size (μm)
1	1	20	4.5	10	0.67	782.6
2	1	30	3	20	0.66	792.5
3	1	30	6	0	0.68	782.5
4	1	30	3	20	0.66	692.1
5	1	30	6	0	0.76	741.1
6	1	25	4.5	10	0.75	791.4
7	1	30	4.5	10	0.68	721.7
8	1	25	4.5	10	0.76	817.7
9	1	25	4.5	20	0.72	795.8
10	1	25	4.5	10	0.65	827.5
11	1	20	6	0	0.74	725.3
12	1	20	3	20	0.67	838.1
13	1	20	6	10	0.65	782.2
14	1	25	4.5	20	0.77	805.9
15	1	25	6	0	0.71	796.7
16	1	20	3	0	0.76	821.8
17	1	25	3	10	0.71	830.3

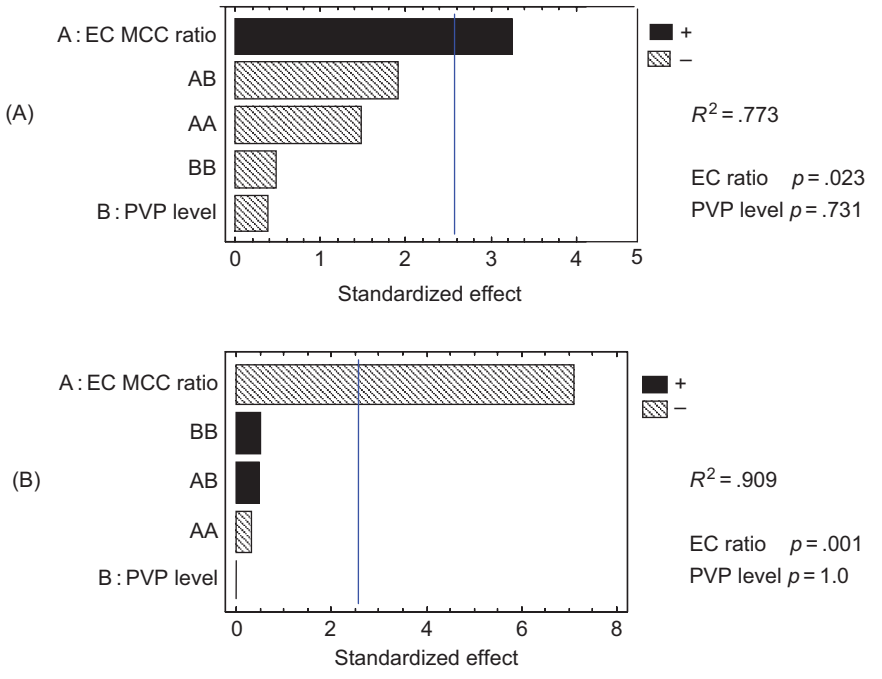

FIGURE 3. Pareto charts for APAP beads: (A) average particle size and (B) bulk density.

different from the 60% EC beads ($p < .05$). However, no significant differences were observed among the placebo bead samples (Table 5). Theoretically, highly spherical beads have advantages of improved flowability, enhanced uniformity of film coating and will also pack together more evenly in a tablet or capsule.

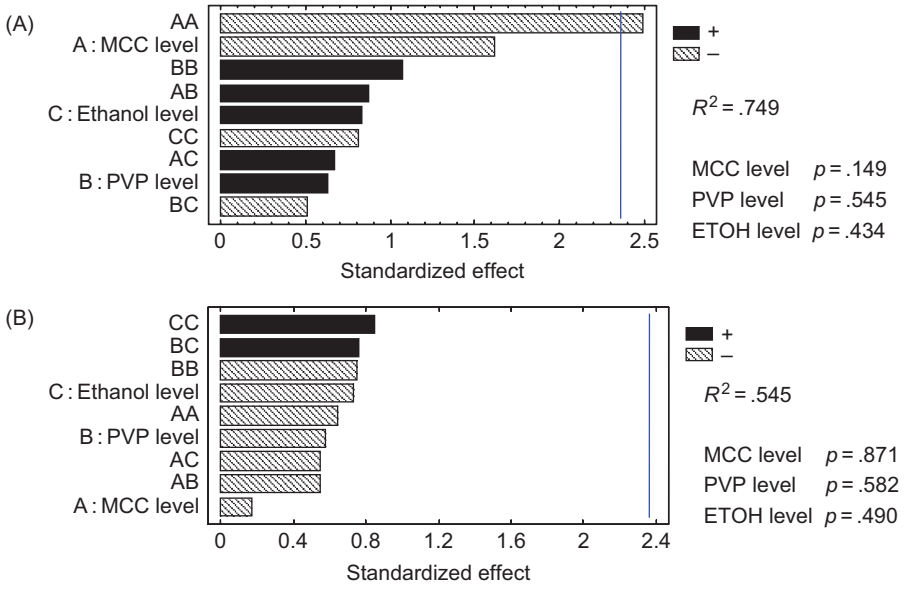

FIGURE 4. Pareto charts for calcium silicate-based placebo beads: (A) average particle size and (B) bulk density.

TABLE 5
Density and Sphericity of APAP Beads and Calcium Silicate-Based Placebo Beads ($M \pm SEM$)

Formulation (g/cm^3)	True Density (g/cm^3)	Sphericity
Drug		
40 % EC	$1.33 \pm 0.0^*$	$0.97 \pm 0.01^*$
51% EC	$1.30 \pm 0.0^*$	0.95 ± 0.01
60% EC	$1.27 \pm 0.0^*$	$0.93 \pm 0.00^*$
Placebo		
0% ETOH	$1.75 \pm 0.0^*$	0.88 ± 0.01
10% ETOH	$1.73 \pm 0.0^*$	0.87 ± 0.02
20% ETOH	$1.77 \pm 0.0^*$	0.90 ± 0.01

$^*p < .05$ using LSD; density $n = 5$; sphericity $n = 20$.

Response Surface Plots for APAP Beads and Calcium Silicate-Based Placebo Beads

Response surface plots generated for both the drug and the placebo beads show the effects of the independent variables on mean particle size (μm) and bulk density (g/cm^3) (Figure 5). For drug beads, the independent variables are more or less proportional to particle size and inversely proportional to bulk density and show little curvature. The particle size increases with increasing EC : MCC ratio up to a point and then it trails off. However, there appears to be a saturation point where some attrition of the EC from the bead surfaces can also occur.

The response surface plot of bulk density can be explained by considering the true densities of the starting materials. The true density of EC is approximately 1.2 g/cm^3 while MCC has a true density of approximately 1.5 g/cm^3. When the EC : MCC ratio is increased to 2.5, a larger proportion of less dense material is present in the beads and therefore, the bulk density decreases with increasing the EC : MCC ratio. For the calcium silicate-based placebo beads, the relationship appears more complex with extensive curvature in both plots. The high degree of curvature in the placebo bead plots may be due to several factors. First, the placebo beads utilized a greater number of batches in building their design space. Additionally, the placebo beads were prepared using a range of alcohol levels while the drug bead used water alone, and there was also more variability in the placebo bead data for both bulk density and particle size.

Effect of Placebo Beads Alone on Tablet Crushing Strength

Because the placebo beads were believed to be very porous and thus mechanically weak, it was desired to prepare tablets from them alone and observe their effect on tablet crushing strength. If the resulting tablets showed evidence of high crushing strength values, then these placebo beads may be able to serve as a new formulation ingredient, which could act to enhance the compactibility of wet granulation formulations and thereby, improve tablet crushing strength. Data are presented in Figure 6 and show that while the data variability is best explained using the 20% alcohol placebo beads (R^2 = .995) as compared with the 0% alcohol placebo beads (R^2 = .872), the latter are more compactible owing to their much higher slope value of 1.06 and ability to achieve comparable crushing strength values at lower compression pressures. However,

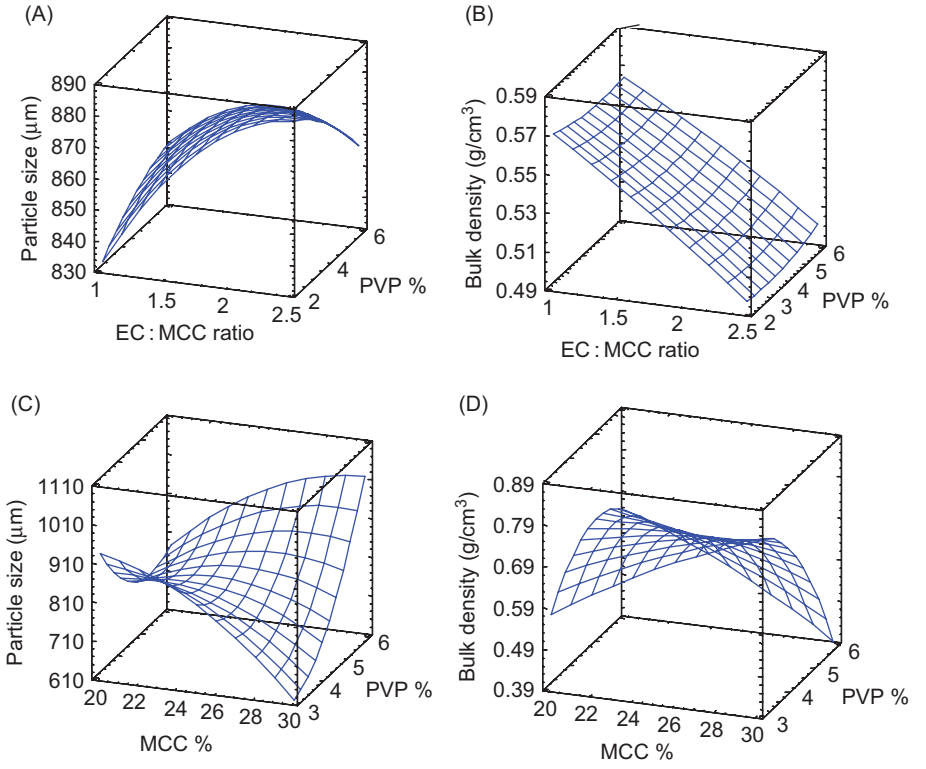

FIGURE 5. APAP beads: (A, B) effects of particle size (µm) and bulk density (g/cm^3). Calcium silicate-based placebo beads: (C, D) effects of particle size (µm) and bulk density (g/cm^3).

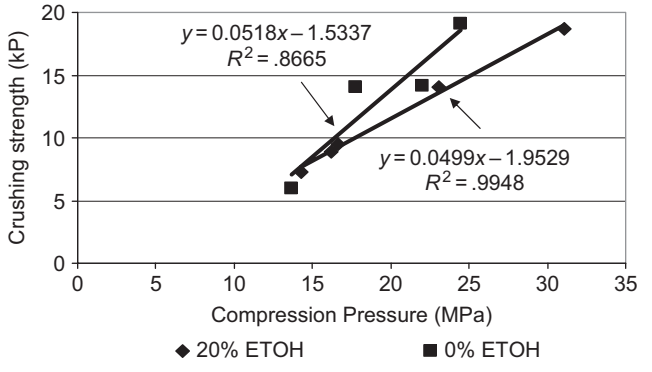

FIGURE 6. Compactibility of calcium silicate-based placebo beads alone. Effect of alcohol level on crushing strength.

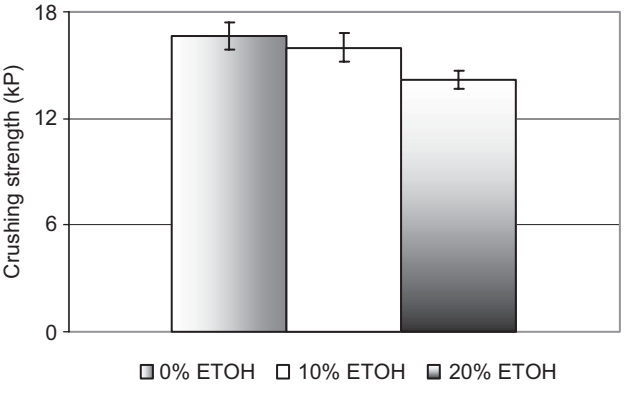

FIGURE 7. Effect of alcohol level of calcium silicate-based placebo beads on tablet crushing strength (n = 6). Error bars represent mean ± *SD*.

further study of this relationship is warranted as crushing strength values can fluctuate and a greater number of tablets would be preferred to draw conclusions.

It was originally thought that the most porous placebo beads (20% alcohol) would produce the hardest tablets due to the greater amount of fragmentation on compression, and thus, contact points were available for interparticulate bonding; however, this was not the case (Figure 7). In fact, it was the 0% alcohol placebos that produced the hardest tablets. Although increased levels of alcohol during placebo bead preparation can improve intraparticle porosity, probably because that increased water is required to achieve a proper wet mass during extrusion, 20% alcohol levels did not improve tablet compactibility nor crushing strength in this study. However, placebo beads prepared with the range of alcohol from 0 to 20% (wt/wt) showed that tablets with crushing strength values in excess of 10 kP could be achieved using reasonable compression pressures (e.g., < 35 MPa). Such crushing strength values are at an adequate level for either a subsequent coating operation or

packaging and handling. Contrary to the results presented herein, tablets were still preferentially prepared using 20% alcohol placebo beads, because at the time the research was conducted, it was believed from a theoretical standpoint that such placebo beads were more likely to produce harder tablets (Millili & Schwartz, 1990).

It is obvious from the data presented in Figures 6 and 7 that the effect of alcohol on placebo bead compactibility is a complicated phenomenon. For example, although the R^2-value for the placebos prepared with 20% alcohol was .995 (Figure 6), these placebos showed a lower average crushing strength value of 14.2 kP (Figure 7). However, more tablets would need to be studied to determine the reason for this discrepancy.

Placebo Beads: Effect of Bead Ratio, Bulk Density, and Alcohol Level on Compactibility of Tablets Prepared with APAP Beads

The ratio of uncoated APAP beads to calcium silicate-based placebo beads (prepared with 20% alcohol) also plays a role in tablet compactibility. The 50:50 ratio showed improved linearity and compactibility (based on R^2 and slope) across the range of compression forces used (slope = 0.79, R^2 = .975) as compared with the 60:40 ratio (slope = 0.42, R^2 = .800). Generally, the 50:50 ratio achieved higher crushing strength values with lower compression pressures (< 35 MPa) as compared with the 60:40 ratio. The 50:50 blends of APAP beads and placebo beads were consistent in giving superior tablet crushing strength values for a similar compression force, and this ratio was predominantly used in future research (Figure 8).

However, in their study, Lundqvist et al. (1998) found that the optimum ratio of coated theophylline beads (8% weight gain) to soft, cushioning placebo beads (containing 30% glyceryl monostearate) was 60:40. These authors also noted that the protective function of their placebo beads was not linear and that using an even higher level of placebo beads did not guarantee that the film coating on the drug beads would be intact following tableting. They theorized that during elastic recovery, the coating on the drug beads would get peeled off and adhere to the surfaces of the placebo beads due to the large contact surface area between the two types of beads. Thus, the controlled release effect of the film coating would be destroyed. The optimum ratio of drug and placebo beads will be highly dependent on the physicochemical makeup of the two types of beads and also on the desired dissolution rate profile expected.

While earlier data using only compacted placebo beads showed that the 0% alcohol (0% ETOH) placebo beads were more compactibile than those prepared using 20% ETOH due to their higher slopes, a much different story is seen when the drug and placebo beads are mixed together. Even though scanning electron microscopy (SEM) micrographs did not show obvious qualitative differences in porosity (number of pores or pore size) among placebo beads, it appears that the use of the calcium silicate-based placebo beads prepared with 20% alcohol (R^2 = .942) showed consistently higher tablet crushing strength values using lower compression pressures as compared with placebos prepared without any alcohol (R^2 = .599) (Figure 9). This graph shows that placebo beads prepared with 20% alcohol showed improved compactibility, as measured by a higher slope, across the range of compression pressures from 10 to 35 MPa during tableting.

The two ways to increase porosity in the placebo beads are by either using a granulating agent such as alcohol or by using an excipient such as calcium silicate. In theory, alcohol will evaporate faster than water, and this may leave a higher percentage of internal and surface pores in the placebo beads. Porosity determinations by the heavy white mineral oil method showed that using 20% alcohol for granulation increased the intraparticle porosity of calcium silicate-based placebo beads, as compared to placebo beads prepared with water alone. Mercury intrusion porosimetry of the 20% ETOH placebo bead sample (n = 1) gave an intraparticle porosity of 26.5%. Because of the small size of the pores being analyzed, a high-pressure intrusion run was necessary to observe the pore size

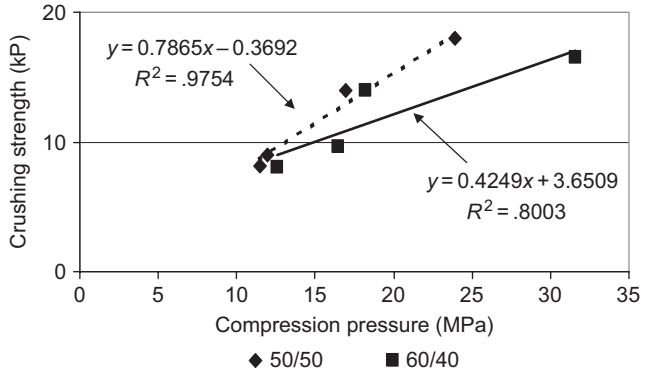

FIGURE 8. Effect of APAP bead : calcium silicate-based placebo bead (20% ETOH) ratio on tablet compactibility.

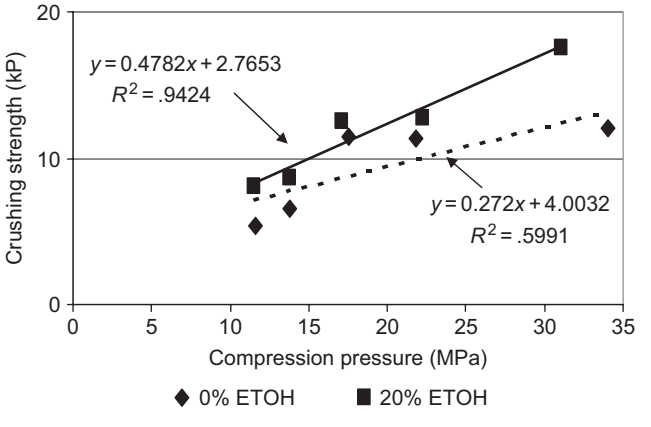

FIGURE 9. Effect of calcium silicate-based placebo bead alcohol level on compactibility of APAP tablets (50:50).

distribution within the particles. However, this value is not close to the 34.0 ± 0.3% porosity determined using heavy white mineral oil. Thus, the accuracy of the intraparticle porosity method based on heavy white mineral oil requires further study if it will be used as a faster replacement method for determining bead porosity.

Under compressive stress, the beads prepared with 20% alcohol may be mechanically weaker than beads prepared with water alone because of their higher porosities. This can thereby enhance compactability, because the drug beads will be surrounded by the fractured particles of placebo beads, and this should lead to increased intraparticle bonding and improved crushing strength values. Although calcium silicate is a highly porous excipient, its levels were not varied in these experiments; more research would need to be done to determine the specific effects imparted to the placebo beads from the calcium silicate. Also, the ability of calcium silicate to imbibe water and produce a satisfactory wet mass for extrusion would also have to be studied.

Compactibility Study Using Coated APAP Beads

As the studies on compacted mixtures of uncoated drug and placebo beads showed that prototypes could be produced using reasonable compression pressures and yielding tablets with crushing strength or hardness values greater than 8 kP, it was desired to further study several parameters including the tablet compactibility, whether the current placebos could protect the coating on the drug beads from rupturing and also what release profile might be achieved from the tablets.

Comparing the compactibility of tablets prepared from APAP beads coated with different levels of Surelease®, it was observed that while the 20% (wt/wt)-coated beads showed higher R^2 values compared to the 10% (wt/wt)-coated beads, .896 and .841, respectively, the slope (m = 0.11) was higher for the 10% (wt/wt)-coated beads compared with the 20%-coated beads (m = 0.04) (Figure 10). It is interesting that while the 10% (wt/wt)-coated beads showed a positive relationship, the 20% (wt/wt)-coated beads showed a negative relationship with crushing strength decreasing as compression force increases. As the size of the 20% (wt/wt)-coated beads will be larger than the 10% (wt/wt)-coated beads, this may impact the ability of the placebos to provide effective cushioning, the size difference has obviously negatively affected the tablet crushing strength. The 15% (wt/wt)-coated beads gave crushing strengths that were relatively stable at 10 kP across the compression force range. However, as the dissolution rate of the compacted 10%-coated beads was too rapid at 92% drug release in 3 h, further work proceeded using the 15% (wt/wt) Surelease®-coated APAP beads.

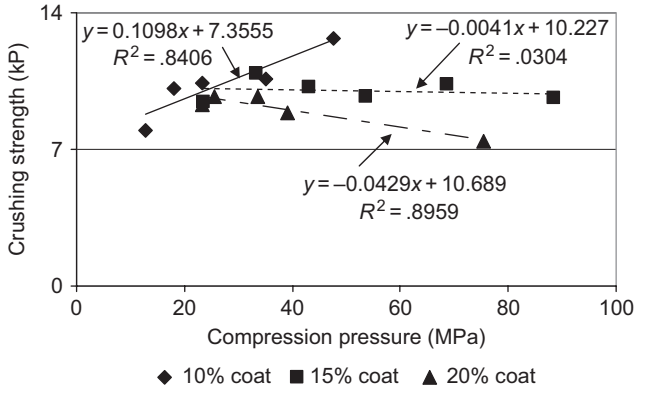

FIGURE 10. Effect of Surelease®-coating level of APAP beads on tablet compactibility (50:50 drug beads: calcium silicate-based placebo beads).

Dissolution Testing of APAP Beads and Tablets

To sufficiently delay drug release to 8 h, it was necessary to coat the APAP beads since even with 60% EC as a hydrophobic matrix, the drug was fully released from the uncoated beads in less than 2 h. However, tablets composed of a 50:50 blend of 15% (wt/wt) Surelease®-coated APAP beads and calcium silicate-based placebo beads still had a rapid release profile of less than 3 h (Figure 11). In comparing Surelease®-coated beads alone with the 50:50 tablet, it is evident that the tablet releases APAP significantly faster (f_2 = 27.8) than the coated beads; this indicates that there has been significant coating damage during tableting, even at low compression pressures of 10–12 MPa. Furthermore, there were no appreciable differences in disintegration time as the tablet fully disintegrated in about 30 min. The similarity factor or f_2 metric was used to compare profiles, and as it is less than 50, it can be concluded that these two profiles are different from each other by more than 10% on a point-to-point basis. These results also indicate that the calcium silicate-based placebo beads are ineffective as cushioning

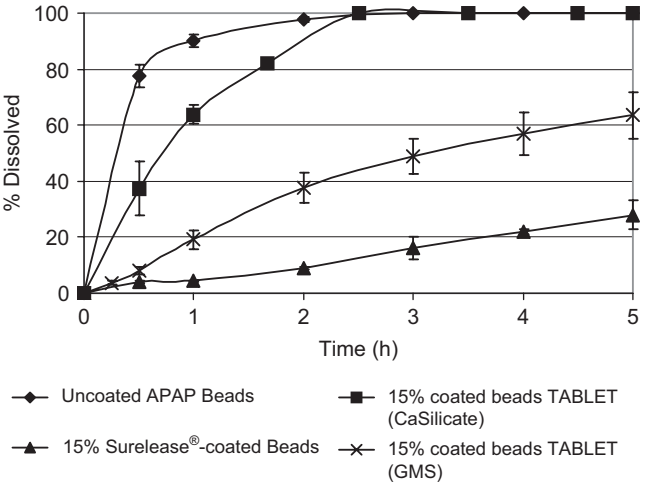

FIGURE 11. Effect of type of placebos used in tablets (50:50) prepared with Surelease®-coated APAP beads compared with coated and uncoated beads alone.

agents, perhaps due to their higher crushing strength values and lack of plastic deformation. Harder materials generally undergo brittle fracture and fragment once their yield point is reached. However, a plastically deforming material with a low-yield pressure, such as GMS, would undergo plastic flow and deform around the coated beads without fracturing into minute hard fragments.

On the other hand, when GMS placebo beads were substituted for the calcium silicate-based placebos, appreciably less coating damage occurred as evidenced by the graph showing that the tablet prepared with the lipid-based placebos had a slower drug dissolution profile (Figure 11). These lipid-based placebos were prepared using 50% (wt/wt) GMS, which is a plastically deforming material. Thus, these beads would be expected to be softer and have lower crushing strengths than the calcium silicate-based placebo beads. However, although the GMS-tablet showed promise to deliver the desired sustained release profile of greater than 8 h by showing 60% release in 5 h, there still appeared to be some bead coating damage (~30%) as the tablet releases drug faster than the beads alone. To examine the extent of bead coating damage in a qualitative way from tablets, SEM would need to be used. Moreover, dissolution studies would have to be repeated many times to evaluate whether the degree of coating damage during dissolution was consistent and whether there was still some evidence of damage present and how much would be tolerable.

Segregation Tendency Testing

Segregation phenomena can occur in blends and is important to study, because it can lead to content uniformity and weight uniformity issues with tablets. The likelihood of segregation increases in mixtures with larger differences in particle size and true density between drug beads and placebo beads. Furthermore, significant differences ($p < .05$) in both particle size and true density were shown to exist between calcium silicate-based placebo beads and uncoated APAP beads. Particle size differences, as measured by the GMD, between the placebo beads (10% alcohol) and drug beads (60% EC) were 787.1 and 864.8 μm, respectively. Furthermore, there were also large differences in true density (1.73 and 1.27 g/cm^3, respectively). This suggests that segregation could be a potential problem during mixing and tableting and needed to be evaluated.

To test whether segregation would be a potential issue on scale-up, the *Standard practice for measuring sifting segregation tendencies of bulk solids* (2004) was performed using a specially designed apparatus that contained an upper mass flow hopper and a lower funnel flow hopper, which created conditions to allow segregation to take place as the blend flowed downward. The difference in drug content between the first and last samples was used as an indicator of segregation tendency. A perfect ratio of 1:1 would indicate no segregation is occurring. Once the bead blend was allowed to flow in the segregation tester, 14 samples were taken for APAP analysis.

The mass flow hopper has steep side walls and a narrow orifice, whereas the funnel flow hopper has wider side walls and a larger orifice. With any blend, mass flow is desired; this means that the homogeneity of the blend remains consistent as it is flowing through the hopper. Mass flow can be described by an acronym, FIFO, or first-in, first-out. However, with funnel flow, because the orifice is larger and the walls are not as steep, smaller particles can percolate downward through the blend. Funnel flow can be described by LIFO – or last-in, first-out – meaning that there will be inconsistencies in the blend homogeneity after flowing through such a hopper because of differences in particle density and size.

The CV% between the first and the middle samples was low at 5.8% (Table 6). However, drug beads exhibited segregation tendency toward the end of the test as the CV% between the middle and the last samples and the CV% between the first and the last samples were greater than 20%. The last : first ratio was 1.51; the closer this value is to 1.0, the smaller the segregation tendency. Segregation reflects the flowability differences between the beads and is caused by differences in bulk density, particle shape, and/or particle size.

One way to potentially ameliorate this situation and minimize the segregation tendency of this blend would be to change the size of the placebo beads during the extrusion step by using a screen with a larger aperture size. While the calcium silicate-based placebos prepared with 10% alcohol are denser than the drug beads, they are approximately 10% smaller than the uncoated drug beads and would be even smaller when compared with coated APAP beads. The solution would be to increase the size of the placebo beads by approximately 20%, and this should help to decrease the placebo bead percolation through the blend. It is important to note that the segregation tendency of a blend can change dramatically for better or worse when the coated drug beads are substituted in place of the uncoated drug beads. Once the final formulation is selected, segregation testing would again be necessary for blend evaluation before scale-up.

TABLE 6
APAP Content in Blend Samples from the ASTM Segregation Tester

Segregation samples	CV%
First/middle	5.8
Middle/last	22.4
First/last	21.6

CONCLUSIONS

Although calcium silicate-based placebo beads were shown to be ineffective cushioning agents in blends with Surelease®-coated APAP beads, they were found to be very compactibile when used alone and gave tablet crushing strength values between 14 and 17 kP under low compression pressures between 15 and 19 MPa. These placebo beads could find utility as tablet compactibility enhancers when added to wet granulation formulations. Because their particle size is similar to the particles produced via wet granulation techniques (~600–800 μm), there is also less chance of blend segregation issues during tableting.

However, the GMS-based placebos offer greater promise as cushioning agents for compacted, coated drug beads as demonstrated in dissolution studies. The percentage of plastically deforming ingredients is greater in the GMS placebos than in the calcium silicate-based formulations. Furthermore, the potential success of the GMS-based placebos during tableting is likely because of the presence of high levels of a low-melting point, plastically deforming wax. The GMS may impart some unique mechanical properties to these beads, and this topic will be studied in more detail in a subsequent paper.

In this study, the hydrophobic EC bead matrix demonstrated little ability to prolong APAP release. However, further study into the utility of this hydrophobic matrix would be needed to determine whether uncoated EC matrix beads would be more effective in slowing the release of less soluble drugs (i.e., theophylline or cimetidine) or whether the performance of these beads could be improved by combining EC with different excipients. These formulation strategies will be fully explored in a subsequent paper.

Based on tablet compactibility, a 50:50 drug bead and placebo bead ratio was shown to be superior over a 60:40 ratio. The extra amount of cushioning placebo beads in the 50:50 blend can help to decrease the extent of coating damage during tableting and observed during dissolution. Furthermore, the composition of the placebo beads will also play a role in preserving coating integrity, with beads composed of softer, plastically deforming lipid materials appearing to be more effective cushioning agents. In fact, tablets prepared with GMS placebo beads released drug much slower than those tablets using calcium silicate-based placebos. However, coating damage was still evident when comparing dissolution profiles of Surelease®-coated drug beads alone with the compacted, coated APAP beads.

Segregation was shown to have occurred during testing of a blend of uncoated APAP beads and placebo beads. This is likely because of the differences in particle size and true density between the drug and the placebo beads. Further study into this phenomenon and ways to minimize its impact during tableting will be necessary, especially once a final formulation is developed containing coated drug beads.

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