Drug Development and Industrial Pharmacy, 2009; 35(6): 683–693

informa
healthcare

RESEARCH ARTICLE

Evaluation of the mechanical properties of extrusion-spheronized beads and multiparticulate systems

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Abstract

Background: The mechanical properties of extrusion-spheronized beads as part of multiparticulate systems has not been adequately studied. *Aim*: The purpose was to study the mechanical properties of such drug beads and blends of drug beads and glycerol monostearate (GMS)-placebo beads. *Method*: Heckel analysis (mean yield pressure, P_y), strain rate sensitivity (SRS), elastic recovery (ER), and total work of compression (TWC) studies were conducted using a Presster™ linear rotary tablet machine simulator operating at several combinations of speed and force. *Results*: The GMS-placebo beads exhibited the lowest P_y values (9.1 ± 1.6 MPa) and TWC (1.9 ± 0.3 J) overall and these values steadily increased with increases in both applied speed and force. Although the placebo beads had the lowest ER values of 3.8 ± 0.7%, these beads showed significant time-dependent deformation behavior based on their SRS value of 70.2%. Heckel analysis showed that uncoated theophylline beads containing 58% ethylcellulose were more compressible than control beads containing 58% dicalcium phosphate dihydrate, the latter having the highest overall P_y of 79.3 ± 3.8 MPa for the low speed/low force condition. Heckel plots also showed that 50:50 ratios of blends containing drug beads coated with either Surelease® or Eudragit® NE30D behaved similarly under increasing force and speed. Surelease®-coated cimetidine beads gave the highest P_y, TWC, and ER values and these values were higher than Eudragit® NE30D-coated beads. The 50:50 blend ratios containing coated cimetidine beads showed higher P_y, TWC, and ER values than the 60:40 ratios. *Conclusion*: Variation in the compressibility of different beads and blends can be attributed to excipients used in their formulation as well as to the drug bead-to-placebo bead ratio.

Key words: *Brittle; compression; extrusion-spheronization; Heckel analysis; multiparticulate system; plastic; yield pressure*

Introduction

There has been increased research interest in formulating modified release tablets composed of multiparticulate systems containing coated drug beads[1–8] due to their therapeutic benefits, that is, less variable drug bioavailability and fewer adverse effects[9,10]. While maintaining the film coat integrity on the drug beads is crucial for a successful modified release dosage form, problems arise when these beads are subjected to compressive stress. Many variables can influence how well the drug bead coating survives tableting, such as the type and level of polymer coating, ratio of cushioning placebo beads to coated drug beads, bead size, and rate and magnitude of the applied pressure. Therefore, it is imperative to examine the mechanical properties of the beads themselves as well as the blends used to produce tablets so that more information can be gained on improving such formulations.

While different cushioning agents have been tried in attempting to protect the drug bead coating from damage during tableting, such as blending with other powdered excipients[3,4,6,11–14] or adding beads containing microcrystalline cellulose (MCC) in different ratios[5], these ideas have either met with varying levels of success or fallen short of expectations. In order to minimize the occurrence of defects in the coating of the drug beads, the cushioning placebo beads should be less dense and mechanically weaker than the coated drug beads;

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(Received 27 Jun 2008; accepted 2 Oct 2008)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.1080/03639040802526797

meaning that the pressure required to deform the placebo beads (i.e., yield pressure) should be less than that required for deformation of the coated drug beads. It was originally thought that the placebo beads should preferentially exhibit fragmentation rather than plastic deformation so that when the beads fractured they would provide a cushion that would help strengthen the tablet via particle–particle contact[11]. However, it was observed that the presence of MCC in the placebo beads increased their crushing strength relative to the drug beads[11,15]. Furthermore, Schwartz et al.[15] pointed out that although MCC powder is very compressible and forms hard tablets at very low compression pressures, MCC beads are not compressible, as measured by their very low tensile strength values and their formation of very soft tablets. Nevertheless, recent successes have been reported by using plastically deforming placebo beads prepared with various waxes[2,7].

Heckel analysis[16,17] is the ideal method to study the mechanical properties of the drug and placebo beads and their blends – as much information can be gained regarding their underlying deformation mechanisms that can assist in the formulation of modified release tablets. Heckel derived an equation relating the volume reduction and therefore densification of a powder sample with increasing pressure. This description of compressibility is assumed to obey first-order kinetics and is given by Equation (1):

$$\ln\left(\frac{1}{1-D}\right) = KP + A, \tag{1}$$

where D is the relative density defined as the apparent density of the compacted beads at pressure/true density of beads, $(1 - D)$ denotes the pore fraction, P is the applied pressure, K and A represent constants and are the slope and intercept, respectively, calculated from the extrapolated linear portion of the Heckel plot. In this study, the fraction $\ln(1/(1 - D))$ or Heckel number is plotted on the y-axis. The reciprocal of the slope of the linear region (K), is termed the mean yield pressure or P_y. The intercept, A, is related to the initial packing density of the beads in the die. The initial curved region of the Heckel plot is attributed to particle rearrangement at lower pressures and its extent can be quantified using the relationship:

$$D_b = D_a - D_0, \tag{2}$$

where D_b is the increase in relative density due to particle rearrangement, $D_a = 1 - e^{-A}$ is the relative density from the intercept (A) of the linear portion of the Heckel plot, and D_0 is the initial relative density calculated by dividing the density at zero pressure by the true density of the beads. The elastic recovery (ER) index (ERI%) is important to know because ER influences the final strength of the compacts. It is calculated based on the following equation and assumes that radial expansion is negligible[18]:

$$\text{ERI\%} = \frac{(T_t - T_m)}{T_m} \times 100, \tag{3}$$

where T_t and T_m are the thickness of the compact after ejection and at maximum load in the die, respectively.

Different results can be obtained depending on whether a rotary tablet machine or a single-station tablet machine is used. A drawback with rotary machines is that a large amount of material is required for compaction, and instrumentation for displacement measurements is more challenging[19,20]. Another main difference between the two types of machines is that while the compression event on a single-station machine is single-sided, that is, the lower punch is stationary; compression on rotary machines is double-ended, that is, the lower punch is in motion during compaction. In this study, compression was carried out using a linear rotary machine simulator (Presster™, Metropolitan Computing Corp., East Hanover, NJ, USA). The mechanics of certain rotary tablet presses can be mimicked by this simulator through the selection of compression wheels with different geometries. Research conducted using this equipment thus provides information that can assist formulators in transferring batches from one tablet press to another during scale-up. Only a small amount of material is required and, with only a single punch system, dwell time, force, and displacement can be easily measured[21].

Understanding the sensitivity of a batch to varying compaction speeds (i.e., strain rate sensitivity or SRS) is critical to developing a robust tablet formulation. Materials exhibiting time-dependent plastic deformation (e.g., MCC) are more sensitive to speed changes when the dwell time decreases during production[22] and this can result in lower tensile strength values. However, materials exhibiting a high degree of reversible elastic deformation (e.g., starch) are more prone to capping and lamination as the tablet expands following ejection from the die[23]. Thus, it is important for a formulator to be cognizant of the material properties of the excipients chosen.

The total work of compression was calculated from the area under the force–thickness curve using the trapezoidal method. The upper and lower punch force traces were almost identical; hence, only the upper punch force profile was used for calculating work done. The net energy expended in compact formation was deduced from the difference of the area under the compression profile and the area under the decompression

profile. While die wall friction may be considered minor in blends containing glycerol monostearate (GMS)-placebo beads due to the lubricating effect of the GMS; it was not accounted for when using unblended beads but was assumed to be minor.

While the mechanical properties of uncoated and coated beads alone have been studied[8,15,18,24–26], few papers have been published studying how blends of beads behave under compressive stress[5]. The overall goal of this research was to gain a more quantitative understanding of the impact of compression parameters on modified release bead compositions. In particular, this research addresses the type of polymeric coating, the drug beads-to-placebo beads ratio, and the role that certain excipients (e.g., EC or dicalcium phosphate dihydrate) play in influencing the material properties of the beads. To this end, yield pressure, total work of compression, percent ER, SRS, and the densification factors (D_a, D_b, and D_0) were determined on uncoated and coated drug beads, placebo beads, and their blends.

Materials and methods

Materials

Fine particle ethylcellulose (EC) 7 cP viscosity grade (Ethocel 7-FP Premium Lot#TI19013T10) with an ethoxyl content of 48.0–49.5% was a gift from Dow Chemical Company (Midland, MI, USA). MCC NF (Avicel® PH-101 Lot#P104814340) was supplied by FMC Corp. (Princeton, NJ, USA). Talc (Imperial 500 USP), used with Eudragit® NE 30D for coating beads, was supplied by Luzenac (Greenwood Village, CO, USA).

Cimetidine USP, theophylline anhydrous USP, and GMS flakes NF were purchased from Spectrum Chemicals (New Brunswick, NJ, USA). Milled calcium phosphate dibasic anhydrous was obtained from Innophos (Cranbury, NJ, USA). Sodium Starch Glycolate NF (Explotab®) was supplied by JRS Pharma (Patterson, NY, USA); Starch 1500 NF and Surelease® (EC pseudolatex dispersion) were supplied by Colorcon (West Point, PA, USA); Eudragit® RS 30D (ammonio methacrylate copolymer 'type B') and Eudragit® NE30D (methacrylic ester copolymer) were supplied by Degussa Pharma Polymers (Piscataway, NJ, USA).

The beads studied for their mechanical properties were uncoated theophylline beads containing either 58% EC or dicalcium phosphate dihydrate anhydrous (controls), coated theophylline, or cimetidine beads containing EC (coated with either 15% w/w Surelease® or Eudragit® NE30D using a fluid bed drier), GMS-placebo beads, and blends of either 50:50 or 60:40 drug beads-to-placebo beads ratio.

Drug beads were prepared using a single-screw extruder at 37 rpm and fitted with a screen of 1 mm aperture size. The extrudates were then immediately spheronized for 1 minute at 500 rpm using a spheronizer equipped with a 375 mm diameter crosshatched plate. The drug beads were dried for 24 hours at 50°C to a final moisture content of <1.0% using a tray drier.

The GMS-placebo beads were prepared by first heating the GMS to 80°C in a stainless steel beaker on a double boiler. A blend of sodium starch glycolate and starch 1500 powders was then slowly added into the GMS while the mixture was being continuously stirred with a metal spatula. This mixture was subsequently homogenized using a high shear homogenizer at 22,000 rpm for an additional 10 minutes. 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 seconds. The material was again sieved on a #30 screen and the fines discarded. These methods were described previously in Cantor et al.[27]

True density

True densities of the individual beads and bead blends were 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 were measured as the average of five determinations and were used in the relative density or *D* term in the Heckel analysis calculations.

Heckel analysis and total work of compression

Tablets were produced using the Presster™, a single-station, linear simulator designed to mimic the action of a rotary tablet press (Metropolitan Computing Corp., E. Hanover, NJ, USA) in conjunction with Presster™ software v. 3.9.7. Material properties of extruded spheronized beads and blends of drug and placebo beads were studied using the tablet-in-die method of Heckel analysis. Compression rolls with the geometries of a high speed rotary tableting machine, Fette PT 2090 IC 36 station using 10 mm round, flat-faced D-tooling (Fette GmbH, Hamburg, Germany) were used for simulation at both low and high speeds and low and high forces. Low speed corresponded with a linear speed of 0.612 m/s or 28 rpm and a dwell time of 25.9 ms, whereas high speed corresponded to a linear speed of 2.103 m/s or 98 rpm and a dwell time of 7.4 ms. Low and high force settings ranged from 7.55–11.97 to 18.27–23.83 kN, respectively, as measured from the upper punch. Heckel analysis was performed three times for each

combination of speed and force conditions and representative plots are presented. Punch movement was measured using linear variable displacement transducers that were calibrated before starting measurements. All displacement measurements were corrected for the elastic deformation of the punches and frame by the software.

Tablet weight was set for 350 mg, except in the case of control samples that required 500 mg to form effective compacts. Stepper motors were used to adjust the compression position of the upper punch as well as depth of fill by adjusting the height of the lower punch. Material was added to the die automatically via gravimetric force using a feeding shoe. All beads were compressed to approximately the same final in-die porosity (i.e., tablet thickness) without lubrication to avoid its influence on material characteristics. Compact thickness was immediately measured using a digital caliper model #3415 (Control Company, Friendswood, TX, USA) and compact crushing strength was determined by diametric compression and measured immediately following ejection using a crushing strength tester (Model HT-300, Key International, Inc., Englishtown, NJ, USA). The linear portion of the Heckel plots was selected by using the method of least squares (R^2 = 0.999) to calculate the yield pressure. The ER was calculated from the force–thickness curves and SRS was calculated according to[22]:

$$\mathrm{SRS} = \left(\frac{P_{y2} - P_{y1}}{P_{y2}} \right) \times 100, \qquad (4)$$

where P_{y1} and P_{y2} are the yield pressures at speeds of 0.61 and 2.1 m/s, respectively.

The total energy or work of compression (J) required in the densification of the beads is a measure of compressibility. This can be obtained from plots of upper punch compression force (N) versus compact thickness (mm) and it is assumed that interparticle friction is negligible. Areas under the force–tablet thickness curves (AUC) were calculated by the trapezoidal method and used as a measure of the extent of volume reduction that the material had undergone over the entire compression pressure range. The AUC was calculated according to Equation (5):

$$\mathrm{AUC} = \mathrm{Work} = \int \mathrm{Force} \times d(\mathrm{tablet\ thickness}). \qquad (5)$$

A representative force–thickness plot is shown in Figure 1. The total work is equal to the (work of compression − work of decompression).

Results and discussion

Heckel analysis

Pressure–volume relationships involving the densification of beads are studied using Heckel analysis and are a measure of the compressibility of a material. Compactibility, on the other hand, involves not only compression but also bond formation and higher tablet tensile strengths give an indication of improved compactibility. Densification of the bulk sample can be thought of as proceeding through two stages in the Heckel plot: (1) the initial curved region describes particle rearrangement at low pressures before deformation and occurs relatively quickly. This is denoted by the constant, A, where the volume of the bead bed begins to decrease as the void spaces are eliminated. However, in this research an initial curved region was not observed in the Heckel plots; the free-flowing beads likely assumed approximately maximum packing density on filling the die and there was negligible particle rearrangement. (2) The next region is the linear portion of the curve and describes the area of plastic deformation, where K is the slope of the line and the reciprocal and $1/K$ describes the mean yield pressure or P_y. The mean yield pressure is defined as the minimum pressure required to induce irreversible deformation of a material. Generally, very low values of P_y at approximately <70 MPa, accompanied by linearity over a wide pressure range suggest plastic deformation while P_y values approximately >100 MPa suggest deformation by brittle fracture, as these materials are usually harder[28,29].

The two methods of Heckel analysis are the tablet-in-die method that was used in this research and the out-of-die or zero-pressure method. Fell and Newton[30] have pointed out that the slope, K, obtained from the tablet-in-die method gives lower values for yield pressure if there is substantial ER present. However, the tablet-in-die method distinguishes effects due to particle size and shape on the general deformation behavior more clearly than the zero-pressure method, especially when ER is considerable. The zero-pressure method would be selected for use when only the factors that affect plastic deformation are studied since elastic deformation does not play a significant role here as it does while the samples are being densified under pressure[31,32].

Heckel plots of uncoated theophylline beads prepared from either 58% EC or 58% dicalcium phosphate dihydrate anhydrous (control) are shown in Figure 2. While EC tablets were 350 mg, control tablets needed to be 500 mg in order to form a compact of sufficient crushing strength. While the initial linear regions and slopes are similar for both samples, there is a dramatic increase in the Heckel number for the EC containing beads at around 90 MPa. This is due to the fact that the

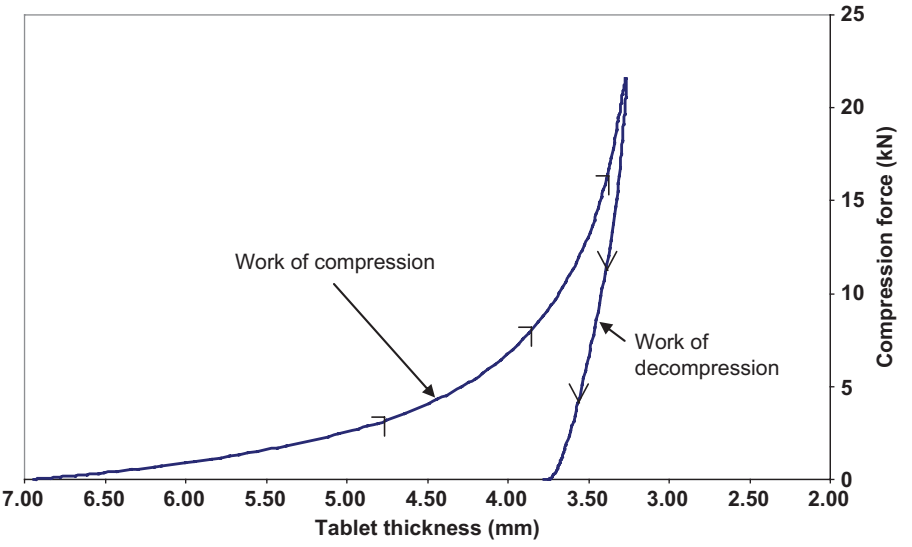

Figure 1. Representative force–thickness plot used in calculating total work of compression.

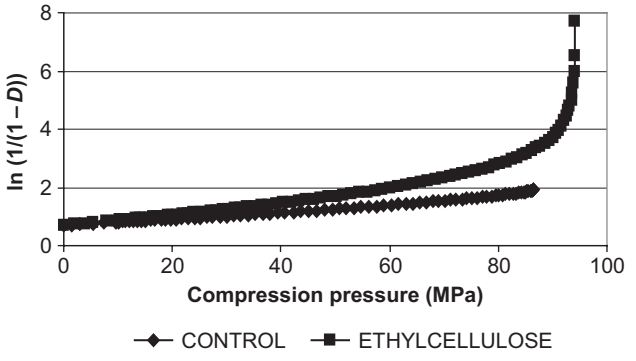

Figure 2. Uncoated theophylline beads alone: ethylcellulose versus control, low speed, and low force.

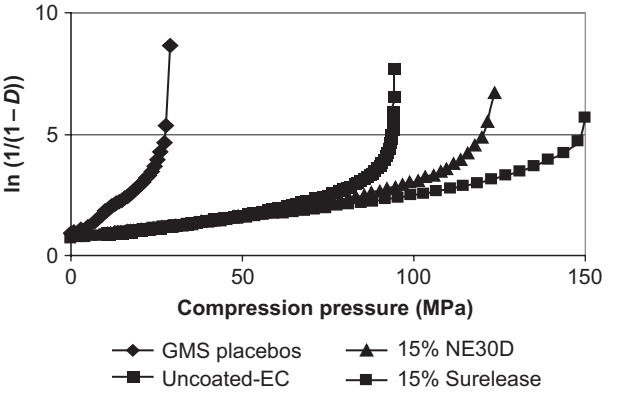

Figure 3. Placebos versus theophylline-ethylcellulose coated and uncoated beads, low speed and low force.

curve slopes sharply upward at higher pressures as the porosity approaches zero; EC is a more compressible material than dicalcium phosphate dihydrate and can sustain more applied pressure before undergoing deformation.

The GMS-placebo beads were prepared with a plastic wax, 50% (w/w) GMS, and therefore would be expected to deform at low yield pressures. The steep slope is characteristic of Heckel plots represented by fatty acids. In this case, there is no particle rearrangement stage and densification is due to plastic deformation and possible asperity melting[29]. Heckel plots indicated that Eudragit® NE30D-coated theophylline beads behaved similarly to uncoated drug beads owing to their similar slopes. The Surelease®-coated beads appeared to have a slightly higher yield pressure and thus higher mechanical strength as compared with the Eudragit® NE30D-coated beads (Figure 3).

In Figure 4, different blend ratios containing coated cimetidine-EC beads were compared against the coated beads alone. The 60:40 blend ratio samples showed similar Heckel behavior with the highest overall slopes, indicating that these samples had lower P_y values than the 50:50 blend ratio samples. In examining coated beads alone, the Surelease®-coated cimetidine beads showed the lowest slope and thus had the highest mechanical strength.

When Surelease® or Eudragit® NE30D-coated beads alone were compared, it was evident that Surelease®-coated cimetidine beads showed only slightly improved mechanical properties as compared with Eudragit® NE30D-coated drug beads. However, the 50:50 ratio using Surelease®-coated beads showed slightly greater plasticity as compared with the same ratio containing Eudragit® NE30D-coated beads. Furthermore, previous dissolution studies of theophylline and cimetidine

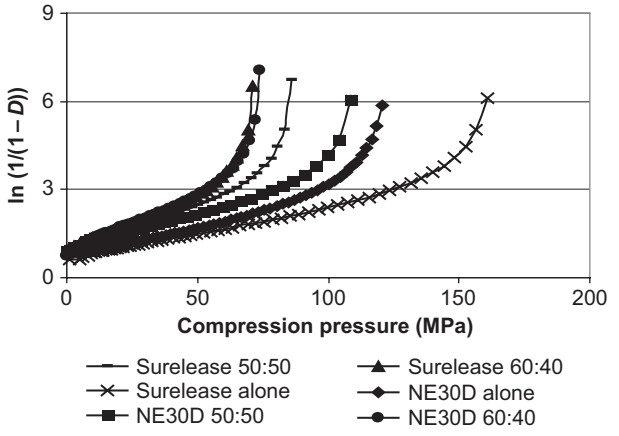

Figure 4. Surelease®- and Eudragit® NE30D-coated cimetidine-ethylcellulose beads alone versus blends with placebo beads at different ratios, low speed and low force.

tablets revealed that the 50:50 blend ratio was superior to the 60:40 ratio in protecting the drug bead coating from damage during compression[27] and was selected for further study using Heckel analysis.

Heckel plots of the 50:50 ratio blends using either Surelease® or Eudragit® NE30D-coated cimetidine beads were studied using both low and high speeds and low and high forces (Figures 5 and 6). Plots showed that higher speeds had slightly improved compressibility profiles for both coated bead blends as the linearity was greater over a wider range of compression forces. The Eudragit® NE30D-coated bead blends appeared to exhibit the highest mechanical strengths. The higher force conditions appear to shift the plots toward the direction of increased compression pressure along with a slight lowering of their slopes; this indicates that these samples will likely show increased P_y values.

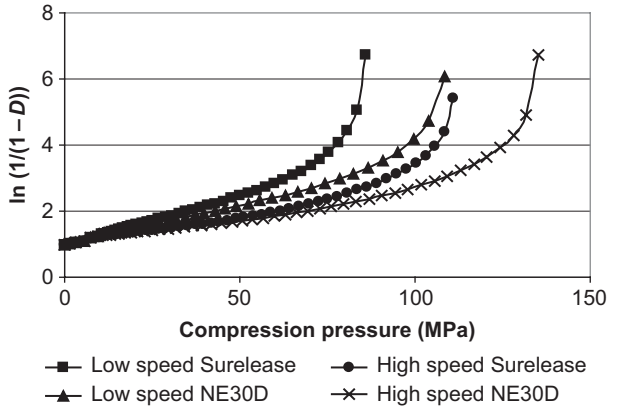

Figure 5. Effect of speed: 50:50 blend of coated cimetidine-ethylcellulose beads and GMS-placebo beads at low force.

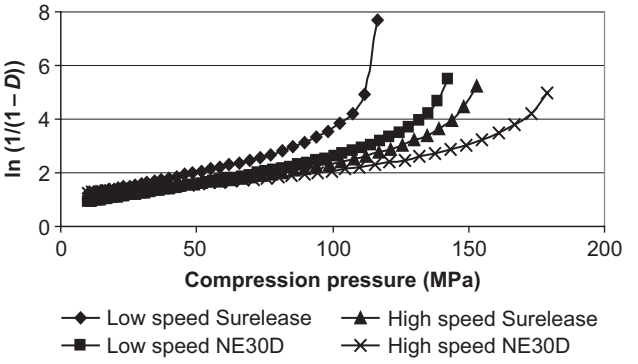

Figure 6. Effect of speed: 50:50 blend of coated cimetidine-ethylcellulose beads and GMS-placebo beads at high force.

Mechanical characterization

The yield pressure, total work of compression, and ER can provide insight into the mechanical properties and deformation mechanisms of a sample. The GMS-placebo beads alone exhibited the lowest yield pressure values (9.1 ± 1.6 MPa) and total work of compression (1.9 ± 0.3 J) overall as expected and these values steadily increased with increases in both applied force and speed. They also showed the lowest percentage ER values as well (3.8 ± 0.7%) (Table 1). This is due to the fact that they contain 50% (w/w) of GMS, a known plastic material.

However, several criticisms of using the Heckel equation to accurately determine a material property, such as yield pressure, have been discussed[33]. For instance, owing to the logarithmic transformation involved in the Heckel equation, an error of just 1% in determining the true density of a material can cause errors of more than 10% in the apparent yield pressure estimate. Sonnergaard also pointed out that these calculated mean yield pressure values are also susceptible to significant fluctuations based on such parameters as peak compression pressure, tooling dimensions, and compact weight. Furthermore, the region where the Heckel plot is linear is only accounting for a small portion of the total densification[34]. Also, in his original work with metal powders, Heckel considered elastic deformation to be

Table 1. Comparison of yield pressure, total work, and percent elastic recovery for GMS-placebo beads*.

Condition	Yield pressure (MPa)	Total work (J)	% elastic recovery
Low speed/low force	9.1 ± 1.6	1.9 ± 0.3	3.8 ± 0.7
Low speed/high force	25.8 ± 1.9	3.9 ± 0.4	7.8 ± 0.5
High speed/low force	30.5 ± 0.8	3.6 ± 0.4	5.6 ± 1.1
High speed/high force	62.1 ± 8.5	6.9 ± 1.0	8.9 ± 2.5

*Results are the mean ± SD; $n = 3$.

negligible, which is not always the case[17]. However, Carstensen et al.[35] have reported that the Heckel plots of Emcompress® were fairly independent of the die diameter and the fill weight. Also, Kiekens et al.[36] have reported that the yield pressures were influenced to a greater extent by parameters, such as punch diameter, filling depth, and compression pressure, in the case of concave punches as compared to flat-faced punches, which is the type of tooling used in the current study. In this study error propagation in yield pressure calculations was minimized by obtaining precise true density measurement and keeping tablet weights constant. Also, unlike metal powders, these beads and blends did exhibit differences in their ER values.

In examining the data for theophylline, it was found that the uncoated control beads alone had the highest yield pressure overall of 79.3 ± 3.8 MPa for the low speed/low force condition, and again this value steadily increased with increases in both applied force and speed (Table 2). This phenomenon in which the pressures required to achieve certain porosities increase as the machine speed is increased, resulting in higher P_y values, has been reported previously[37]. This is because higher speeds will not allow a sufficient dwell time for the punches or allow sufficient time for ER as a low speed/low force condition and therefore higher pressures will be required.

The theophylline control beads contain 58% (w/w) dicalcium phosphate dihydrate a known hard, brittle material that does not compact well. Initially under low speed/low force conditions, this material shows some plasticity based on the yield pressure. However, as both the speed and force are increased, the material shows a significantly higher yield pressure at 164.0 ± 4.7 MPa. A value of this magnitude, greater than 100 MPa can be classified as showing brittle fracture; and even the Eudragit® NE30D sample exhibits some brittleness under high speed/high force conditions (P_y = 111.2 ± 9.7 MPa). While the total work and ER were similar for both control and theophylline-EC beads; the Eudragit® NE30D beads generally had higher elastic recoveries, especially at higher speeds. Increasing either the speed or the applied force appears to increase the ER as the compact is not given enough time to expand in the die and is only allowed to expand axially as the upper punch is withdrawn. The greater the ER, the less permanent are the interparticulate bonds formed. This will ultimately lower the tablet tensile strength and thus show a decreased compactibility for the material.

Table 2. Comparison of yield pressure, total work, and percent elastic recovery for theophylline beads*.

Sample and condition	Yield pressure (MPa)	Total work (J)	% elastic recovery
Low speed/low force			
Control, uncoated	79.3 ± 3.8	8.1 ± 0.5	8.7 ± 1.6
Ethylcellulose, uncoated	43.7 ± 0.6	8.1 ± 0.5	8.7 ± 1.6
Ethylcellulose, Eudragit® NE30D	49.3 ± 2.1	8.7 ± 0.7	13.2 ± 0.5
Low speed/high force			
Control, uncoated	89.8 ± 1.7	10.6 ± 0.6	11.5 ± 1.7
Ethylcellulose, uncoated	49.7 ± 4.0	10.6 ± 0.6	11.5 ± 1.7
Ethylcellulose, Eudragit® NE30D	66.3 ± 2.0	11.0 ± 0.6	16.7 ± 1.2
High speed/low force			
Control, uncoated	146.5 ± 5.4	11.0 ± 0.6	7.1 ± 0.4
Ethylcellulose, uncoated	76.4 ± 3.3	8.8 ± 0.3	12.6 ± 4.0
Ethylcellulose, Eudragit® NE30D	98.2 ± 4.5	15.0 ± 1.3	23.3 ± 1.2
High speed/high force			
Control, uncoated	164.0 ± 4.7	16.9 ± 1.1	10.6 ± 3.4
Ethylcellulose, uncoated	86.2 ± 0.7	14.5 ± 0.2	21.9 ± 0.6
Ethylcellulose, Eudragit® NE30D	111.2 ± 9.7	18.6 ± 1.4	20.0 ± 6.9

*Results are the mean ± SD; n = 3.

The cimetidine data showed that overall Surelease®-coated beads alone gave the highest yield pressures, total work of compression, and ER values and that these values were higher than for Eudragit® NE30D-coated beads alone (Table 3). It was surprising that the 50:50 blends of both Surelease®-coated beads and placebo beads and Eudragit® NE30D-coated beads with placebo beads showed slightly higher yield pressures and total work of compression as compared with the data from the 60:40 ratio (60% drug beads:40% placebo beads). It was thought that the blend containing 10% w/w additional plastic GMS-placebo beads (50:50 ratio) would have had lower yield pressures and total work values but this was not the case. The ER values for all the other samples were comparable. It appears that a plausible explanation for the increased P_y values in the 50:50 blends is that level of starch and starch derivatives in the GMS-placebo beads was higher than in the 60:40 blends. Starch is a known viscoelastic material and therefore would require more pressure to deform[38,39].

The Heckel densification factors provide some additional information concerning the compression properties of the materials used in this study. The three parameters include D_0, the relative apparent density or bulk density in the die before compression, D_a, the total densification due to the filling of the die and particle arrangement, and D_b, the density contribution from individual particle movement and rearrangement. In examining the data of the Heckel densification factors for GMS-placebo beads (Table 4), it was found that the D_a values were much greater than the D_b values under all speed and force conditions, indicating that more densification was occurring by bead deformation than by rearrangement and bead movement[40]. The tablet crushing strength values were relatively similar regardless of changes in speed or force.

Table 3. Comparison of yield pressure, total work, and percent elastic recovery for cimetidine beads and blends with GMS-placebo beads*.

Sample and condition	Yield pressure (MPa)	Total work (J)	% elastic recovery
Low speed/low force			
Surelease-coated only	60.5 ± 1.5	10.7 ± 0.4	15.1 ± 0.3
Surelease/placebos 50:50	33.1 ± 1.3	5.2 ± 0.2	9.1 ± 0.9
Surelease/placebos 60:40	28.0 ± 2.9	4.5 ± 0.6	9.0 ± 0.8
Eudragit® NE30D only	47.7 ± 2.6	7.9 ± 0.3	10.3 ± 1.1
Eudragit® NE30D 50:50	45.7 ± 1.9	7.6 ± 0.5	12.1 ± 0.9
Eudragit® NE30D 60:40	33.2 ± 4.2	5.3 ± 0.7	9.1 ± 1.6
Low speed/high force			
Surelease-coated only	71.5 ± 1.8	13.0 ± 0.3	20.9 ± 1.2
Surelease/placebos 50:50	49.9 ± 1.7	8.1 ± 0.5	14.0 ± 0.8
Surelease/placebos 60:40	40.9 ± 2.5	6.9 ± 0.6	11.7 ± 1.5
Eudragit® NE30D only	61.1 ± 0.9	10.2 ± 0.2	14.3 ± 0.7
Eudragit® NE30D 50:50	58.0 ± 1.8	9.6 ± 0.1	16.9 ± 1.3
Eudragit® NE30D 60:40	44.7 ± 1.4	7.3 ± 0.4	12.0 ± 0.9
High speed/low force			
Surelease-coated only	104.9 ± 1.3	18.9 ± 0.4	19.9 ± 5.9
Surelease/placebos 50:50	71.4 ± 3.3	8.0 ± 1.1	11.4 ± 2.7
Surelease/placebos 60:40	62.1 ± 3.5	5.5 ± 0.3	7.2 ± 0.6
Eudragit® NE30D only	82.4 ± 1.0	9.0 ± 0.3	16.8 ± 0.2
Eudragit® NE30D 50:50	86.2 ± 5.0	9.9 ± 1.1	15.6 ± 3.4
Eudragit® NE30D 60:40	62.1 ± 3.5	6.9 ± 0.7	12.5 ± 3.4
High speed/high force			
Surelease-coated only	116.5 ± 6.1	21.9 ± 2.3	30.9 ± 1.8
Surelease/placebos 50:50	102.9 ± 2.2	11.9 ± 0.2	14.9 ± 2.8
Surelease/placebos 60:40	83.3 ± 7.4	10.2 ± 1.5	15.2 ± 2.8
Eudragit® NE30D only	109.2 ± 3.9	16.4 ± 1.8	25.0 ± 1.5
Eudragit® NE30D 50:50	113.6 ± 6.2	14.6 ± 1.0	17.7 ± 2.8
Eudragit® NE30D 60:40	89.7 ± 7.0	12.0 ± 1.7	15.0 ± 2.6

*Results are the mean ± SD; $n = 3$.

The Heckel factors were also examined for theophylline beads (Table 5) and cimetidine beads (Table 6). Theophylline-EC beads showed consistently lower D_b values as compared with control samples. Generally, while tablet crushing strength values for theophylline samples were reasonable, blends of both Surelease®- or Eudragit® NE30D-coated cimetidine beads had some of the lowest tablet crushing strength values (<3 kP), indicating poorer interparticulate bonding. It appears that the presence of hydrophobic GMS from blends has a detrimental effect on the tablet crushing strength. Furthermore, Surelease®-coated cimetidine beads showed the lowest D_b values and the largest fluctuation of these values with changes in speed and force, indicating significant changes in the extent of particle rearrangement. The D_b factor is primarily a function of particle geometry and decreases as the particle size decreases or as the particle shape becomes more nearly spherical[16].

This is in agreement with the data from[27], which showed that uncoated EC beads were slightly more spherical than their controls and therefore would have lower D_b values. The sphericity values of either Surelease®- or Eudragit® NE30D-coated beads were identical at 0.91 ± 0.04; however, the sphericity for GMS placebos was much lower at 0.73 ± 0.08. While this explains why the blends of coated drug beads with GMS beads under low speed conditions had higher D_b values, this relationship did not hold true under high speed conditions as the values were much closer together.

SRS is an important factor to consider when going from a laboratory scale tablet press to a production tablet press as the dwell times will be much shorter on a faster tablet press. It is known that plastically deforming and viscoelastic materials such as MCC and corn starch will have significantly higher SRS values as compared to brittle materials such as dicalcium phosphate dihydrate[22]. However, while the two speed conditions for previous research were ideal at 0.033 and 300 mm/s to calculate SRS due to the wide gap between them[41], this research used press speed conditions (i.e., 612 and 2103 mm/s), which may not have been spaced far enough apart due to the limitations of the equipment used. Ideally, SRS determinations should be made using a compaction simulator as was used in the research of Muller and Augsburger[41]. More experimental work would need to be performed to ascertain whether the accuracy and precision of SRS values is similar using both types of equipment. It was interesting to observe that the plastically deforming GMS-placebo beads showed a significantly higher SRS (70.2%) as compared with all other samples, coated or uncoated (Table 7). Typical SRS reference values for other

Table 4. Comparison of densification factors and tablet crushing strength values for compacts prepared from GMS-placebo beads*.

Sample and condition	D_0 (g/cm^3)	D_a (g/cm^3)	D_b (g/cm^3)	Crushing strength (kP)
Low speed/low force	0.152 ± 0.001	0.518 ± 0.051	0.366 ± 0.051	5.23 ± 0.15
Low speed/high force	0.156 ± 0.005	0.685 ± 0.008	0.529 ± 0.009	5.55 ± 0.13
High speed/low force	0.175 ± 0.001	0.713 ± 0.003	0.538 ± 0.003	4.98 ± 0.21
High speed/high force	0.176 ± 0.009	0.731 ± 0.010	0.555 ± 0.008	4.65 ± 0.33

*Results are the mean ± SD; $n = 3$.

Table 5. Comparison of densification factors and crushing strength values for compacts prepared from theophylline beads*.

Sample and condition	D_o (g/cm^3)	D_a (g/cm^3)	D_b (g/cm^3)	Crushing strength (kP)
Low speed/low force				
Control, uncoated, 500 mg	0.079 ± 0.002	0.488 ± 0.009	0.409 ± 0.011	4.87 ± 0.84
Ethylcellulose, uncoated	0.126 ± 0.004	0.440 ± 0.013	0.314 ± 0.009	5.57 ± 0.91
Ethylcellulose, Eudragit® NE30D	0.135 ± 0.001	0.499 ±0.025	0.489 ± 0.009	8.57 ± 0.15
Low speed/high force				
Control, uncoated, 500 mg	0.081 ± 0.002	0.484 ± 0.003	0.403 ± 0.004	10.17 ± 0.64
Ethylcellulose, uncoated	0.129 ± 0.002	0.470 ± 0.005	0.340 ± 0.003	6.80 ± 0.65
Ethylcellulose, Eudragit® NE30D	0.133 ± 0.004	0.510 ± 0.021	0.520 ± 0.007	8.33 ± 0.40
High speed/low force				
Control, uncoated, 500 mg	0.089 ± 0.004	0.508 ± 0.001	0.419 ± 0.004	7.50 ± 0.41
Ethylcellulose, uncoated	0.092 ± 0.070	0.484 ± 0.004	0.392 ± 0.074	2.57 ± 0.29
Ethylcellulose, Eudragit® NE30D	0.127 ± 0.004	0.500 ± 0.018	0.373 ± 0.014	7.43 ± 0.21
High speed/high force				
Control, uncoated, 500 mg	0.088 ± 0.005	0.502 ± 0.005	0.414 ± 0.005	13.2 ± 1.20
Ethylcellulose, uncoated	0.130 ± 0.003	0.482 ± 0.004	0.352 ± 0.005	5.40 ± 0.08
Ethylcellulose, Eudragit® NE30D	0.130 ± 0.003	0.510 ± 0.021	0.380 ± 0.019	6.90 ± 0.10

*Results are the mean ± SD; $n = 3$.

Table 6. Densification factors and tablet crushing strength for compacts of cimetidine-ethylcellulose beads and blends with GMS-placebo beads*.

Sample and condition	D_o (g/cm^3)	D_a (g/cm^3)	D_b (g/cm^3)	Crushing strength (kP)
Low speed/low force				
Surelease-coated only	0.134 ± 0.002	0.500 ± 0.006	0.366 ± 0.005	7.43 ± 0.49
Surelease/placebos 50:50	0.153 ± 0.006	0.608 ± 0.027	0.456 ± 0.022	1.87 ± 0.74
Surelease/placebos 60:40	0.168 ± 0.002	0.604 ± 0.014	0.435 ± 0.013	1.47 ± 0.35
Eudragit® NE30D only	0.133 ± 0.003	0.493 ± 0.019	0.360 ± 0.017	7.75 ± 0.47
Eudragit® NE30D 50:50	0.149 ± 0.005	0.644 ± 0.011	0.495 ± 0.009	3.15 ± 0.57
Eudragit® NE30D 60:40	0.148 ± 0.008	0.620 ± 0.016	0.472 ± 0.015	2.15 ± 0.40
Low speed/high force				
Surelease-coated only	0.133 ± 0.003	0.517 ± 0.003	0.383 ± 0.001	7.43 ± 0.32
Surelease/placebos 50:50	0.150 ± 0.005	0.636 ± 0.006	0.486 ± 0.011	1.67 ± 0.25
Surelease/placebos 60:40	0.160 ± 0.003	0.624 ± 0.009	0.464 ± 0.012	1.50 ± 0.10
Eudragit® NE30D only	0.134 ± 0.001	0.527 ± 0.010	0.393 ± 0.009	8.23 ± 0.47
Eudragit® NE30D 50:50	0.150 ± 0.009	0.649 ± 0.011	0.499 ± 0.002	3.37 ± 0.35
Eudragit® NE30D 60:40	0.150 ± 0.005	0.633 ± 0.006	0.483 ± 0.006	2.57 ± 0.42
High speed/low force				
Surelease-coated only	0.129 ± 0.002	0.501 ± 0.004	0.487 ± 0.008	6.47 ± 0.15
Surelease/placebos 50:50	0.166 ± 0.007	0.646 ± 0.006	0.480 ± 0.004	1.73 ± 0.40
Surelease/placebos 60:40	0.148 ± 0.008	0.620 ± 0.016	0.472 ± 0.015	1.13 ± 0.21
Eudragit® NE30D only	0.139 ± 0.006	0.527 ± 0.006	0.388 ± 0.009	5.3 ± 0.53
Eudragit® NE30D 50:50	0.169 ± 0.010	0.684 ± 0.006	0.515 ± 0.009	2.33 ± 0.39
Eudragit® NE30D 60:40	0.158 ± 0.007	0.646 ± 0.006	0.489 ± 0.002	1.60 ± 0.26
High speed/high force				
Surelease-coated only	0.128 ± 0.008	0.506 ± 0.005	0.520 ± 0.006	6.40 ± 0.30
Surelease/placebos 50:50	0.166 ± 0.007	0.659 ± 0.002	0.493 ± 0.009	1.80 ± 0.14
Surelease/placebos 60:40	0.150 ± 0.005	0.633 ± 0.006	0.483 ± 0.006	1.25 ± 0.21
Eudragit® NE30D only	0.134 ± 0.005	0.539 ± 0.011	0.405 ± 0.013	6.45 ± 0.24
Eudragit® NE30D 50:50	0.165 ± 0.008	0.691 ± 0.004	0.525 ± 0.004	2.43 ± 0.05
Eudragit® NE30D 60:40	0.156 ± 0.006	0.659 ± 0.007	0.503 ± 0.002	1.83 ± 0.34

*Results are the mean ± SD; $n = 3$.

Table 7. Comparison of strain rate sensitivity (SRS) data at low force. Uncoated beads, blends of coated beads and GMS-placebo beads.

Sample composition	Strain rate sensitivity %
GMS-placebo beads	70.2
Cimetidine-ethylcellulose Surelease beads	42.3
Cimetidine-ethylcellulose Eudragit® NE30D beads	42.1
Theophylline control beads	45.9
Theophylline-ethylcellulose beads	42.8
Theophylline-ethylcellulose Eudragit® NE30D beads	49.8
Cimetidine-ethylcellulose Eudragit® NE30D 50:50 blend	47.0
Cimetidine-ethylcellulose Eudragit® NE30D 60:40 blend	46.5
Cimetidine-ethylcellulose Surelease 50:50 blend	53.6
Cimetidine-ethylcellulose Surelease 60:40 blend	54.9

plastically deforming materials such as corn starch and Avicel®-PH 101 were previously reported as 49.3% and 38.9%, respectively[22].

Conclusions

The GMS-placebo beads alone exhibited the lowest yield pressure values (9.1 ± 1.6 MPa) and total work of compression (1.9 ± 0.3 J) overall as expected and these values steadily increased with increases in both applied force and speed. While they also showed the lowest percentage ER values of 3.8 ± 0.7%, these beads showed significant time-dependent deformation behavior based on their SRS value of 70.2%. Heckel analysis showed that the D_a values were much greater than the D_b values under all speed and force conditions, indicating that more densification was occurring by bead deformation than by rearrangement and bead movement. These results are due to the fact that these placebo beads contain 50% (w/w) of GMS, a known plastic material.

Heckel analysis showed that uncoated theophylline-EC beads were more compressible than control beads containing 58% (w/w) of a hard, brittle excipient such as dicalcium phosphate. It was also found that the uncoated theophylline control beads had the highest yield pressure overall of 79.3 ± 3.8 MPa for the low speed/low force condition; however, this value steadily increased to 164.0 ± 4.7 MPa under high speed/high force settings. Heckel plots also showed that 50:50 ratios of blends containing drug beads coated with either Surelease® or Eudragit® NE30D behaved similarly under increasing force and speed, with the higher force and speed samples showing improved compressibility as measured by their increased linearity over the compression force range.

Compared with Eudragit® NE30D-coated cimetidine beads, Surelease®-coated beads showed higher values for yield pressure, total work of compression, and ER values. However, although the P_y differences among the beads were relatively small numerically (i.e., 10 MPa for P_y values under the low speed/low force condition), there were performance differences observed during dissolution between blends of compacted beads using the different coatings. For example, 8 hours cimetidine release was 21.5 ± 2.6% and 14.5 ± 1.3% from tablets containing either 50% (w/w) Surelease®-coated or Eudragit® NE30D-coated beads, respectively. This indicates that Surelease® blends may not be as well suited to withstand the compressive stress under these experimental conditions as the Eudragit® NE30D blends. Generally, while tablet crushing strength values for theophylline samples were reasonable, blends of Surelease®-coated cimetidine beads had some of the lowest tablet crushing strength values, indicating poorer interparticulate bonding. Furthermore, Surelease®-coated cimetidine beads showed the lowest D_b values and the largest fluctuation of these values with changes in speed and force, indicating significant changes in the extent of particle rearrangement. Generally, the 50:50 blend ratios containing coated beads showed somewhat higher yield pressures, total work, and elastic recoveries as compared with the 60:40 blend ratios. This is likely due to the presence of increased levels of starch and starch derivatives (e.g., sodium starch glycolate) from the GMS-placebo beads. Furthermore, starch is known to be a viscoelastic material that will require more applied force to undergo deformation.

Although such a difference in the blend ratio (i.e., 10%, w/w) may appear minor, scientists need to be aware that as components of a formulation are adjusted, the mechanical properties of key ingredients are also affected and this can lead to subsequent issues with drug release, and so on. Interestingly, although the Surelease® blends showed slightly higher mechanical strength (i.e., P_y values), they also displayed higher amounts of drug release after 8 hours compared with the Eudragit® NE30D blends[27]. This release difference can be due to the fact that the Eudragit® NE30D polymer forms more flexible films that can better survive the compaction process. The 60:40 ratios showed higher drug release compared to the 50:50 ratios as expected due to the presence of less cushioning placebo beads. However, since there still appears to be some conflicting data on the benefits of using Eudragit® NE30D blends for this type of work, further study is warranted.

While most previous research has focused on the study of the mechanical properties of neat materials or powdered blends, little work has been published on the study of blends of extruded spheronized beads used for tableting. Improved understanding of material

properties of uncoated and coated extruded spheronized beads alone and in blends as well as tablet characteristics can result in more robust modified release formulations being produced with less chance of quality control issues.

Acknowledgments

The authors wish to express their sincere gratitude to MCC Corp. for the use of their Presster™ in performing the Heckel analysis.

Declaration of interest: The authors report no conflicts of interest.

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