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COMMUNICATION

Weight and Weight Uniformity of Hard Gelatin Capsules Filled with Microcrystalline Cellulose and Silicified Microcrystalline Cellulose

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ABSTRACT

The objective of this study was to investigate the weight and weight uniformity of hard gelatin capsules filled with microcrystalline cellulose (MCC) and silicified microcrystalline cellulose (SMCC) powdered formulations. A tamping-type encapsulation apparatus was used to fill the capsules. The four formulations that were tested included MCC alone, MCC blended with fumed silica, SMCC, and high-density SMCC (SMCC-HD). The mean capsule weight and the average variation in mean capsule weight of each formulation were determined. Both SMCC products exhibited better flow than the MCC alone, with SMCC-HD being the freest flowing of the powders investigated. Capsules filled with the SMCC products had higher fill weights than those containing the MCC powders. The SMCC-containing capsules exhibited the lowest variation in weight, although these findings were not significantly different from either of the MCC-containing capsules. Significantly higher weight variations were found in capsules filled with SMCC-HD. A relationship between Carr's compressibility index and capsule weight variation was found, with more compressible materials producing more uniformly filled capsules. No relationship could be established between powder flow and capsule weight uniformity. These findings suggest that powder flow may not be a critical parameter in ensuring capsule weight uniformity when the encapsulation equipment utilizes a tamping-type filling system.

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Key Words: *Capsule weight variation; Powder flow; Carr's compressibility index; Tamp-filling machine*

INTRODUCTION

Microcrystalline cellulose (MCC) is a partially depolymerized cellulose that is widely used as a diluent in tablet and capsule formulations. Due to its low bulk density, high lubricant sensitivity, influence of moisture on compression properties, and poor flow characteristics (1), a new material, silicified microcrystalline cellulose (SMCC), was developed. The latter is produced by a process of silicification, where silicon is deposited on the outer surface and on exposed inner surfaces of the MCC particle (2).

Although no discernable chemical or polymorphic differences between the two materials have been reported (2,3), researchers have noted several advantages of the SMCC product over conventional MCC. Improved compactibility of SMCC has been reported for both direct compression and wet granulation processes (4,5). Guo and Augsburger (6) suggested that the high compactibility of both MCC and SMCC at low compression forces may be beneficial in plug formation and plug transfer during tamp-filling encapsulation operations.

Another reported advantage of SMCC compared to MCC is improved powder flow (2,7). Previous researchers have determined powder flow in an effort to evaluate various excipients and predict formulation performance (8–11). More recently, Sherwood and Becker (5) compared MCC- and SMCC-containing tablets and found that the enhanced flow properties of SMCC produced tablets with improved weight uniformity. No studies, however, have evaluated the performance of MCC and SMCC during capsule-filling processes. The objective of the current study was to investigate the weight and weight uniformity of hard gelatin capsules filled with MCC and SMCC powdered formulations.

MATERIALS AND METHODS

Materials

Microcrystalline cellulose (Emcocel® 90M) and silicified microcrystalline cellulose (Prosolv® 90 and Prosolv® HD 90) were supplied by Penwest Pharmaceuticals Company (Patterson, NY). These materials had a mean particle size of 90 μm. Colloidal silicon dioxide or fumed silica (Cab-O-Sil® M5-P) was donated by Cabot Corporation (Tuscola, IL). Size 1 clear-clear hard gelatin capsules were purchased from Shionogi Qualicaps Incorporated (Whitsett, NC). The materials were stored and all work was conducted in a humidity-controlled environment (20% relative humidity).

Methods

Capsule Production

The four powdered formulations that were investigated in this research endeavor are shown in Table 1. To avoid problems associated with over-lubrication, no lubricating agents were used in any formulation. All powders were passed through a 40 mesh screen prior to use. For the formulation that contained fumed silica, MCC and the glidant were mixed for 10 min in a V-shell blender (Erweka

Table 1

Density, Compressibility Index, and Flow Index of the Powdered Formulations

Formulation	Bulk Density (g/cc)	Tap Density (g/cc)	Compressibility Index (%)	Flow Index (mm)
MCC	0.290	0.386	24.9	18
MCC-silica blend	0.300	0.388	22.5	12
SMCC	0.318	0.416	23.4	16
SMCC-HD	0.436	0.510	14.5	7

USA, Inc., Milford, CT). Powders were filled into size 1 hard gelatin capsules using a Bosch GKF-400S tamp-filling machine (Bosch-TL Systems Corp., Minneapolis, MN). Based on previous research that showed the fill weight variation was nearly independent of tamping pin settings for moderate flowing powders (12), the pins in the current study were adjusted to the lowest compressional setting. The filled capsules were collected in an appropriate container and then stored in plastic bags until analyzed for weight and weight uniformity. The machinery was disassembled after each production run and cleaned to remove residual powder.

Analysis of Capsule Weight and Weight Uniformity

To determine the capsule fill weight and weight uniformity, 50 capsules from each formulation were weighed individually using an analytical balance. The arithmetic mean and relative standard deviation for each formulation were calculated. Next, the difference between individual samples and the mean capsule weight for each formulation was determined. The absolute values of these figures were then used to calculate an average and relative standard deviation of the variation from the mean capsule weight. An analysis of variance (ANOVA) and Student *t*-test were used to determine statistical differences in the data.

Powder Flow Index

The flow of the MCC and SMCC powders was determined using the Hansen Flodex Powder Flowability Test Instrument (Hanson Research Corp., Chatsworth, CA). Fifty grams of each of the powdered formulations were placed in a cylinder. After a 30-sec equilibrium period, a lever was opened to allow the powder to flow through an orifice in the bottom of the container. The procedures were repeated three consecutive times. The flow index was recorded as the smallest diameter opening through which the powder flowed.

Density Determination

The bulk and tap densities of the various MCC and SMCC powders were determined using a VanKel Tap Density Tester (VanKel Technology Group, Cary, NC). Approximately 14 g of each powdered formulation were accurately weighed then carefully transferred to a 50-mL glass graduated cylinder. The volume of the powder was then determined. Bulk density was calculated as the weight divided by the volume of the powder, and the data are presented in Table 1. The graduated cylinder was then fixed to the platform of the testing apparatus and the machine was programmed to tap for 2 min at a rate of 300 taps/min. The platform also rotated approximately 10 times/min to ensure an evenly packed surface. After tapping was complete, the volume of the powder was again determined. Tap density was calculated by dividing the weight by the volume of the powder after tapping, and these data are presented in Table 1. Finally, the densities were used to calculate Carr's compressibility index C using Eq. (1), where ρ_T is the tap density and ρ_B is the bulk density (13). The compressibility indices of the four powdered formulations are also presented in Table 1.

$$C = \frac{(\rho_T - \rho_B)}{\rho_T} \times 100 \quad (1)$$

RESULTS AND DISCUSSION

Capsules that are filled by volume and filling processes generally rely on gravity and powder flow properties. Many variables may affect powder flow, including particle size, shape, density, roughness, and moisture content (14). Since MCC and SMCC have been shown to be nearly identical chemically yet possess different powder flow properties (4), these materials were selected for this study. The current research investigated the relationship between powder flow and weight uniformity when a tamp-filling encapsulation method is used to manufacture capsules. A tamping encapsulation machine utilizes both gravity and light compression to fill capsules. Pins are pushed through a powder bed to form plugs, and these plugs are subsequently inserted into the capsule bodies (12,15).

The powder flow index of each of the formulations investigated in this study is shown in Table 1. As expected, the addition of fumed silica to MCC resulted in an increase in powder flow, as evidenced by a decrease in the flow index. These findings are in agreement with previously published studies, that showed the small particle size and large surface area of silicon dioxide improved the flow properties of powder (16). Powder flow of MCC when blended

with silica was greater than the coprocessed SMCC (powder flow index of 12 and 16, respectively). These findings are quite interesting, since the SMCC product contained the equivalent of 2% fumed silica in the formulation (5), whereas only 0.5% silica was used in the MCC-blend in this study. Of the four formulations tested, powder flow was greatest (lowest flow index) for the high-density SMCC (SMCC-HD). These findings are in agreement with previous researchers, who have shown higher density powders generally exhibit improved powder flow properties (11).

Table 2 shows the average capsule weight and relative standard deviation for each of the four powdered formulations investigated in this study. The capsule weights for the MCC-containing products averaged approximately 224–234 mg, whereas the capsule weights were nearly 50 mg higher when the SMCC products were used to fill the capsules. These findings are in agreement with data presented by Sherwood and Becker (5), who showed that the mean fill weight of tablets prepared by direct compression was significantly higher when SMCC was used in comparison to MCC. These researchers suggested that the higher fill weights were due to the ease of powder flow and consolidation, thus creating a greater packing density of the SMCC. In the present study, however, the average fill weights of the capsules containing SMCC and SMCC-HD were not significantly different.

As seen in Table 2, the relative standard deviation of the MCC capsules increased when silica was added to the powdered formulation (2.06 and 2.22%, respectively), despite the fact that the blended powder flowed better. The most uniform capsules (lowest relative standard deviation in mean capsule weight) were obtained when the SMCC formulation was used. These findings are quite interesting, since the MCC-silica blend was more free-flowing than the SMCC formulation. The SMCC-HD formulation that exhibited the lowest flow index also produced capsules with the largest relative standard deviation (3.06%). Based on previous research that has shown a direct relationship between powder flow and weight uniformity (8,11,17), this free-flowing, high-density material was expected to produce the most uniform capsule weights. These findings suggest that powder flow may not be critical in achieving weight uniformity of capsules filled using a tamping-type encapsulation system.

In contrast to our findings, Sherwood and Becker (5) showed that enhanced powder flow led to improved tablet weight uniformity, with lower relative standard deviations noted in the data. The differences in the data were greater when the tablet press was operated at higher speeds. The authors, however, did not evaluate the variation within the data for significance, and it is difficult to determine if the relative standard deviations of the average tablet weights were statistically different.

To determine if the relative standard deviations of the various capsule formulations in the present study differed significantly, the average variation from mean capsule weight was determined and the data are presented in Table 2. These values were obtained by taking the absolute value of the difference between each individual capsule weight and the average capsule weight for the given formulation. These values were then used to calculate an average and relative standard deviation for the variation in mean capsule weight. A one-way ANOVA was then used to demonstrate significance of the data ($p < .001$). A pairwise multiple comparison (Tukey test) showed that the MCC, MCC-silica blend, and SMCC were not significantly different, indicating that the uniformity of capsule fill weight was similar for all three formulations. The only formulation that differed significantly in the average variation in mean capsule weight ($p < .001$) was the formulation that exhibited the greatest powder flow, SMCC-HD. These findings again suggest that powder flow may not be a critical parameter in manufacturing uniform capsules using a tamping-type encapsulation apparatus.

Table 2

Average Fill Weight and Variation in Fill Weight for Capsules Containing MCC and SMCC Powdered Formulations

Formulation	Average Capsule Weight (mg) (RSD)[a]	Average Variation from Mean Capsule Weight (mg) (RSD)
MCC	223.9 (2.06%)	3.5 (3.00%)
MCC-silica blend	234.4 (2.22%)	3.6 (3.70%)
SMCC	278.2 (1.51%)	3.4 (2.36%)
SMCC-HD	279.0 (3.06%)	6.7 (5.14%)

[a]RSD = relative standard deviation.

The literature regarding the relationship between capsule weight uniformity and powder flow is quite contradictory. Several researchers have reported that poor powder flow may result in high weight variations since capsules are filled by gravity (8,11,17). Other researchers, however, have found no correlation between powder flow and weight uniformity (18). Still others have suggested that free-flowing powders may not be able to sufficiently densify, thus impairing plug formation and resulting in higher capsule weight variations when using a tamp-filling encapsulation system. In the current study, the freest flowing powder (SMCC-HD) did exhibit higher variation in weight. However SMCC-HD compresses extremely well, and impaired plug formation was not observed during the capsule-filling process.

In the current study, the average variation from mean capsule weight was plotted against the powder flow index and Carr's compressibility index, as shown in Figs. 1 and 2, respectively. No clear relationship was found between powder flow index and average variation from mean capsule weight. However, good correlation between the Carr's compressibility index and the average variation from mean capsule weight was observed ($r^2 = 0.960$), with more compressible powders producing more uniformly filled capsules. In contrast, Fassihi and Kanfer (13) found an opposite relationship for tablets prepared on a single station press, with higher variations in tablet weight associated with the more compressible powders. These results may be related to the differences in the filling processes. For low speed tabletting, powders flow into a die cavity and are compressed. In contrast, the tamp-filling encapsulation system utilizes several low compression stages, which compress the powder then allow additional powder to fill the cavity. Our findings are in agreement with Podczeck and Newton (12), who showed that the tamp-filling encapsulation method was less sensitive to powder flow problems than the conventional capsule-filling machines. The results presented in this study may not be applicable to dosator nozzle types of encapsulation equipment that rely only on gravity to fill capsules.

CONCLUSIONS

The SMCC products exhibited better flow than the MCC alone, with the high-density coprocessed SMCC-HD exhibiting the freest flowing properties of the powders investigated. Fill weights were higher when SMCC products were used to fill the capsules. The only formulation found to exhibit statistically significant higher weight variations was the most free-flowing powder, SMCC-HD. A relationship between Carr's compressibility index and

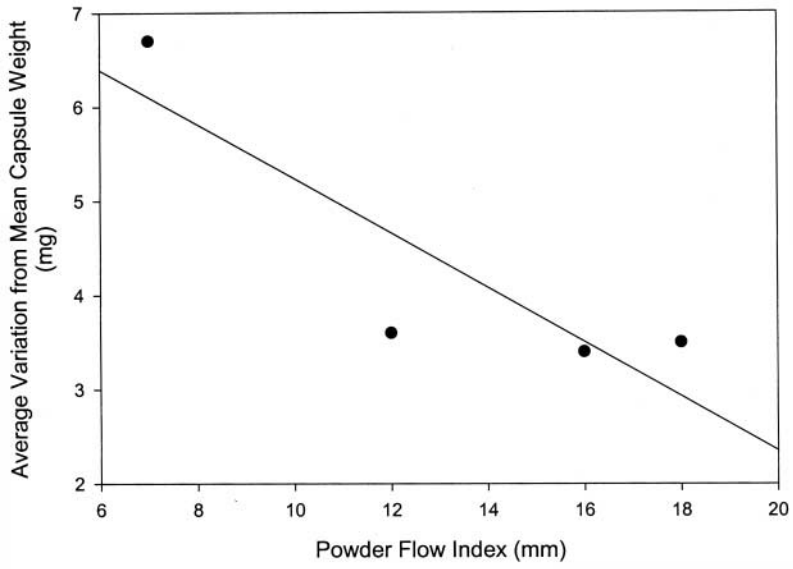

Figure 1. Relationship between average variation from mean capsule weight and powder flow index ($r^2 = 0.764$).

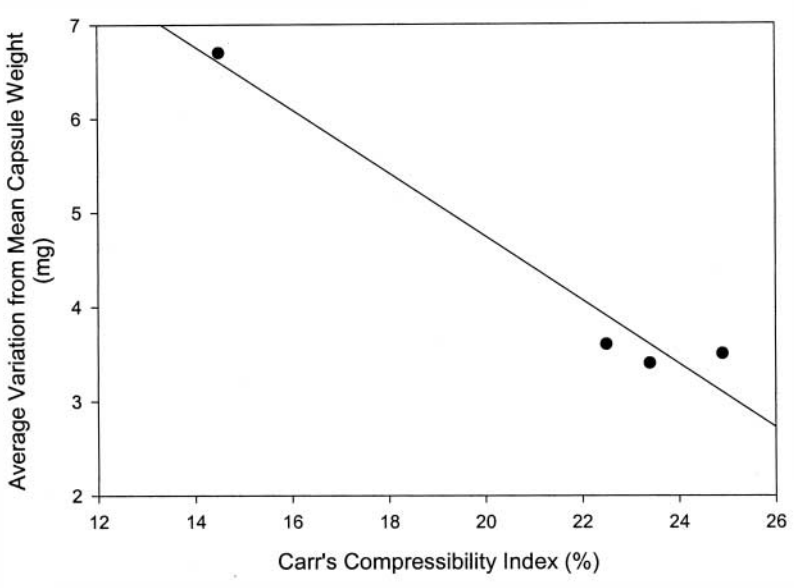

Figure 2. Relationship between average variation from mean capsule weight and Carr's compressibility index ($r^2 = 0.960$).

capsule weight uniformity was found, although no relationship between powder flow index and capsule weight uniformity could be established. These findings suggest that powder flow may not be a critical parameter in ensuring capsule weight uniformity when the encapsulation equipment utilizes a tamping system.

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