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Enhancement of Xcelodose Capsule-Filling Capabilities Using Roller Compaction

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Using a novel automated microfilling system, the authors demonstrate that roller compaction followed by milling is a viable preprocessing technique for high-dose chemical-in-capsule dosage forms. The process results in higher bulk and tapped densities for drug substances compared with milling alone.

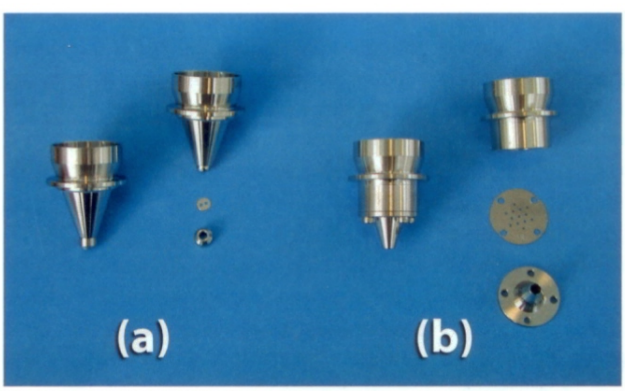

Figure 1: Xcelodose dispense heads showing (a) standard type and (b) high-flow type.

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Chemical in capsule (CIC) is a dosage form proposed to support early clinical studies, including Phase I safety, pharmacokinetic, and proof-of-concept evaluations. CIC reduces development time, conserves drug substance, and allows better management of resources against compound attrition (1, 2).

The Xcelodose 600 (Capsugel, Morris Plains, NJ) microfilling system is an innovative, automated, and programmable machine for the precise metering of drug substances into capsules (3). It is designed for single components (*i.e.*, drug substances) without excipients and precisely fills sizes 00, 0, 1, 2, and 3 gelatin and hypromellose (HPMC) capsules at a rate of several hundred capsules per hour, depending on the level of precision required and the physical characteristics of the powder being filled. Doses from 100 μg to 300 mg are possible, with a typical relative standard deviation (RSD) of <2%.

Because of the absence of a tamping mechanism on the Xcelodose machine, the actual amount of powder that will fit in a capsule is limited by the powder's physical characteristics. In some cases, drug substances may require preprocessing to increase density and enable high-dose CIC.

The objective of this study was to fill 100 mg of Compound X into size 0 capsules using the Xcelodose system. First, allowable capsule-fill weights were calculated using the bulk density of the drug substance. According to the compound's bulk density value, we determined that 100 mg of Compound X could be contained in size 0 capsules. During development of the 100-mg dose, however, it was discovered that 100 mg of the drug substance did not fit into the requested size 0 capsules or in the maximum available capsule size (size 00).

Apparently, bulk density alone could not predict the amount of particles a given capsule space would accommodate. Previous work has suggested that the effective bulk density of the same material could vary under different dynam-

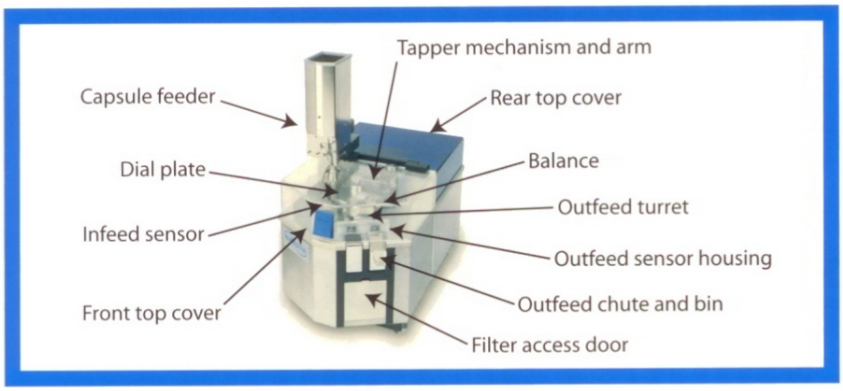

Figure 2: Xcelodose 600 microfilling system.

ics (4, 5). Processing means exist to facilitate favorable, effective bulk density under specific dynamics (6, 7). Two options were evaluated for modifying the physical characteristics of the drug substance before the filling process to increase the allowable fill weight in capsules:

- roller compaction of the drug substance without the addition of excipients, followed by milling
- milling the drug substance alone.

Therefore, to enable 100 mg of Compound X to be filled in a size 00 capsule shell or smaller, roller compaction followed by milling was used to densify the drug substance (8–10). Milling of the drug substance alone also was attempted to determine the effect of particle-size reduction (narrower distribution and smaller aspect ratio) on actual fill capacity (11).

Microfilling system design

The Xcelodose operating principle is as follows: Material is dispensed through a mesh at the base of a dispense head (see Figure 1). Powder is released by the tapping action of a solenoid on the dispense arm cradling the dispense head. Parameters defining the tapping process, including tapping frequency and desired dispense rate, as well as the dispense head itself, including mesh hole size and number of holes, are chosen by the operator and depend on the physical characteristics of the material and desired dose. The supervisory PC accurately controls capsule weights by continuously monitoring the weight being dispensed in real-time and adjusting as necessary. As the weight approaches the target value, the rate of powder delivery is reduced and then stopped.

A capsule feeder supplies the system, and each capsule is oriented and opened automatically. The machine then dispenses the requisite quantity of powder into the body of each capsule. After the capsule-fill amount is weighed for acceptance or rejection, which is determined by control limits specified by the operator, the cap and body sections of each capsule are rejoined, and the closed length is measured for acceptance. The capsules are then segregated into the requisite "good" or "bad" hoppers (see Figure 2).

Methods

Roller compaction and milling. Roller compaction of Compound X was performed using the Freund TF Mini Roll compactor (Vector Corp., Marion, IA) fitted with smooth rolls. Compactor conditions were set as follows: feeder 40 rpm, roller 1 rpm, and pressure 100 kg/cm^2. Milling was conducted using a Comil 193AS cone mill (Quadro, Millburn, NJ) fitted with a square impeller (no. 2B-1609-002) and a 0.001-in. spacer. The roll-compacted material was milled through a 0.991-mm round-hole screen (no. 2B039R03125173), and the milled-only drug substance was passed through a 0.152-mm round-hole screen (screen no. 2B006R005). An impeller speed of 2630 rpm was used for both experiments.

Table I: Quali-V HPMC (Shionogi) and Coni-Snap (Capsugel) hard gelatin capsule volumes.

Casule size	Shionogi Quali-V HPMC capsule volume (mL)*	Capsugel Coni-Snap hard gelatin capsule volume (mL)**
00	0.93	0.91
0	0.68	0.68
1	0.49	0.50
2	0.37	0.37
3	0.28	0.30

*From Reference 12.
**From Reference 13.

Physical characterization. Microscopy. Samples were prepared for examination by gently dispersing a small amount of drug substance into heptane with 0.1% Span 80 on a glass well slide. Preparations were observed at a magnification of 40–400× using Eclipse ME600 and Optiphot light microscopes (Nikon, Florham Park, NJ),

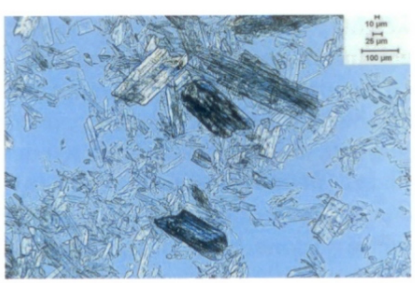

Figure 3: Microscopy of unprocessed drug substance.

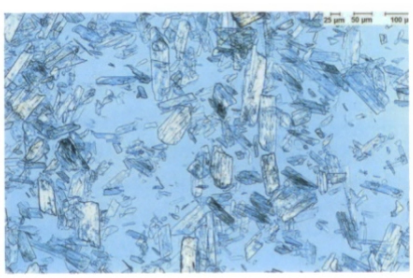

Figure 4: Microscopy of milled-only drug substance.

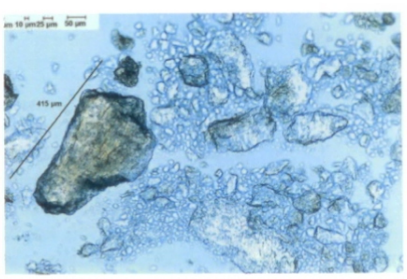

Figure 5: Microscopy of roll-compacted and milled drug substance.

Table II: Physical characteristics of unprocessed, roll-compacted and milled, and milled only Compound X.

Processing	Bulk density (g/cm^3)	Tap density (g/cm^3)	Particle size range (μm)	D50 (μm)	D90 (μm)	D[4,3]* (μm)	Surface area (m^2/g)
None	0.22	0.45	2–700	44	208	84	1.6
Roll compacted and milled	0.41	0.66	2–664	200	536	249	1.3
Milled only	0.21	0.46	2–276	32	98	45	1.7

*D[4,3] is the volume mean diameter.

Table III: Fill weight assessment results.

Drug substance preprocessing type	Capsule #1 allowed fill weight (mg)	Capsule #2 allowed fill weight (mg)	Capsule #3 allowed fill weight (mg)	Average allowable fill weight of three capsules (mg)	%RSD of three capsule fill weights	Filled density (g/mL)
Unprocessed	31.14	29.98	31.26	30.79	1.874	0.083
Roll-compacted and milled	90.43	86.83	80.46	85.91	4.799	0.232
Milled only	29.94	29.89	32.25	30.69	3.587	0.083

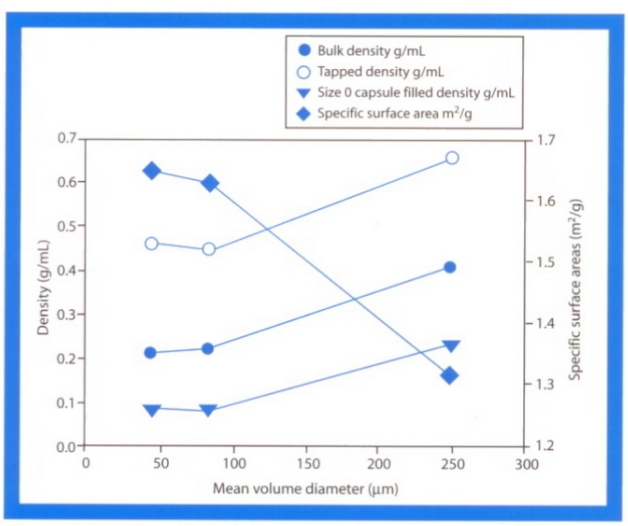

Figure 6: Relationship between physical properties and filled densities of roll-compacted and milled, milled-only, and unprocessed drug substance. Each preprocessing type is represented by its mean volume diameter.

in reflected light and transmitted light, with and without polarizers, quarter-wave and full-wave interference filters. Photomicrographs were collected using a SPOT model 3.2.0 color digital camera with SPOT for Windows software version 3.5.6 and Image-Pro Plus version 4.5.1.27 for Windows software (Diagnostic Instruments, Sterling Heights, MI).

Particle size. The particle size distributions of the samples were measured using a light diffraction particle sizer (Mastersizer model APA 2000, Malvern Instruments, Worcestershire, UK) with a small-volume liquid recirculating disperser (Malvern Hydro 2000SM). Drug substance was dispersed in heptane with 0.1% Span 80 for particle size measurement.

Specific surface area. Surface area measurements were made using a surface area analyzer (Gemini 2370, Micromeritics, Norcross, GA). Samples were outgassed at 25° C under a nitrogen purge for 2 h. Surface areas were calculated using the Brunauer-Emmett-Teller theory from nitrogen adsorption measurements over a relative pressure range of 0.07–0.25.

Bulk and tapped density. Bulk and tapped density were measured using a 100-mL graduated cylinder and a tap density tester set at 2000 taps (Vanderkamp, Vector Corp.).

Fill weight evaluation and capsule filling. The allowable fill weights of the unprocessed, roll compacted and milled, and milled-only drug substances in a given capsule size were determined by filling each material into size 2 HPMC capsules (Quali-V, Qualicaps, Whitsett, NC) on the Xcelodose system. Manual mode was used to fill the capsules. The parameters of pulse width and frequency were set, and each capsule was filled using a series of bursts of taps. The duration of each burst (*i.e.,* the number of taps) was specified. Pulse width is directly proportional to tapping force, and 6 ms is the maximum pulse width achievable on the Xcelodose system.

As the drug substance approached the top of the capsule body, the bursts were set for shorter durations to not exceed the allowable capsule fill weight. A dispense head comprising 19, 1.5-mm diameter holes was chosen for the test. The tapping frequency was varied between 5 and 25 Hz, and the pulse width was set to 6 ms. For each material, three separate capsules were filled, and the maximum allowable fill weight was determined visually. The results of the three capsule fills were averaged and reported as the average allowable fill weight. Once the average allowable fill weights were determined, the filled densities for each material were calculated using the following equation:

$$\text{Filled density (g/mL)} = \text{allowable fill weight (g)} \div \text{capsule volume (mL)}$$

Capsule volumes of sizes 00, 0, 1, 2, and 3 Quali-V HPMC and Coni-Snap hard-gelatin capsules are listed in Table I. Rearranging the equation shows the allowable fill weight as a function of filled density and capsule volume, thereby enabling the determination of the allowable fill weight of each material in various other capsule sizes and ignoring capsule wall effects.

On the basis of the fill weight study described previously,

Table IV: Xcelodose parameters for size 0 capsules with 100-mg fill of roll-compacted and milled Compound X.

Step change for auto-adjusting pulse width (ms)	0.01
Target weight offset (mg)	0
Amount of slow tapping (mg)	10
Acceptable weight change for stability (mg)	0.006
Number of balance readings to take when checking for stability	13
Control limit as percentage of target weight	5
Target dispense rate at high speed (mg/s)	100
Target dispense rate at low speed (mg/s)	25
Tap frequency (Hz)	25
Required dose (mg)	100
Suggested dispense head	RK
Drug name	Roll-compacted and milled Compound X
Dispense timeout	20
Dispense fingers used (yes–no)?	no
Dispense head clamped (yes–no)?	yes

we determined that 100 mg of roll-compacted and milled Compound X could fit into a size 0 capsule. This result was confirmed on the Xcelodose system using automatic-mode and size 0 Coni-Snap gelatin capsules.

Results and discussion

Physical characterization. Microscopy and laser diffraction studies indicated that the primary particle morphologies for the drug substance, including the unprocessed, roll-compacted and milled, and milled-only material, were lathe and agglomerates. A particle-size range of 2–700 μm and 2–664 μm in length were observed for the unprocessed and roll-compacted and milled drug substance, respectively. The milled-only drug substance had a smaller particle size range of 2–276 μm in length (see Figures 3–5).

Table V: Run results for size 0 capsules with 100-mg fill of roll-compacted and milled Compound X.

Average weight of acceptable capsules (mg)	100.205
Relative standard deviation (RSD) of acceptable capsules (standard deviation/target fill weight)	0.86%
Number of capsules within weight specification	54
Number of capsules outside weight specification	0
Yield	100%
Mean dispense time of acceptable capsules (s)	11.4
Overall Throughput (capsules/h)	268

Laser diffraction studies indicated that the volume mean diameters were 84, 249, and 45 μm for the unprocessed, roll-compacted and milled, and milled-only drug substance, respectively. A two-fold increase in bulk density of the roll-compacted and milled drug substance (0.41 g/mL) was observed over the unprocessed drug substance (0.22 g/mL). No changes in the bulk or tapped density were observed for the milled-only drug substance (0.21 g/mL). A minor loss of surface area occurred after roller compaction as expected based on the increase in drug substance particle size. The specific surface areas of the unprocessed, roll-compacted and milled, and milled-only drug substance were 1.6, 1.3, and 1.7 m^2/g, respectively (see Table II).

Fill weight assessment. The allowable fill weights for the unprocessed, roll-compacted and milled, and milled-only drug substances in the size 2 Quali-V capsules were determined on the Xcelodose 600 microfilling system, and the filled densities were calculated. For each material, the total number of taps required and the allowable fill weights varied between each of the three capsule fills for each type of preprocessing. The results, including the percent RSD of the three capsule fills are reported in Table III.

Table VI: Xcelodose parameters for size 0 capsules with 150-mg fill of roll-compacted and milled Compound X.

Step change for auto-adjusting pulse width (ms)	0.01
Target weight offset (mg)	0
Amount of slow tapping (mg)	10
Acceptable weight change for stability (mg)	0.006
Number.of balance readings to take when checking for stability	13
Control limit as percentage of target weight	5
Target dispense rate at high speed (mg/s)	100
Target dispense rate at low speed (mg/s)	25
Tap frequency (Hz)	25
Required dose (mg)	150
Suggested dispense head	RK
Drug name	Roll-compacted and milled Compound X
Dispense timeout	20
Dispense fingers used (yes–no)?	no
Dispense head clamped (yes–no)?	yes

The roll-compacted and milled material allowed for nearly a threefold increase in filled density over the unprocessed and milled-only drug substances (see Table III). The filled density of the milled-only drug substance was similar to that of the unprocessed drug substance.

Using the bulk density of the unprocessed drug substance, the original allowable fill in size 0 capsules was calculated to be 150 mg. The filled density of 0.083 g/mL indicated an actual allowable fill weight of only 56.4 mg.

A correlation between the filled densities of the roll compacted and milled,

Table VII: Run results for size 0 capsules with 150-mg fill of roll-compacted and milled Compound X.

Average weight of acceptable capsules (mg)	150.064
Relative standard deviation (RSD) of acceptable capsules (standard deviation/ target fill weight)	0.50%
Number of capsules within weight specification	36
Number of capsules outside weight specification	4
Yield	90%
Mean dispense time of acceptable capsules (s)	15.3
Overall throughput (capsules/h)	249

milled-only, and unprocessed drug substances to their bulk and tapped densities and specific surface areas is shown in Figure 6.

Capsule-filling. Based on a filled density of 0.232 g/mL of the roll-compacted and milled material, the allowable fill weight in size 0 Coni-Snap hard gelatin capsules is 158 mg. As originally desired, size 0 capsules containing a 100-mg dose of the roll-compacted and milled drug substance were successfully manufactured in automatic mode on the Xcelodose system. We confirmed that 100 mg of roll-compacted and milled drug substance easily fit into size 0 capsules. The capsule body was approximately three-fourths full after powder dispensation.

Tables IV and V summarize the dispense head and dosing parameters used and the run results for the 100-mg dose of roll-compacted and milled material. The method file parameters were based on manufacturer-recommended default settings. The yield was 100% and the RSD was acceptable (see Table V). The method was not optimized to improve capsule throughput, however.

According to operator judgment, the actual maximum allowable fill weight of roll-compacted and milled Compound X in size 0 capsules was 150 mg. This assessment was based on the need to leave a small amount of headspace in the capsule body to prevent spillage of the powder before capsule closure. Size 0 gelatin capsules were filled with 150 mg of roll-compacted and milled Compound X. The dispense head and dosing parameters as well as the run results for the 150-mg dose are summarized in Tables VI and VII. The dispense head and dosing parameters were not optimized for yield or throughput.

Although the size 2 capsule results did not demonstrate a fill-weight improvement in the milled-only drug substance over the unprocessed drug substance, the maximum amount of milled-only drug substance in size 0 capsules was evaluated. The maximum recommended fill amount was 69.4 mg.

Summary and conclusion

High-dose capsule filling using the Xcelodose system poses challenges because of the inability to use material bulk density to accurately predict allowable capsule fill weights. The allowable fill weight in a particular capsule size depends on the material physical characteristics and is limited by the Xcelodose filling mechanism.

Roller compaction followed by milling of Compound X resulted in nearly a threefold increase in the allowable fill weight on the Xcelodose system. A twofold increase in the bulk density of the roll-compacted and milled drug substance was observed over the unprocessed drug substance, but no changes in the bulk and tapped densities were observed for the milled-only drug substance. Milling alone reduced the particle size range compared with the unprocessed and roll-compacted and milled drug substances. These results demonstrate roller compaction followed by milling to be a viable preprocessing technique for high-dose capsule filling using the Xcelodose system. Any effects roller compaction may have on drug substance dissolution may need to be evaluated before using this method for manufacturing.

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