Effect of Powder Characteristics and Operating Conditions on Filling 1mg Weights Using an Xcelodose®* 600 Micro-Dosing System

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Objective

To evaluate the effect of powder characteristics, dispensing heads, and tap frequencies on filling different excipients at a target fill weight of 1 mg using an Xcelodose® 600 powder micro-dosing system.

Background

The Xcelodose® 600 powder micro-dosing system delivers powder directly into a hard gelatin capsule by controlled tapping of a dispensing head. It is typically used to place unformulated active ingredients directly into capsules to accelerate "first in human" studies. This system is capable of reproducibly dosing weights as small as 100 µg when using suitable materials and optimized filling parameters.

The ability to control the flow of materials is influenced by the physical characteristics of the powders and the configuration of the Xcelodose® operating conditions. In general, freely flowing materials filled at low weights (0.1mg-50mg) require a dispensing head that restricts the flow. Conversely, a poorly flowing material at higher weights (+100mg) requires a less restrictive dispensing head. The optimum dispensing head is usually determined either by trial and error, or by historical data of similar materials and fill weights.

To better understand the influence of the various conditions on fill weight variation, two excipients were selected for evaluation, hypromellose and pregelatinized starch. These excipients were chosen for their difference in flow properties while maintaining a similar particle size distribution. Each excipient was filled at a target weight of 1.0 mg using four different dispensing heads and varying tapping frequencies. The dispensing head was kept continually full of excipient during the filling process. The weight and time to achieve the target weight were monitored for each capsule produced.

It should be noted that under normal operating conditions, capsule fill weights which exceed the user specified tolerance are rejected and their fill weights excluded from the standard deviation calculation. For the purposes of this study, all capsule weights were included with the exception of failures due to capsule opening, closing, and other non-filling related occurrences.

Methods

Figure 1. Xcelodose® 600 powder micro-dosing system

The Xcelodose® 600 powder micro-dosing system is supplied by Capsugel in Greenwood, SC (Figure 1). A wide range of dispensing heads is available to accommodate a variety of fill materials. Dispensing heads used in this evaluation are designated as BZ, DZ, FP, and DL (Figures 2, 3, 4, 5, respectively).

Figure 2. Dispensing Head BZ

Figure 3. Dispensing Head DZ

Methods (cont.)

Figure 4. Dispensing Head FP

Figure 5. Dispensing Head DL

Dispensing head BZ has 163-0.2 mm holes, dispensing head DZ has 195-0.3 mm holes, dispensing head FP has 41-0.4 mm holes, and dispensing head DL has 22-0.3 mm holes.

In addition to the hole size and number, the configuration of the screen relative to the dispensing head is variable. As shown in figure 5, the screen is located at the bottom of the conical dispensing head and is 3 mm in diameter. The remaining dispensing heads have the screen located higher and provide a larger screen diameter of 9.5 mm. This difference impacts the extent of material compaction, which can cause poor flow of the material during dispensing.

Other parameters such as tap frequency and the fraction of the target weight at which the Xcelodose® changes from "fast" filling mode to "slow" also influence the variability in weight. For the purposes of this study, the frequency was evaluated; however, the change from "fast" to "slow" mode was kept constant at 0.7 mg of 1.0 mg.

The materials chosen for the evaluation are as follows (Table 1):

Table 1. Materials Evaluated

Material	Grade	Manufacturer
Hypromellose	Methocel E5 Premium LV USP/EP	The Dow Chemical Company, Plaquemine, LA
Pregelatinized Starch	Starch 1500	Colorcon, West Point, PA

Both materials were characterized using the following tests (Table 2):

Table 2. Characterization Tests

Test	Equipment	Manufacturer
Bulk and Tap Density	Tap Density Meter Model 10700	Vankel
Particle Size	LS 13 320 Particle Size Analyzer	Beckman Coulter
Flowability	Flowdex Model 21-101-050	Hanson Research

Bulk densities were measured by pouring a known weight of powder slowly into a graduated cylinder and calculating the mass per unit volume. Tap densities were measured by tapping the graduated cylinder until a stable volume was achieved and calculating the mass per unit volume. The compressibility index was calculated by dividing the difference between the tap and bulk densities by the tap density x 100. The results are presented in Table 3.

Table 3. Density Values

Material	Bulk Density (g/mL)	Tap Density (g/mL)	Compressibility Index
Hypromellose	0.419	0.594	29.5%
Pregelatinized Starch	0.577	0.813	29.0%

Particle sizes of the materials were generated using a dry powder feeder system on the Beckman Coulter light scattering analyzer. The optical model used was the Fraunhofer and the results are shown in table 4 and figures 6 and 7.

Methods (cont.)

Table 4. Particle Size Values for Hypromellose and Pregelatinized Starch

Material	d_{10}	d_{50}	d_{90}
Hypromellose	30.88 µm	82.98 µm	170.3 µm
Pregelatinized Starch	16.79 µm	82.19 µm	159.9 µm

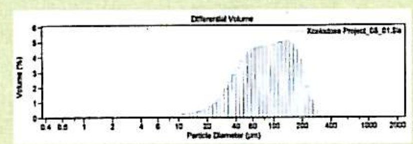

Figure 6. Particle Size Distribution of Hypromellose

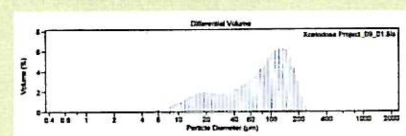

Figure 7. Particle Size Distribution of Pregelatinized Starch

Flowability was measured by first determining the smallest orifice of the Flowdex device through which both materials would pass. Using a balance, the weight gain over time during material flow was measured. The slope of the line generated during the flow was used to determine the flow of the material per unit time. For hypromellose, the flow rate was found to be 13.8 g/second. For pregelatinized starch, the flow rate was found to be 23.6 g/second. The flow tests were performed in triplicate using a constant volume of material in each trial.

Results

Hypromellose was originally evaluated using all 4 dispensing heads; however, the small screen opening and screen placement in dispensing head DL resulted in excessive material bridging and was ultimately removed from the evaluation. A summary of the data collected is shown in Table 5.

Table 5. Summary of Hypromellose Trials

Dispensing Head	Tap Frequency (Hz)	Average Fill Weight (mg)	Fill Weight RSD (%)	Average Time to Fill (sec)
BZ	10	0.986	1.198	11.855
BZ	15	0.977	1.990	10.225
BZ	20	0.989	1.404	11.518
DZ	10	1.037	3.939	5.822
DZ	15	0.997	3.915	6.259
DZ	20	1.026	4.621	6.061
FP	10	1.079	5.771	5.590
FP	15	1.017	4.451	5.562
FP	20	1.009	3.991	5.560

Of the three dispensing heads evaluated, the BZ head produced the lowest average relative standard deviation (RSD) of 1.53%. This average was based on the individual RSDs of the 10 Hz, 15 Hz, and 20 Hz samples. The individual RSDs ranged from 1.20% to 1.99% and did not follow a trend related to the tap frequency. The fill weights are presented in Figure 8.

Although the fill weights were consistent, the fill times increased nominally throughout the process suggesting some compaction or bridging of the material inside the dispensing head. During the beginning of the filling process, the fill times were between 8 and 10 seconds. At the end of the run, the fill times increased to between 12 and 16 seconds (Figure 9).

Results (cont.)

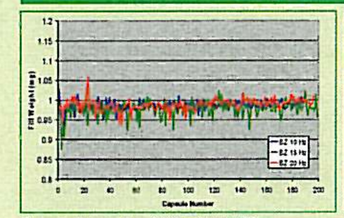

Figure 8. Hypromellose Fill Weight using BZ

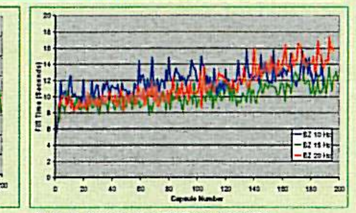

Figure 9. Hypromellose Fill Times using BZ

Using the DZ dispensing head, the average RSD for the 3 frequencies increased to 4.16%. The individual RSDs ranged from 3.92% to 4.62% and showed no trend with the tap frequency (Figure 10).

The fill times were consistent throughout the process indicating little to no compaction/ bridging occurred. The fill times also decreased when compared to dispensing head BZ (Figure 11).

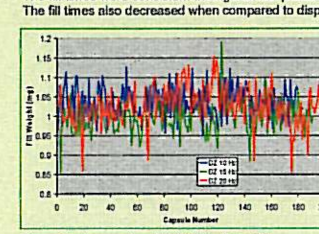

Figure 10. Hypromellose Fill Weights Using DZ

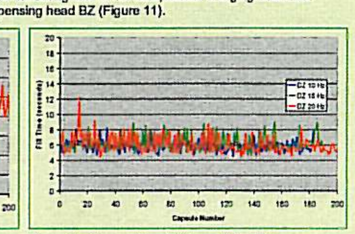

Figure 11. Hypromellose Fill Times Using DZ

Using the FP dispensing head, the average RSD for the 3 frequencies increased to 4.74%. The individual RSDs ranged from 3.99% to 5.77% and showed a trend of decreasing RSDs with increasing tap frequency (Figure 12).

The fill times were very consistent throughout the process indicating little to no compaction/ bridging occurred. The fill times also decreased in comparison to the times observed when using dispensing heads BZ and DZ (Figure 13).

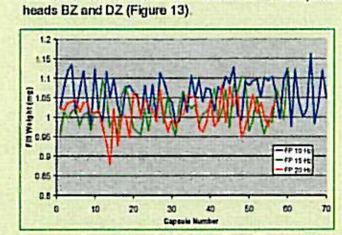

Figure 12. Hypromellose Fill Weights Using FP

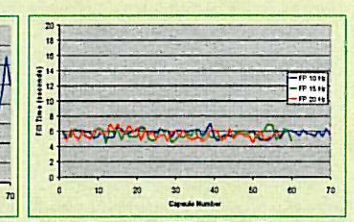

Figure 13. Hypromellose Fill Times Using FP

Pregelatinized starch was evaluated using only 2 dispensing heads since those with the larger open areas allowed too much material flow to control the fill weight. A summary of the data collected is shown in Table 6.

Table 6. Summary of Pregelatinized Starch Trials

Dispensing Head	Tap Frequency (Hz)	Average Fill Weight (mg)	Fill Weight RSD (%)	Average Time to Fill (sec)
BZ	10	0.986	2.925	13.159
BZ	15	0.982	3.178	7.082
BZ	20	0.988	2.739	7.768
DL	10	0.974	2.009	9.153
DL	15	0.981	3.056	7.018
DL	20	0.971	2.785	6.725

Results (cont.)

Filling using dispensing head BZ produced an average RSD of 2.95%. The individual RSDs ranged from 2.74% to 3.18%. There was no correlation between the tap frequency and the fill weight variation (Figure 14).

The fill times using dispensing head BZ varied considerably between the different tap frequencies. As shown in Figure 15, at 10 Hz the fill time started at approximately 6 seconds and increased to over 40 seconds at the end of the filling process. This disparity in fill time is attributed to compaction of the pregelatinized starch in the dispensing head. This was confirmed during emptying of the dispensing head after processing as a spatula was required to break apart the cake of material that had formed. The 15 Hz and 20 Hz filling trials did not exhibit any problems due to compaction inside the dispensing head (Figure 15).

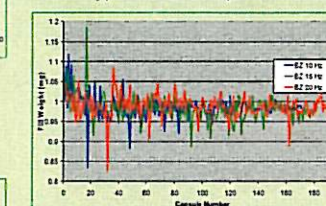

Figure 14. Pregelatinized Starch Fill Weights using BZ

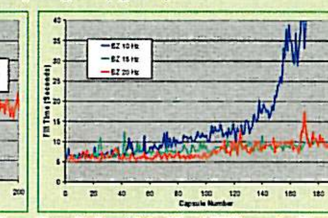

Figure 15. Pregelatinized Starch Fill Times using BZ

Filling using dispensing head DL produced an average fill RSD of 2.62%. The individual RSDs ranged from 2.01% to 3.06%. There was no correlation between the tap frequency and the fill weight variation (Figure 16).

The fill times using dispensing head DL increased slightly over time but no trend was observed with respect to tap frequency. (Figure 17).

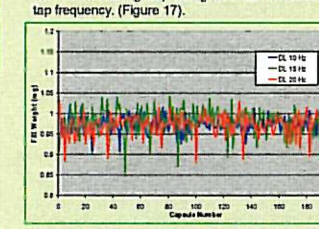

Figure 16. Pregelatinized Starch Fill Weights using DL

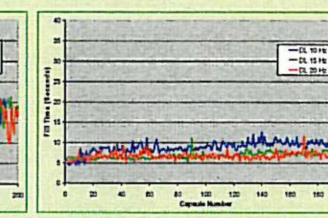

Figure 17. Pregelatinzed Starch Fill Times using DL

Conclusions

Optimal conditions for achieving a fill weight of 1 mg for poorly flowing materials such as hypromellose are larger surface area screens with small openings (such as BZ). The tap frequency did not have a noticeable effect on the accuracy of the fill weight or stability of fill time.

Optimal conditions for achieving a fill weight of 1.0 mg for more freely flowing materials such as pregelatinzed starch are smaller diameter screens with larger openings (such as DL) using moderate tap frequencies (15-20 Hz). A tap frequency of 10 Hz using a small screen opening resulted in compaction/ bridging of the material and increased filling times as the process progressed.

A relationship is seen between filling time and the precision of capsules weights, particularly with poorly flowing hypromellose. Use of smaller dispensing heads (with lower flow rates) results in longer fill times but lower RSDs of capsule weights. This correlation is less pronounced in the filling of pregelatinized starch.

In both cases, low fill weights combined with narrow acceptance criteria will necessitate smaller surface area screens and smaller screen openings to achieve low reject rates. This translates into longer filling times. If the acceptance criteria for the fill weights are widened or higher reject rates can be tolerated, larger screen areas and openings can be used to accelerate the filling process.

References

•"Xcelodose" product brochure, accessed Oct. 4, 2007, from http://www.capsugel.com/pdf/XcelodoseBrochure.pdf.
•General Chapter <1174> Powder Flow, *United States Pharmacopeia*, Vol. 30, United States Pharmacopeia, Rockville, 2007.
•J. K. Prescott and R. A. Barnum. On Powder Flowability. *Pharmaceutical Technology* 24: 60-84 (2000).
•R. L. Carr. Classifying Flow Properties of Solids. *Chem Eng* 72: 69-72 (1965).