Investigation of Various Factors Affecting Encapsulation on the In-Cap Automatic Capsule-Filling Machine

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Renuka Nair,[1] Murti Vemuri,[1] Praful Agrawala,[1] and Soo-il Kim[1]

[1]Sanofi-Aventis Pharmaceuticals, Bridgewater, NJ 08807.

ABSTRACT

The purpose of this study was to determine the factors that influence fill weight and weight variability of capsules produced on the In-Cap and to assess any differences in terms of capsule defects between gelatin and HPMC (Quali-V) shells. The In-Cap is an automatic tamping type capsule-filling machine and the low output of ~3000 capsules/hour makes it ideal for early formulation development and phase I/IIa clinical supplies manufacture. Four commonly used excipients (Avicel PH101, Avicel PH302, A-Tab, and Prosolv HD90) and a poorly flowing drug blend were encapsulated at various pin settings and powder bed heights. The average fill weight and coefficient of weight variation were determined. The percentage of defective capsules formed during encapsulation was calculated. Results of the study showed that pin setting was critical for controlling the fill weight and the weight variation. The order of pin setting with pin 1 (closer to the powder chute) set to a relatively higher position and pin 4 (before ejection) set to a lower position was found to give higher fill weights with relatively lower weight variability. The powder bed height influenced the fill weight for poorly flowing powders. The capsule machine speed did not appear to significantly influence the fill weight. The fill weight and weight variation were found to depend on the flow property of the material. A large percentage of defective capsules was obtained using HPMC shell size #00. Some of the commonly observed defects included split caps and improperly closed filled capsules. In general, appropriate selection of pin settings and bed height can reduce the weight variability seen, especially with poorly flowing high-dose formulations.

KEYWORDS: In-Cap, capsules, HPMC capsules, capsule-filling equipment, flow

INTRODUCTION

Capsule dosage forms are often preferred by the pharmaceutical industry for phase I/IIa clinical study due to several factors. The goal during early-stage development is to develop a simple and stable exploratory formulation that fulfills the clinical discovery goals to evaluate safety of the compound and proof-of-concept in the intended therapy. Stable small-scale capsule formulations can be simpler and quicker to develop and require less active pharmaceutical ingredient (API) compared with tablets. The amount of API available for early formulation development is usually very limited. In addition, aggressive timelines associated with phase I studies often favor the use of capsule dosage form.

The clinical supply requirements for phase I studies can range from a small batch size of a few hundred capsules to a few thousand depending on the first-in-human dose in single-dose safety studies, multiple-dose study, clinical protocols, and the drug product stability protocol. Several options for encapsulating API or formulations in hard shell capsules are available. The type of capsule-filling machines may vary from manual filler to a semiautomatic Type 8 filling machine and fully automatic machines like Bosch GKF models (Robert Bosch, Waiblingen, Germany).

With a manual filling machine, powder is spread over a tray with several holes containing the open capsule bodies. The capsules are filled by spreading the powder over the bodies with a scraper and the fill weight increased by tamping the powder manually into the capsule body with a set of tamping pins. The filled capsules are then weight sorted to obtain capsules within the desired weight limits. Thus, the manual filling process can be time consuming and the filling process of scraping the powder and tamping needs to be optimized prior to clinical supply manufacture. In comparison, the high filling speed associated with an automatic filling machine may require a good flowing formulation for acceptable weight variability. In addition, output of an automatic capsule-filling machine necessitates a larger blend size that may be difficult for early formulation development and a phase I/IIa clinical supply manufacture. Currently, the In-Cap (Dott Bonapace and C, Milan, Italy) is one of the smallest automatic capsule-filling machines available in the US market. It combines the advantages of the low blend size requirement of manual machines with the efficiency of automatic machines.

The In-Cap is a tamping type capsule-filling machine with an average encapsulation rate of 3000 capsules/hour. The low output makes it ideal for early formulation development and phase I/IIa supplies compared with large-scale automatic filling machines with minimum output of 6000 capsules per hour. It can encapsulate capsule sizes 4 to 00. Four sets of

Corresponding Author: R. Nair, Sanofi-Aventis Pharmaceuticals, Mailstop - BWE103B, Rt. 202-206, Bridgewater, NJ 08807. Tel: 908-231-4574; E-mail: Renuka.Nair@Aventis.com.

cylindrical tamping pins compress powders into plugs within cavities in a dosing disk. The dosing disk is a stainless steel plate of defined height. At each of the 4 tamping stations, powder fills the die and is compressed into a plug or dense powder column by the downward motion of the pin. Additional powder is filled in the subsequent tamping station followed by additional tamping. Thus, powder in each die is tamped 4 times before it is ejected by an ejection pin into the capsule body. The operation of the In-Cap is similar to larger tamping machines that have been described in detail with schematics in the book *Pharmaceutical Capsules*.[1]

The primary objective of this study was to determine the influence of process parameters such as tamping pin height, height of powder bed in the dosing disk, capsule-filling speed, and the flow property of powders on the fill weight and weight variability of powder blend fill using the In-Cap. The study is not intended to be exhaustive since tamping machines have been discussed in detail in the literature.[1-4] Rather it is to provide general guidance for encapsulation on the In-Cap capsule-filling machine.

Capsules of vegetable origin, namely, hydroxypropylmethylcellulose (HPMC) capsules, are being considered as an alternative to gelatin capsule shells. The type of capsule shell can influence encapsulation on the In-Cap. The authors experienced several encapsulation issues with HPMC hard shell capsules, Quali-V (Shionogi Qualicaps, Whitsett, NC), on the In-Cap capsule-filling machine. The low moisture content (4%-6% wt/wt of HPMC vs 13%-16% wt/wt for gelatin) combined with low hygroscopicity make HPMC suitable for hygroscopic and deliquescent drugs that cannot be encapsulated in hard gelatin capsules. The decreased dissolution due to cross-linking of gelatin shell can also be a disadvantage although this has been shown to have no in vivo relevance.[5] Moreover, gelatin shells have a tendency to become either soft or brittle when exposed to relatively high and low humidity, respectively. In comparison with gelatin, the vegetable origin of HPMC capsules eliminates the need for Bovine spongiform encephalopathy/Transmission spongiform encephalopathy (BSE/TSE) certification. One of the important differences between the 2 shell types that can affect encapsulation is their mechanical properties. Podczeck[6] showed that the HPMC capsules are less resistant to indentation and have lower tensile strength and elastic modulus. The differences in mechanical properties can influence the capsule processing, especially the occurrence of capsule defects. There appears to be no information in the literature regarding the processing differences on the 2 shell types. Therefore, a secondary objective of this study was to examine the processability of HPMC capsules on the In-Cap.

Materials and Methods

Materials

Microcrystalline cellulose, Avicel PH101, lot number 1034, and Avicel PH302, lot number 2222, (FMC Biopolymer, Newark, DE), silicified microcrystalline cellulose, Prosolv HD90 (lot number k9b2h63, JRS Pharma LP, Patterson, NY), anhydrous calcium phosphate dibasic, A-Tab (lot number 2118, Rhodia, Cranbury, NJ), magnesium stearate (lot number A38392, Mallinckrodt Chemicals, Phillipsburgh, NJ), cornstarch, Purity 21 (lot number AK-4712, National Starch and Chemical Co, Bridgewater, NY), and empty hard gelatin shells, size #0, lot number 613738, and size #00, lot number 603934 (Capsugel, Greenwood, SC) were received as samples. Empty HPMC shells, size #0, lot number A31ZA6A3iZA6/1, and size #00, lot number A41YF1, were purchased from Shionogi Qualicaps, Whitsett, NC. Drug A was obtained from Aventis Pharmaceuticals, Bridgewater, NJ.

Methods

Capsule Filling

Four commonly used excipients, Avicel PH101, Avicel PH302, A-Tab, and Prosolv HD90, were selected. Each of these excipients was mixed with 0.5% magnesium stearate to prevent sticking to the tamping pins and the dosing disk. Blending was done in a twin shell V-blender for 3 minutes. A poorly flowing blend of a model drug A containing 50% Prosolv HD90 and 0.5% magnesium stearate was also encapsulated. The drug was a crystalline lath-shaped material with an average particle diameter of 10 μm. The drug blend was prepared by mixing the screened drug and Prosolv for 10 minutes in a twin shell V-blender followed by addition of magnesium stearate and mixing for an additional 3 minutes. All blends were encapsulated in size #0 and size #00 capsules. The empty capsule shells and blends were stored in tightly closed containers prior to encapsulation to protect them from moisture. The following factors were investigated for the influence on fill weight and weight variation: (1) tamping pin position, (2) powder bed height, (3) filling speed, (4) shell type—HPMC and gelatin. Approximately 200 capsules were made under each of the filling conditions. Fifty capsules were collected at various time intervals throughout the run and individually weighed on a calibrated analytical balance. All weights reported in this paper refer to the net fill weight of the contents alone obtained by correcting for the weight of an empty capsule shell. The capsules were visually inspected for any defects and their percentages recorded. The height of the dosing disks used for encapsulation was 20.5 mm and 23.0 mm for size #0 and #00, respectively.

Table 1. Cumulative Pin Setting and the Corresponding Individual Pin Setting in the Ascending and Descending Pin Setting Order in the In-Cap

	Individual Pin Settings							
	Ascending				Descending			
Cumulative Pin Setting	Pin #1	Pin #2	Pin #3	Pin #4	Pin #1	Pin #2	Pin #3	Pin #4
12.0	3	3	3	3	3	3	3	3
22.5	3	6	6	7.5	7.5	6	6	3
30.0	3	6	9	12	12	9	6	3
33.0	3	7.5	10.5	12	12	10.5	7.5	3
36.0	6	7.5	10.5	12	12	10.5	7.5	6

Density Determination

Bulk density was measured by a Scott volumeter (Paul N. Gardner Co., Inc., Pompano Beach, FL) according to the USP method <616>.[7] Tap density was obtained similar to the USP method using a dual autotap (Quantachrome Corporation, Boynton Beach, FL). An accurately weighed quantity of powder was placed in a 100-mL cylinder. The volume of the cylinder after 500 and 1300 taps was recorded. If the 2 volumes did not differ by more than 2%, the final volume after 1300 taps was used for tap density calculation. Alternatively, tapping was continued in increments of 500 taps until 2 successive taps did not result in volume variation greater than 2%. The densities were finally used to calculate Carr's compressibility index given by the following equation[8]:

$$CarrIndex = \left(\frac{TapDensity - BulkDensity}{TapDensity} \right) \times 100 \quad (1)$$

Flow Rate Index

Flow rate index was measured with the Johanson flow rate indicizer (Johanson Innovations, San Luis Obispo, CA). Flow rate index is defined as the maximum flow rate expected after deaeration of a powder in the bin.[9] A cylindrical cup of defined volume was evenly filled with powder. Care was taken to ensure that no lumps were present. The powder was subjected to a defined force using a piston for a preset time period. Air was introduced from the bottom of the cylinder, thus creating a vertical and upward air passage within the powder. The Johanson indicizer uses this air permeability or airflow resistance to calculate the flow rate index. All calculations are based on the default value of a 12-inch hopper outlet diameter and hopper angle of 20°. Relationship between a small flow rate index and increased tablet weight variability has been reported.[10]

Critical Orifice Diameter

The smallest orifice through which a powder can flow freely is referred as the critical orifice diameter. Critical orifice diameter was measured using a flowdex tester (Hansen Research Corp, Chatsworth, CA). Powder was filled in a stainless steel cylinder. The base of the cylinder was covered with a plate having a fixed diameter hole in the center. The hole was closed with a shutter during powder filling. After filling the cylinder with powder, the shutter was opened and powder allowed to flow through the hole. The base plate was replaced with different plates with various sizes of holes.

Results and Discussion

Influence of Pin Position on Fill Weight and Weight Variation

Five pin settings were chosen to obtain a general understanding of the pin position and fill weight. These settings encompass the range of tamping force that can be encountered on the In-Cap. The sum of these settings is expressed as the cumulative pin setting. Table 1 lists the individual pin settings for the various cumulative pin settings. For example, a setting of pin #1 – 3, pin #2 – 6, pin #3 – 9, pin #4 – 12 refers to the settings for each of the 4 pins with a cumulative pin setting of 30. The lower the cumulative pin setting the deeper is the pin penetration into the dosing disk and the higher is the tamping force. It should be cautioned that tamping pin settings might not always necessarily correlate with tamping force. The tamping pins have an overload spring mechanism and in the case of In-Cap the springs will deflect beyond a force of 295 N. In other words, the tamping pin will not move further into the dosing disk once a force of 295 N is encountered even if the pin setting is decreased. It is important to note that these individual pin settings are integer values and do not express distance in mm. The numbers are present to help the operator achieve reproducible pin penetration or position. The pin numbers and the corresponding pin position within the dosing disk may vary on other models of the In-Cap.

The vendor-recommended pin height adjustments include setting pin #1 to a relatively low position such that the pin position is #1 < #2 < #3 < #4 (ascending) to achieve the desired fill weight. However, differences in fill weight and weight variability were observed when this order was reversed with pin 1 set at a higher position, #1 > #2 > #3 > #4 (descending). All encapsulation studies were therefore done with cumula-

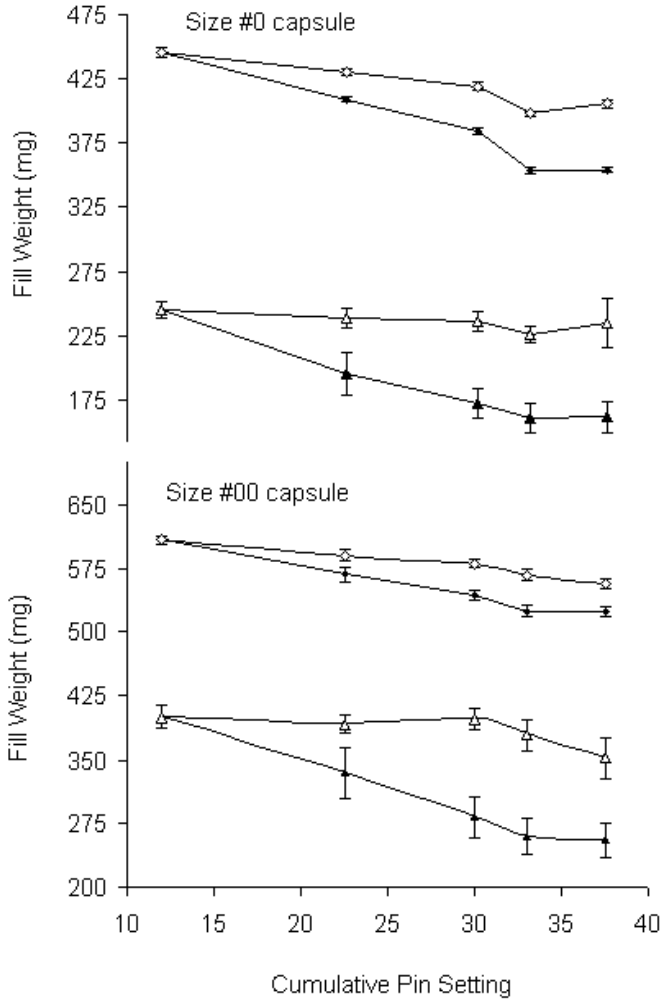

Figure 1. Influence of cumulative pin setting on the fill weight of Prosolv HD90 and drug blend (low powder bed height) in size #0 and size #00 capsules (◇ Prosolv HD90 - descending pin setting; ◆ Prosolv HD90 - ascending pin setting; △ drug blend - descending pin setting; ▲ drug blend - ascending pin setting).

tive setting achieved in 2 different orders. For example, setting 30 was achieved by encapsulating at 2 different settings of #1 – 3, #2 – 6, #3 – 9, #4 – 12 (ascending) and #1 – 12, #2 – 9, #3 – 6, #4 – 3 (descending). The pin settings of 7.5 and 10.5 indicate that the pin was set between the numbered pin setting of 6 and 9, and 9 and 12, respectively. The influence of pin setting was studied on a good flowing material like Prosolv HD90 and a poorly flowing drug blend.

Figure 1 shows the change in fill weight for drug blend and Prosolv HD90 in a size #0 and a size #00 capsule. As the cumulative pin setting decreases, fill weight increases for Prosolv HD90 and the drug blend in size #0 and #00 capsules. At a lower cumulative pin setting, more force is applied to the powder, subsequently resulting in a denser and smaller plug height or powder column. This configuration allows more powder to fill in the disk when it reaches the next tamping station. Thus, more and more powder is filled at each consecutive station resulting in an increase in fill weight. Similarly, at higher cumulative pin settings, less force is applied to the powder, resulting in a relatively loose and large plug height or powder column. This leads to less powder being filled at subsequent tamping stations with a relatively lower fill weight. Increase in fill weight with tamping force on an H & K GKF 330 machine (Bosch Packaging Machinery Division, Piscataway, NJ) has been reported by Shah et al.[11] Podczeck and Newton[12] observed an increase in fill weight with certain excipients on a GKF-400S (Robert Bosch, Waiblingen, Germany) machine while relatively small increases were found with others.

The order of individual pin settings also appears to influence the fill weight for both capsule sizes and powder blends. The fill weight is significantly higher in the descending setting when pin 1 is set to a higher setting compared with pin 4. The difference in fill weight at the 2 different settings is more pronounced with a poorly flowing blend compared with free-flowing Prosolv HD90. This can be explained in terms of the powder bed level in the dosing disk. The powder flows from the hopper to the dosing disk near pins 1 and 2 resulting in a heap of powder near these pins in the case of the poorly flowing drug blend. In contrast, the bed height near pins 3 and 4 was relatively low. Pins 1 and 2 were always in the powder bed at all the cumulative pin positions due to this high powder bed height while pins 3 and 4 were in the powder bed only at lower cumulative pin positions. Presence of all pins in the powder bed will lead to more powder being tamped at all tamping stations with higher fill weight compared with only a few pins submerged in the powder bed. The uneven powder bed height will be more pronounced for poorly flowing materials. It is not surprising that the order of pin settings have a large influence on the fill weight of a poorly flowing drug blend compared with Prosolv HD90. The position of pins 3 and 4 appear to be critical in controlling the fill weight and weight variability of powders on the In-Cap. Podczeck and Newton[12] noticed a similar influence of pins 1 and 2 on the fill weight during encapsulation of a poorly flowing powder, cornstarch, on a GKF-400S machine (Robert Bosch, Waiblingen, Germany). Analogous to pins 3 and 4 on the In-cap, pins 1 and 2 in their study were not immersed in the powder bed even at the highest pin depth.

Another factor to consider during capsule filling is the coefficient of weight variation (CV). The CVs for Prosolv HD90 and the drug blend are given in Figure 2 for both the capsule sizes. Prosolv HD90 formed a plug at all the cumulative pin settings with loose plugs at the highest setting. The plug formation combined with the good flow property of Prosolv HD90 resulted in a low CV of less than 1% at all cumulative pin settings in both capsule sizes and was unaffected by the setting. A different trend is observed for the poorly flowing drug blend. Plugs were not formed even at the maximum tamping pressure or the lowest cumulative pin setting. The CV value was the lowest at the lowest cumulative setting

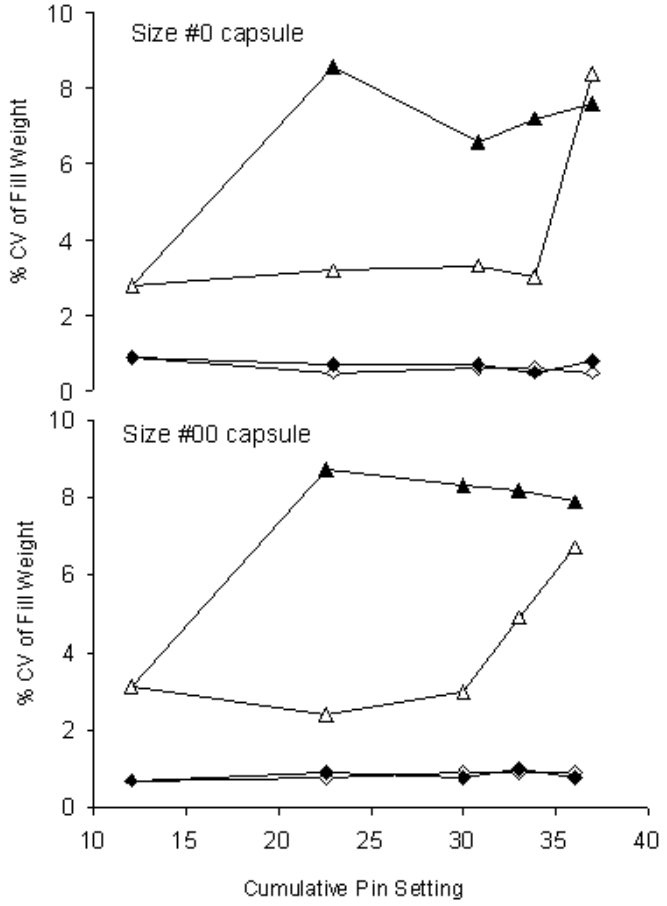

Figure 2. Influence of cumulative pin setting on the weight variation of Prosolv HD90 and drug blend in size #0 and size #00 capsules. (◇ Prosolv HD90 - descending pin setting; ◆ Prosolv HD90 - ascending pin setting; △ drug blend - descending pin setting; ▲ drug blend - ascending pin setting).

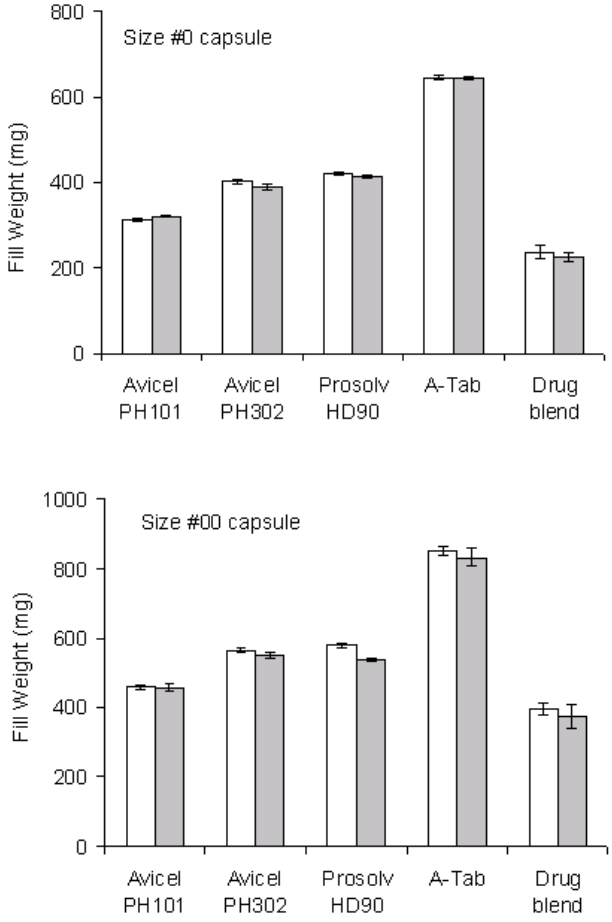

Figure 3. Influence of speed on the fill weight and weight variation of various excipients in size #0 and size #00 capsules (☐ low speed, ■ high speed).

probably due to a denser powder fill. The CV values decreased in the descending pin setting order due to the higher fill weight forming a more dense powder bed within the capsule. The CV of the drug blend ranged from 3% to 8% for both capsule sizes depending on the pin setting. In general, formulations with poor flow can be encapsulated on the In-Cap by selecting the appropriately sized capsule and low cumulative pin setting to form a plug or dense powder column. All subsequent studies were done with pin settings in the descending order.

Effect of Speed on Fill Weight and Weight Variation

The In-Cap can be operated at a low speed of 2400 capsules/hour and and a high speed of 3600 capsules/hour. The filling or machine speed could affect the fill weight by changing the time available for the material to flow or densify in the dosing disk. The fill weight for the lubricated excipients and the drug blend was obtained at a pin setting of #1 – 12, #2 – 9, #3 – 6, #4 – 3 at both speeds. All the excipients and drug blend showed similar fill weight and weight variation at both speeds for size #0 capsules (Figure 3). The fill weight for A-Tab, Prosolv HD90, and the drug blend decreased by a small extent at the high speed in size #00 capsules. This decrease in fill weight is accompanied by a relatively small increase in variability in the weights for A-Tab and the drug blend. This variability may be related to the poor flow of the drug blend and good flow and poor compactibility of A-Tab.

Influence of Powder Bed Height on Fill Weight

The powder bed height on the In-Cap can be adjusted by means of a blade attached to the powder chute. The blade was set to the minimum and maximum allowable height corresponding to a low and high powder bed height, respectively. Figure 4 shows the influence of powder bed height on the fill weight of Prosolv HD90 and drug blend in size #0 and size #00 capsules. Fill weight and weight variability of Prosolv HD90 remained similar at both the powder bed heights for size #0 capsules. Encapsulation of Prosolv HD90 in size #00 capsules at the high powder bed height resulted in damaged capsules and jamming of the turntable. This is due to overfilled capsules caused by a large quantity of powder within the dosing disk. Overfilling was evident by plugs pro-

Table 2. Flow Characterization of Lubricated Excipient Blends and a Drug Blend

Material	Bulk Density (g/mL)	Tap Density (g/mL)	Carr Index	Flow Rate Index (kg/s)	Critical Orifice Diameter (mm)
Avicel PH101	0.32	0.48	33	0.795	20
Avicel PH302	0.43	0.58	26	2.085	16
A-Tab	0.73	0.85	15	29.00	4
Prosolv HD90	0.49	0.61	19	3.015	9
Drug A	0.16	0.39	58	0.105	>34
Drug blend	0.31	0.63	51	0.195	24

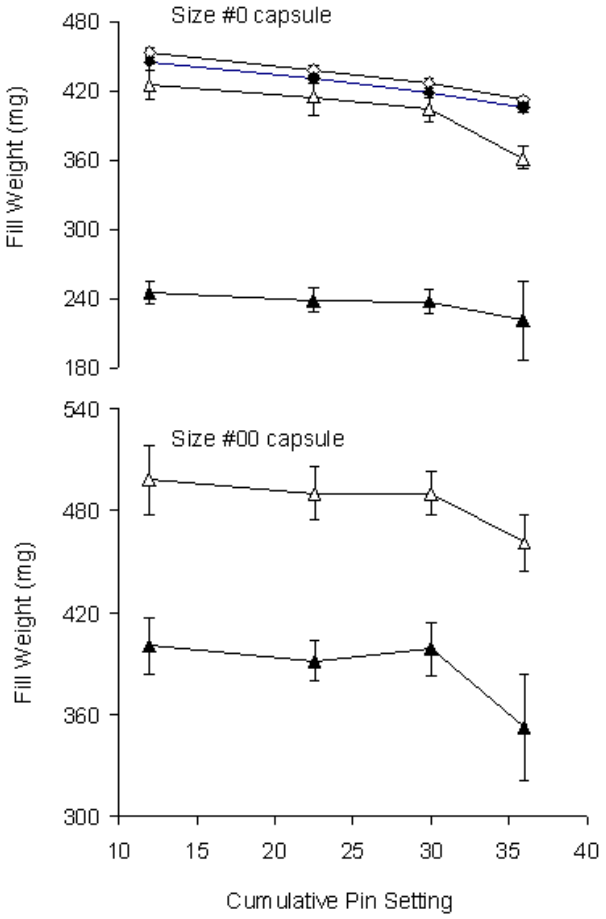

Figure 4. Influence of powder bed height on the fill weight of drug blend and Prosolv HD90 in size #0 and size #00 capsules (◇ Prosolv HD90 - high bed height; ◆ Prosolv HD90 - low bed height; △ drug blend - high bed height; ▲ drug blend - low bed height).

truding from the capsule body. The drug blend, however, could be filled in size #00 at the high powder bed height without any difficulty. The poorly flowing drug blend did not result in any overfilled capsules. The fill weight of the drug blend increased by more than 100 mg for both capsule sizes at the higher bed height. The powder bed level was uniform with the tamping pins in the powder bed for most of the settings for Prosolv HD90 at both the bed heights. In the case of the poorly flowing drug blend, the bed height was uneven with pins 3 and 4 not completely immersed in the powder at the low bed height. Fill weight variation due to uneven powder bed levels at the different tamping stations for poorly flowing blends was also observed by Kurihara and Ichikawa[13] while working on a GKF-1000 machine (Robert Bosch, Waiblingen, Germany).

Powder Characteristics and Capsule Filling

The relationship between capsule weight variation and powder flow has been the subject of numerous articles and contradictory observations have been reported in the literature. Whereas Felton et al[14] suggested that good powder flow might not be critical to achieving uniform fill weight on a tamping type machine, others have reported an increase in weight variation with poorly flowing powders.[15-16] Yet others suggested the need for an optimum flow property as a requirement for low capsule weight variation.[13,17] The flow of powders is influenced by various factors including interparticle forces, surface irregularities, moisture, particle size, density, and particle shape. The use of any single flow test cannot account for all these factors[18] and a combination of flow tests is recommended. Some of the commonly used tests include use of Carr index, flow rate, shear analysis, and critical orifice diameter.

Table 2 shows the results of flow testing of the lubricated excipients and drug blend used for this study. The flow properties are ranked as drug < drug blend < Avicel PH101 < Avicel PH302 < Prosolv HD90 < A-Tab based on all 3 tests. The Johanson flow rate indicizer appears more discriminating among the 3 tests. This is evident by the large difference in flow rate index between Avicel PH101 and PH302. All the excipients including Avicel PH101 with relatively poor flow in this study showed a low CV of less than 2% at both speeds at a cumulative pin position of 30 in both capsule sizes. The drug blend with poor flow showed a CV of 7.1% in size #00 and 3.3% in size #0 at the low speed. Although the tamping pressure encountered is too low to affect compaction, it is likely that the compactibility of the materials in addition to the flow property may influence the weight variability. This may explain the low CV values obtained for Avicel PH101 and high CV values for the drug blend despite their poor flow. Avicel PH101 formed good plugs compared with the loose powder filled capsules observed with the drug blend.

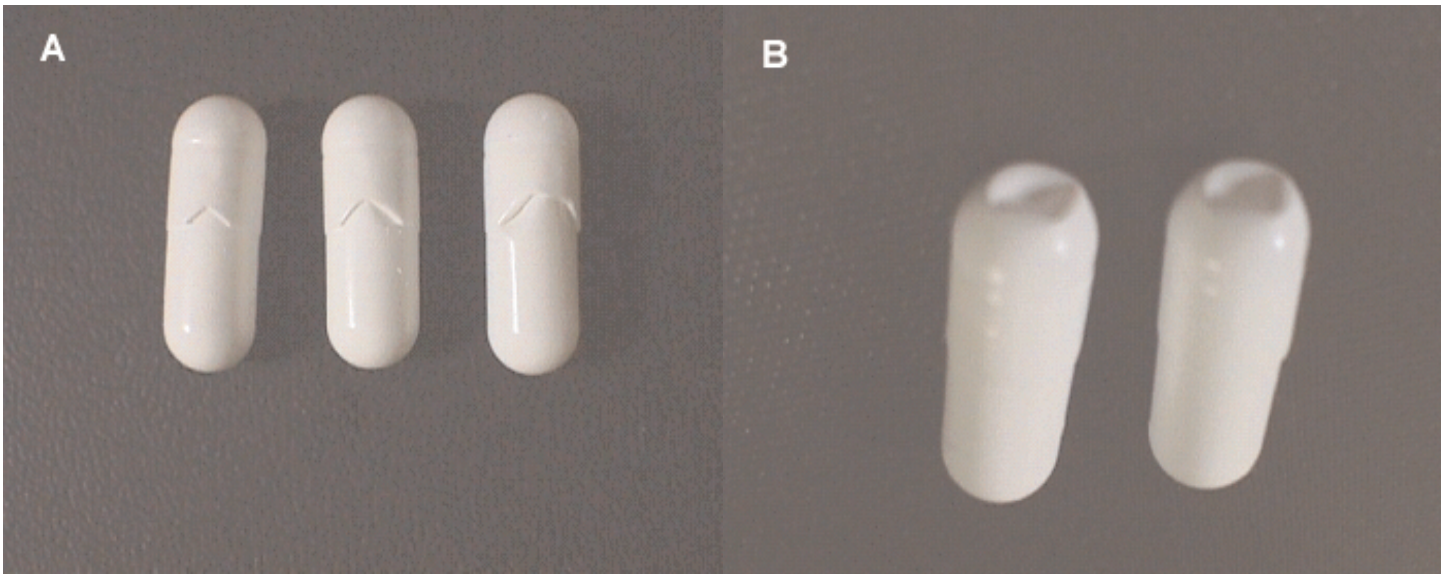

Figure 5. HPMC, Quali-V, size #00 capsule defects. (A) Split capsules; (B) Dimpled capsules.

Capsule Shell Type and Defects

Use of HPMC size #00 capsules resulted in a significant number of defective capsules. Some of the commonly observed defects with HPMC capsules were dimpled bodies, split caps, and improperly closed caps (Figure 5). More important, a large number of capsules failed to open during the rectification step. No such defects were observed for size #0 HPMC and gelatin capsules.

Dimpled capsules refer to the formation of a dented cap during the capsule-filling process. Dimpling occurred during the closing of the filled capsules. One of the main reasons for dimpled capsules is excessive closing pressure, which is controlled by the distance of the closing pin. In addition, overfilling of capsules could also result in dimple formation. Initial studies with HPMC capsules resulted in ~10% of dimpled capsules under acceptable closing pin distance (sufficient to completely close the capsule). Altering the fill weight resulted in higher or no change in the percentage of the dimpled capsules. In other words, formation of dimpled capsules occurred irrespective of the fill weight or the closing pin pressure. Interestingly, gelatin capsules did not show any dimple formation under identical filling conditions. The relatively low resistance of the HPMC shells to indentation load compared with gelatin[6] may be responsible for the observed dimpled capsules.

One of the methods to eliminate dimpling is to improve the mechanical property of the HPMC film. An alternate approach is to modify the closing pin such that the capsules can be effectively closed without exerting excessive pressure on the cap. The vendor-supplied closing pin for the In-Cap is a cylindrical metal pin with a flat base that comes in contact with the cap during closing. In order to reduce the force exerted on the pin, a small circular piece of rubber with diameter similar to the base of the pin and a thickness of ~1.5 mm was attached to the base of the pin. This eliminated the dimple formation since the rubber preferentially reversibly deforms under pressure leaving the HPMC capsule intact.

Split capsules continue to be one of the major problems with the HPMC #00 capsules. Split here refers to filled capsules with a portion of the cap edge missing and is different from telescoped capsules. In the case of telescoped capsules, either the cap or body will have a tear resulting in a portion of the body outside the cap or portion of cap inside the body. Percentage of split capsules observed in this study ranged between 1% and 15%. Split capsules occurred at all the pin settings. Their presence is a problem since they are classified as defective capsules and will fail the appearance test for drug product specifications. It is often very difficult to differentiate them from the nonchipped capsules and their removal can be time consuming. It is important to note that this defect seems to depend on the fill material. The defect is nonexistent or significantly low for fine cohesive powder blends such as the drug blend. This was further confirmed with another fine cohesive powder such as cornstarch. The reason remains unclear at this point.

A third defect that is observed with the HPMC #00 capsules is the presence of filled capsule bodies with missing caps. In addition, a significant number of empty capsule shells failed to open during the orientation process. This caused the bushings to become dirty and led to product waste and extra capsule polishing. The percentage of unclosed capsules ranged from 1% to 4% and the unopened capsules ranged from 4% to 15%.

CONCLUSION

General consideration for encapsulating on the In-Cap:

1. The tamping pins should be adjusted in descending order with pin #1 set at a relatively higher position

compared with pin #4. This will reduce the weight variation and increase the fill weight.

2. It is advisable to set the powder bed to the highest setting. This will ensure that the pins are immersed in the powder bed for most of the settings irrespective of the flow property.
3. The capsule size and pin settings should be selected such that the required powder can be filled as a plug. If plug formation is difficult to achieve, use the smallest capsule size and lowest pin setting possible to obtain a dense powder column.
4. It may be necessary to consider the loss due to defective capsules when using size #00 HPMC, Quali-V capsules.

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