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Research Article

The Manufacture of Low-Dose Oral Solid Dosage Form to Support Early Clinical Studies Using an Automated Micro-Filing System

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Abstract. Automated powder dispensing systems enable supplying early clinical studies using drug-in-capsule approach, which is material sparing and requires a minimum amount of resources. However, the inability of accurately filling the capsule with a small amount, e.g., several micrograms, of drug limits the use of these systems for potent drugs. We demonstrate that formulated powder blends can be used to successfully fill capsules containing 5 μg to 5 mg of drug with adequate content uniformity. Effective formulation and process strategies that enable this approach are presented with examples.

KEY WORDS: automated powder dispensing system; early clinical studies; low-dose oral solid.

INTRODUCTION

There are an increasing number of highly potent and selective drugs being discovered. This trend means that a lot of these drugs will need to be dispensed in low doses, especially if the therapeutic window is narrow. This need presents manufacturing challenges of ensuring that the low dose units have acceptable content uniformity. The small amount of drug substance that is typically used for the manufacture of these low dose units must first be evenly distributed in a powder blend. For a poor flowing and cohesive drug substance, this is difficult to achieve (1). Various approaches have been used to address these issues and thus improve the blend and content uniformity of low-dose solid dosage forms. These approaches include (a) dissolving or dispersing the drug in a liquid vehicle and spraying the resulting solution onto the powder bed (2–8), (b) blending micronized drugs with excipients and granulating the blends by the addition of granulating liquid (9–14), (c) spraying the binder solution onto an inert carrier matrix followed by spraying microdose drug particles (15), (d) blending micronized drugs with appropriate carrier excipients to form an interactive mixture in which the micronized drug particles are adsorbed onto the carrier particles (16–20), (e) using dry granulation approach (21), and (f) dissolving or dispersing microdose drugs into either liquid or semi-solid vehicles and encapsulating them into capsules (22,23). Although the aforementioned approaches have shown some successes, they require, based on the technique, either a long development time, a large amount of drug substances, a lot of human resources, or combinations thereof. Because of these shortcomings, these approaches are not preferred in the early stage of drug development.

A low-dose powder mixture with adequate blend uniformity can be manufactured with relative ease by increasing the drug concentration in the powder blend, but a lighter unit dose has to be manufactured in order to meet the specified low strength. In the case of capsules, less than 5 mg fill weight might be required but this fill weight is beyond the filling capability of most commercial encapsulators. Automated powder dispensing systems have the capability to fill ≥100 μg unit weight into different size capsules (24). These systems are innovative and programmable machines capable of accurately dosing drug substances into capsules at production rates between 200 and 600 capsules per hour. These automated systems provide the ability to balance the risk of attrition against the need to conserve limited active pharmaceutical ingredient (API), development time, and development resources (25,26). However, the system is designed to dispense pure API into capsules (27) with the requirement of a unit filling weight >100 μg. Thus, it would have not been able to use for filling potent new chemical entities (NCEs) with a dosage strength <100 μg. Theoretically, this disadvantage can be overcome if a drug-containing powder blend can be filled uniformly into capsules. However, it is unknown if such an approach will work because of the potential for segregation when filling a powder blend. Automated powder filling systems utilize a programmable tapping method at a high and low frequency to dispense the powder but the tapping motion of the hopper can potentially induce segregation. No systematic studies have been performed to date to assess the performance of the automated system for dispensing powder blends or granulations. Consequently, it is not clear whether low-dose capsules with acceptable content uniformity (CU) can reliably be made by using formulated powders. It is hypothesized that powder blend segregation might be reduced or eliminated during filling by applying following strategies, such as proper selection of formulation excipients, proper

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Table I. Formulation Compositions of AMG X −5, −10, and −500 μg Capsules

Ingredients	Percent *w*/w (5 μg/cap)	g/Batch (5 μg/cap)	Percent *w*/*w* (10 μg/cap)	g/Batch (10 μg/cap)	Percent *w*/*w* (500 μg/cap)	g/Batch (500 μg/cap)
AMG X	2.8	0.168	5.5	0.330	14.2	0.852
Lactose monohydrate FF 316	97.2	5.830	94.5	5.670	85.8	5.148
Total	100.0	6.000	100.0	6.000	100.0	6.000

selection of blend manufacturing processes, and using low tapping intensity.

The objective of this study is to test whether or not capsules with as low as 5–5,000 μg strength can be manufactured by filling powder blends into capsules to support early clinical studies involving a number of NCEs.

MATERIALS AND METHODS

Materials

All model compounds were discovered and manufactured at Amgen, Inc. Compound "AMG X" was used as is. Compounds "AMG Y" and "AMG Z" were micronized, resulting in a particle size of 1.70 μm<d50<2 μm and 4.1 μm<d90<5 μm, respectively. White Opaque hard gelatin capsules, size 2, were purchased from Capsugel (Peapack, NJ, USA). Excipients used include lactose monohydrate FF 316 (Foremost Farms USA, Baraboo, WI, USA), microcrystalline cellulose (Avicel PH 105 and PH102, FMC, Philadelphia, PA, USA), syloid 244 FP (Grace Davison, Columbia, MD, USA), starch 1500 (Colorcon, West Point, PA, USA), and povidone K 29/32 and polyplasdone XL (ISP, Wayne, NJ, USA). All other chemicals were of analytical grade and used as received.

Methods

AMG X Capsule Preparation

A dose strength of less than 500 μg AMG X was required for clinical studies. A binary powder blend-in-capsule was explored. Lactose monohydrate FF 316 was selected as the excipient to enhance the mixing of the binary blend before co-micronization (28). Three low capsule strengths were manufactured to demonstrate the feasibility of the concept. The following processes were used to prepare low-dose capsules with a target batch size of 6 g: (a) weighing the formulation ingredients for each strength as specified in Table I, (b) manually sieving the ingredients through #40 sieve (US standard), (c) loading the sieved mixture into a 45 cc high-density polyethylene (HDPE) bottle, (d) blending the mixture using Turbula (Model T2F, GlenMills Inc, NJ, USA) for 5 min at 42 rpm, (e) co-micronizing the blended mixture using Jet Mill (Model: 50 AS, HOSOKAWA ALPINE, MA, USA) with inject air pressure of four bars and grinding pressure of two bars, resulting in a particle size of d50<2 μm and d90<4 μm for all blends. The resulting mixture was then encapsulated using Xcelodose (Xcelodose™ 600, Meridica Limited) with encapsulation parameters shown in Table II.

It is known that micronization process may result in amorphous formation, which may alter the moisture sorption characteristics of the powders and unintentionally impact chemical stability, dissolution/release rate, balance readings during filling. It is recommended to check the physicochemical properties of the milled materials before placing them in the formulation. All drug substances listed in this study were found to be crystalline after micronization.

Analytical Method for AMG X Capsule Assay and Content Uniformity

AMG X capsule was placed into an amber glass vial, an appropriate amount of N, N-Dimethyl-Formamide was then added and vortexed for 10 min. The resulting suspension was filtered through a 0.45 μm PTFE syringe membrane filter and collected into a high-performance liquid chromatography (HPLC) vial for injection. The chromatography was carried out on an Agilent HP 1100, equipped with multi-wavelength detector (MWD, G1365A) and Chromeleon™ software for data analysis. The mobile phase consisted of A: 0.1%

Table II. Encapsulation Methods of AMG X −5, −10, and −500 μg Capsules

Method parameter	Parameter value		
	5 μg/cap	10 μg/cap	500 μg/cap
Amount of slow tapping (0–40% of required fill-weight, mg)[a]	0.01	0.08	1.05
Required fill-weight (mg)[b]	0.22	0.20	3.86
Fill weight control limit	10%	10%	5%
Tap intensity (0.001–0.04 ms)	0.01	0.01	0.01
Tap frequency (10–40 Hz)	25	25	25
Dispensing head code	BS[c]	BS	HM[d]

[a] A fraction of total fill weight filled in this step
[b] Total fill weight needed to be filled into capsules to achieve the target strength
[c] BS dispensing head comprises 55, 0.2 mm diameter holes
[d] HM dispensing head comprises 26, 0.5 mm diameter holes

Table III. Formulation Compositions of AMG Y −20, −100, and −1,000 μg Capsules

Ingredients	Percent *w*/*w*	g/batch
AMG Y	4.0	2.0
Avicel PH105	95.0	47.5
Syloid 244 FP	1.0	0.5
Total	100.0	50.0

Table V. Formulation Composition of AMG Z −1,000 and −5,000 μg Capsules

Ingredients	Percent *w*/*w*	g/batch
AMG Z intra-granulation	95.00	47.50
Syloid 244 FP	5.00	2.50
Total	100.00	50.00

trifluoroacetic acid/99.9% water and B: 0.1% trifluoroacetic acid/99.9% acetonitrile. A gradient program (mobile phase B from 32% to 50% during the first 7 min followed by 100% mobile phase B for 2 min and then 32% mobile phase B for the next 2 min) was used to elute AMG X. The separation was achieved by using a Phenomenex Synergy Polar-RP column (4 μm, 150×4.6 mm, Agilent Technologies, CA, USA). A flow rate of 1.2 ml/min, an injection volume of 5 μl, a column temperature of 5°C, and run time of 11 min were employed. Chromatograms were recorded at 220 nm.

AMG Y Capsule Preparation

Three low-dose strengths of AMG Y were needed for clinical studies. A tertiary powder blend-in-capsule was explored. Avicel PH 105 and syloid 244 FP were selected as the excipients of the tertiary blend. Avicel PH 105 was selected because of its poor flow and cohesive properties that would help minimize segregation during the capsule-filling process. Syloid 244 FP, an anti-adherent and flow-enhancing agent, was selected to reduce the loss of the API to contact surfaces during blend preparation. The following processes were used to prepare low-dose AMG Y capsules with a target batch size of 50 g: (a) formulation ingredients were weighed into a 200-cc glass bottle in the proportions indicated in Table III; (b) the bottle was shaken manually for about 60 s and the mixture was sieved through #60 sieve (US standard); (c) the mixture was placed back into the glass bottle and blended using Turbula for 10 min at 42 rpm; (d) the blended mixture was manually sieved once again through #60 sieve; (e) the blended and sieved mixture was again placed into the glass bottle and re-blended one more time using Turbula for 10 min at 42 rpm. The resulting final blend was encapsulated using the parameters shown in Table IV.

Analytical Method for AMG Y Capsule Assay and Content Uniformity

AMG Y capsule was placed into a glass container and an appropriate amount of mobile phase was then added and sonicated for 15 min. The resulting suspension was centrifuged for 10 min at a speed of 12,000 rpm. About 1 ml of the top clear solution was then transferred into an HPLC amber vial for HPLC analysis. The chromatography was carried out on an Agilent HP 1100, equipped with MWD (G1365A) and Chromeleon™ software for data analysis. The mobile phase consists of 20 mM phosphate buffer/acetonitrile at 70%/30% *v*/*v* with a pH value of 6.1. An isocratic method was used to elute AMG Y. The separation was achieved by using a Zorbax XDB-C18 analytical column (3.5 μm, 50×4.6 mm, Agilent Technologies, CA, USA). A flow rate of 1.0 ml/min, an injection volume of 100 μl, a column temperature of 35°C, and run time of 12 min were employed. Chromatograms were recorded at 316 nm.

AMG Z Capsule Preparation

AMG Z tablet was manufactured via a high shear wet granulation process and the same intra-granulation powder was used to fill the capsules at a very low dose to test the hypothesis. The intra-granulation contains common excipients such as Avicel PH 102 and Starch 1500.

The following processes were used to manufacture low-dose AMG Z capsules with a target batch size of 50 g: (a) the intra-granulation was mixed with Syloid 244 FP as shown in Table V and manually sieved through #60 sieve; (b) the sieved mixture was placed into a 200-cc HDPE bottle and blended using Turbula for 5 min at 42 rpm. The final blend was then encapsulated using the parameters shown in Table VI.

Table IV. Encapsulation Methods of AMG Y −20, −100, and −1,000 μg Capsules

	Parameter value		
Method parameter	20 μg/cap	100 μg/cap	1,000 μg/cap
Amount of slow tapping (mg)	0.1	0.2	5.0
Required fill-weight (mg)	0.5	2.5	25.0
Fill weight control limit	7.5%	5%	5%
Tap intensity (msec)	0.01	0.01	0.01
Tap frequency (Hz)	25	25	25
Dispensing head Code	DL[a]	DL	HZ[b]

[a] DL dispensing head comprises 22, 0.3 mm diameter holes
[b] HZ dispensing head comprises 178, 0.5 mm diameter holes

Table VI. Encapsulation Methods of AMG Z −1,000 and −5,000 μg Capsules

Method parameter	Parameter value	
	1,000 μg/cap	5,000 μg/cap
Amount of slow tapping (mg)	1.2	3.888
Required fill-weight (mg)	4.0	19.44
Fill weight control limit	5%	5%
Tap intensity (msec)	0.01	0.01
Tap frequency (Hz)	20	20
Dispensing head Code	FP[a]	JR[b]

[a] FP dispensing head comprises 41, 0.4 mm diameter holes
[b] JR dispensing head comprises 48, 0.6 mm diameter holes

Analytical Method for AMG Z Capsule Assay and Content Uniformity

AMG Z capsule was placed into a glass container and an appropriate amount of sample diluent [30:70:0.1 CH_3CN/water/glacial acetic acid (*v*/*v*/*v*)] was added and sonicated for 5 min. The resulting suspension was centrifuged for 10 min at a speed of 13,000 rpm. About 1 ml of the top clear solution was then transferred into an HPLC amber vial for HPLC analysis. The chromatography was carried out on an Agilent HP 1100, equipped with MWD (G1365A) and Chromeleon™ software for data analysis. The mobile phase consists of 0.035% TFA and 17.5 mM SDS in 65/35 CH_3CN/Water (*v*/*v*). An isocratic method was used to elute AMG Z. The separation was achieved by using a Symmetry Shield RP18 Column (5 μm, 4.6×150 mm; Waters, MA, USA). A flow rate of 1.0 ml/min, an injection volume of 50 μl, a column temperature of 40°C, and run time of 10 min were employed. Chromatograms were recorded at 260 nm.

Table VII. Assay and CU Data for AMG X Capsules (n=10)

Lot#	Dose (μg)	Assay	%RSD
Dose −5 μg	5	104.6	2.8
Dose −10 μg	10	96.6	2.8
Dose −500 μg	500	94.0	0.5

RESULTS

Shown in Fig. 1 is the plot of the individual capsule fill-weights of AMG X −5, −10 and −500 μg capsules obtained from their respective encapsulation electronic batch records. The results indicate that more than 92% of the capsules were accepted for the 5-μg dose while almost 100% of the 10- and 500-μg doses were accepted. The acceptance rate of filled capsules mainly depends on the capsule fill weight, the upper and lower limit of which has been specified in each encapsulation method. The %RSD of the weights of the accepted capsules was 2.04, 2.44, and 1.26 for the 5, 10, and 500 μg capsules, respectively. The results presented in Fig. 1a indicate that the average fill weight of the accepted capsules was 6% lower than the target fill weight. The results shown in Fig. 1b and c indicate that the average fill weights of the accepted capsules for the 10- and 500-μg doses were also less than the target fill weight but by a percent less. Even though not all the capsules were accepted, the overall results showed that powder blends can be successfully filled into capsules.

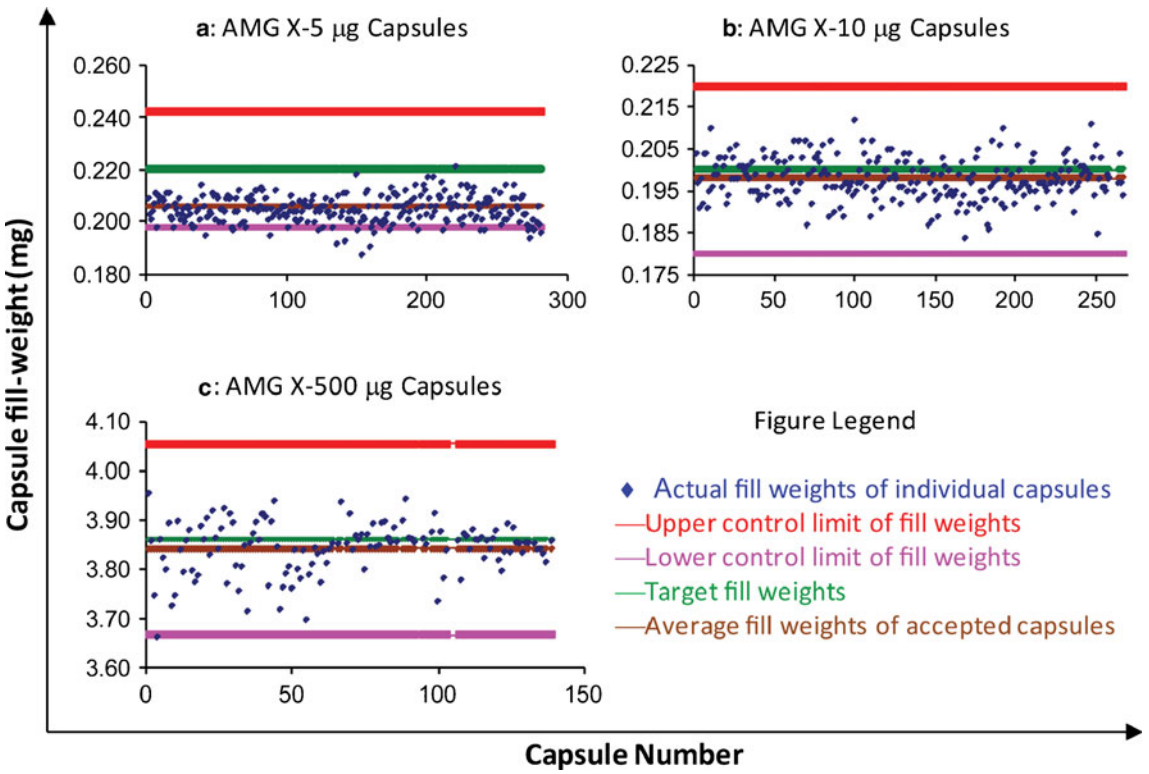

Fig. 1. Actual individual capsule fill-weight of AMG X capsules

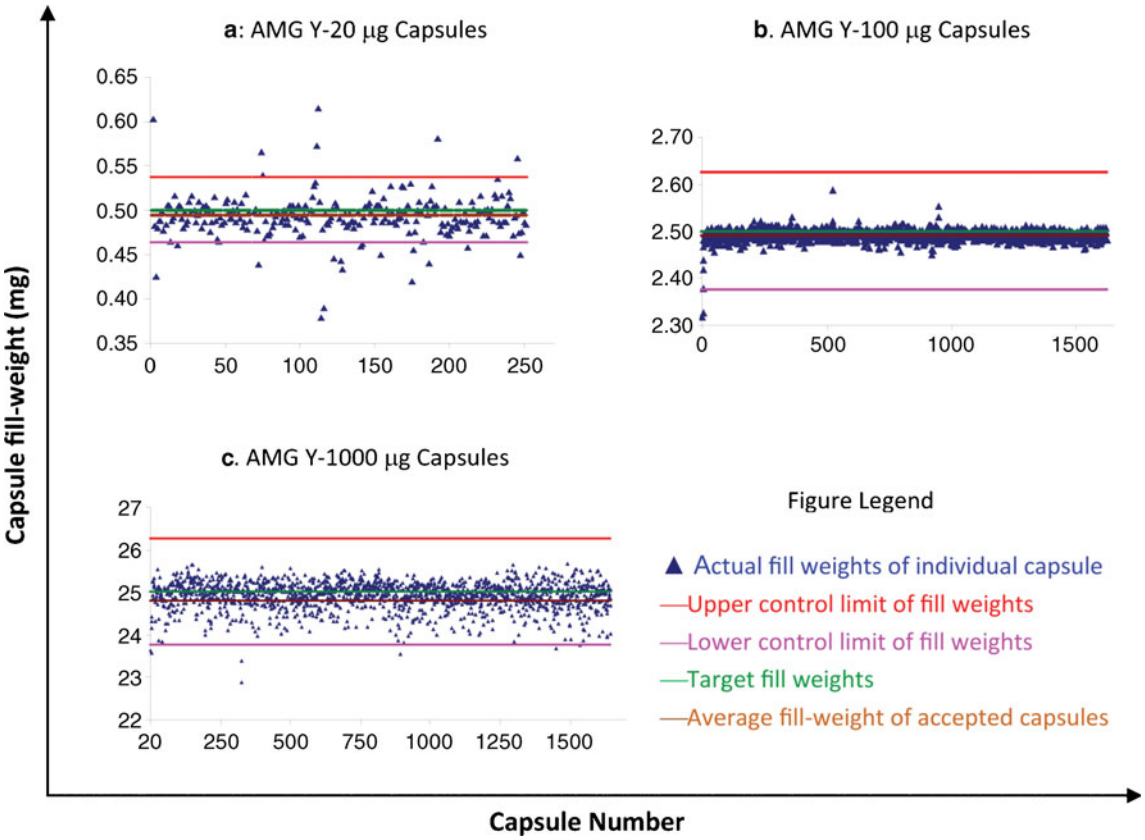

Fig. 2. Actual individual capsule fill-weight of AMG Y capsules

The results presented in Table VII indicate that the automated system has the ability to fill blends into capsules to the desired microdose strengths for AMG X. Minimal segregation was observed and the results obtained indicate that powder blend-in-capsule can be prepared in a consistent manner to be used to support early phase clinical studies.

The results shown in Fig. 2 represent the individual capsule fill weights of AMG Y −20, −100, and −1,000 µg capsules. The results show that most of the filled capsules were accepted with %RSD value of 2.78, 0.42, and 1.25 for the 20, 100, and 1,000 µg capsules, respectively. It is clear from the results presented in Fig. 2a that the encapsulation method for the 20-µg strength needs optimization. This can be achieved by either increasing the amount of slow tapping from 0.1 to 0.2 mg or optimizing the dispensing head selection to reduce the number of capsule rejection. Generally, the more fill weight is dispensed by slow tapping step, the more accurate the overall fill weight will be but the filling time will increase and the filling efficiency will decrease. By optimizing the dispensing head, such as selecting a dispensing head with less number of sieve holes or the same number of sieve holes but with smaller diameters, the encapsulation efficiency usually will not be affected but the filling accuracy may increase. Figure 2 also indicated that average fill-weight of the accepted capsules is only 1% less than the target fill-weight. The conclusion is that powder blend can be successfully filled into capsules.

The results presented in Table VIII indicate that there was little or no segregation of the powder blend and that the microdose capsules can be manufactured with a sufficiently high degree of consistency to enable their use in early clinical studies for AMG Y.

The distribution of fill weights for the AMG Z −1,000- and −5,000-µg capsules is shown in Fig. 3. The results indicate that more than 95% of filled capsules were accepted for both doses with %RSD of 1.77 and 1.26 for the 1,000 and 5,000 µg, respectively. Some of the capsule fill weights were outside of the control limit but this could be remedied by increasing the amount of slow tapping from 1.2 to 1.6 mg or by optimizing the dispensing head selection. The results shown in Fig. 3 also indicate that the average capsule fill weight of the accepted capsules was only 1% less than the target fill weight further supporting the conclusion that granulation powders can be filled into capsules with high degree of precision and accuracy.

The results presented in Table IX show that there was little or no segregation in the granulation powder and that the granulation can be filled into capsules to achieve acceptable content uniformity to enable their use in AMG Z clinical studies.

DISCUSSION

The results show that it is possible to use either direct powder blend or granulation to fill capsules using automated

Table VIII. Assay and CU Data of AMG Y −20, −100, and −1,000 µg Capsules (n=10)

Lot#	Dose (µg)	Mean % Label Claim	% RSD
Dose −20 µg	20.0	98.5	2.5
Dose −100 µg	100.0	100.5	1.2
Dose −1,000 µg	1,000.00	99.3	1.7

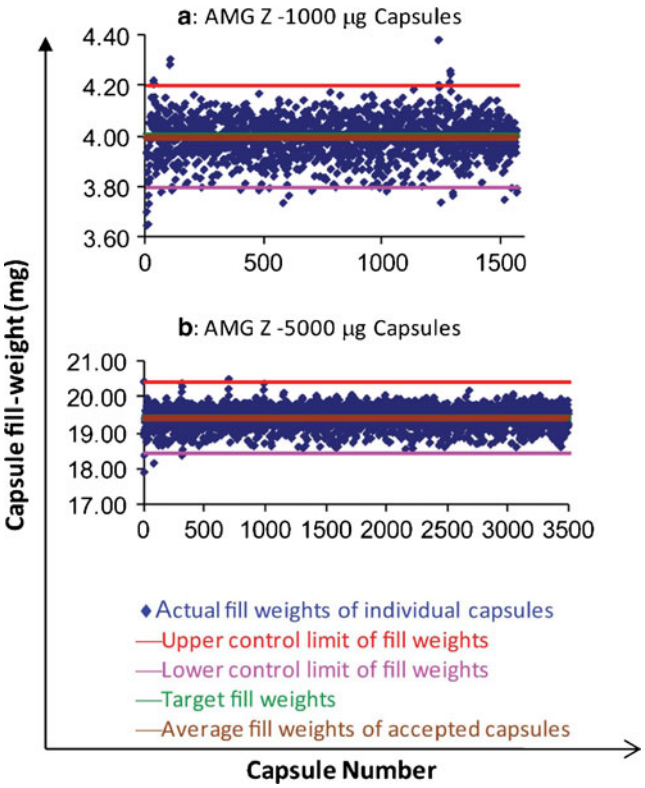

Fig. 3. Actual individual capsule fill-weight of AMG Z capsules

filling system. The results presented above however indicate that the filling method for AMG X −5-µg capsules needs to be optimized to improve the precision and accuracy of the average capsule fill-weight. It is proposed that, for AMG X −5 µg, optimization of the filling process can be achieved by increasing the amount of slow tapping from 0.01 to 0.088 mg or by a careful selection of the dispensing head. But overall results, including the results from AMG X −5-µg encapsulation, indicate that both powder blend and granulation can be successfully filled into capsules with a sufficient degree of accuracy.

The results also show that acceptable capsule content uniformity results were obtained in all three examples where formulated powder was used to fill the capsules. The content uniformity of all the studied capsules was below 3%. This was due, in part, to the proper selection of the excipients used in the studies. Factors that need to be considered in the proper selection of excipients include consideration of the potential interaction between the studied API and the selected excipients. Lactose monohydrate was selected for AMG X blend because of its fast powder flow property and this property enabled a homogeneous blend to be achieved with relative ease. This type of homogenous blend, however, has a high potential to demix due to its random mixing nature and, because of this, co-micronization of the homogenous blend was undertaken. The resulting micronized blend was more homogenous, more cohesive and had stronger interaction between the API and the lactose particles and significantly reduced the de-mixing potential. The surface of lactose particles is usually more irregular and has high proportions of large pores and asperities and as a result of this micronized API particles are more strongly adsorbed onto its surface and prevent easy segregation of the blend (29).

Avicel PH 105 was selected for AMG Y blend because it is cohesive and its particle size is similar to that of micronized AMG Y. Similarity of the AMG Y and Avicel PH 105 particle sizes was very helpful in achieving homogenous blend. The cohesive nature of Avicel PH 105 was the key to reducing the potential for de-mixing after the homogenous blend was achieved.

Avicel PH 102 and starch 1500 were selected for AMG Z blend because these two excipients have sufficient flow properties and this enabled a homogenous blend to be easily achieved. The ease of achieving homogeneous blend with these two excipients, however, did not remove the high potential for the blend to de-mix (19,20). Previous studies (19,20) have indicated that wet granulation of blends of this type will help to reduce the de-mixing potential.

Although it is out of scope of this study, it is very important to note that API particle size and distribution is critical for meeting USP CU requirement. Several excellent papers (30–32) have been published in the past to address this issue. It is highly recommended to read these references and

Table IX. Assay and CU Data of AMG Z −1,000 and −5,000 µg Capsules (n=10)

Lot#	Dose (µg)	Mean % Label Claim	%RSD
Dose −1,000 µg	1,000.0	104.2	2.7
Dose −5,000 µg	5,000.0	100.2	1.9

predict what particle size and distribution is needed to achieve USP CU for an oral solid dosage form, especially for a low-dose oral solid dosage form.

Blend uniformity (BU) is critical to achieving consistent content uniformity of capsule dosage forms. The BU obtained for all the above-described studies were acceptable (<3% RSD) and that was attributable to the selection of excipients with adequate flow properties and having similar particle size as that of the model compounds. Also contributing to the BU were such factors as the use of proper manufacturing processes including co-micronization, sieving, and wet granulation. Co-micronization of the homogenous blends using Jet mill enabled the API and the excipients to be homogenized and evenly distributed further in the mill chamber through air-facilitated particle–particle collision. By sieving through small opening, agglomerates of API were broken and immediately mixed with the excipients which further facilitated BU. Wet granulation process facilitates BU by enabling the drug particles and excipients to form granule thus reducing segregation.

All powder blends prepared in this study were not characterized in detail with respect to the nature of total mix as that was beyond the scope of this paper. It is typical for several types of powder mixtures, i.e., perfect ordered mixture, imperfect ordered mixture, pseudo-random mixture, partially ordered random mixture, ideal random mixture, random mixture, and non-random mixture, to exist in a total mix. The proportion of each type of mixture in a total mix will affect the practical performance characteristics, such as homogeneity and segregation, of the total mix. The definition and detailed information about each type of aforementioned mixture and its effect on the performance characteristics of the total mix is described in the paper published by J. N. Staniforth (29).

Three factors might contribute to powder blend segregation during encapsulation and these are tapping length, tapping frequency, and tapping acceleration. Tapping motion is different from vibration motion as it has the tendency to induce percolation type of segregation and not trajectory and vibrofluidisation type of segregation, the latter two usually being induced by vibration motion. Therefore, tapping motion alone might induce less segregation than vibration motion would. With tapping motion the powder bed becomes more and more dense as the tapping continues and this is especially true for the lower part of powder bed which, in turn, prevents the percolation type of segregation to occur. Prevention of the percolation type of segregation occurs because the drug particles have difficulty percolating the dense bed. The above statements indicate that the tapping length will not contribute much to segregation because it will help to form a denser powder bed. The denser powder bed, as previously noted, prevents drug particle percolation to the lower part of bed. As far as tapping frequency is concerned, Staniforth's studies (29) indicated that vibration frequency between 20 and 1,000 Hz did not segregate powder blends of potassium chloride and crystallite lactose. Staniforth concluded that proper selection of drugs/excipients combination is important to minimize segregation. Tapping acceleration or intensity may induce fluidization or percolation type of segregation. It is therefore important to keep tapping acceleration or intensity to a minimum by selecting dispensing heads with more sieve holes or the same number of sieve holes but with larger diameters. The sieve options may decrease the capsule acceptance rate but it may help to reduce the blend segregation during encapsulation process.

Acceptable content uniformities obtained in our examples suggest that segregation was minimal during the handling and the filling of the studied capsules. The CU results also suggest that blend uniformity was achieved during the filling. The tendency for blends to segregate is lower for more cohesive powders. In all the three examples presented in this paper, the final blends were cohesive. The cohesiveness of the powder was achieved by (1) micronization of the mixture as in the AMG X blend, (2) using poorly flowing excipient as in the AMG Y blend, and (3) affixing the drug particles to the excipients in the granules of AMG Z to prevent segregation.

CONCLUSIONS

The results of the studies presented in this paper suggest that powder blends can be accurately filled into capsules to generate dosage units with more than 90% acceptance rate. The filled capsules showed acceptable assay and consistent content uniformity values. Low-dose capsules from 5 μg to 5 mg were successfully manufactured with minimal amounts of drug substance (<10 g) and the procedure used lesser amount of time and resources than is typical for processes of this type. This study also indicated that there was little or no powder blend segregation during the handling and encapsulating process as long as the following strategies were adhered to: (1) proper selection of the formulation excipients, (2) proper selection of the blend manufacturing processes, and (3) the use of low tapping intensity. Low tapping intensity was achieved by selecting dispensing heads with more sieve holes or same number of sieve holes but with larger diameters.

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