Drug Development and Industrial Pharmacy, 2011, 37(1): 24–32

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI:10.3109/03639045.2010.489561

informa
healthcare

ORIGINAL ARTICLE

Low powder mass filling of dry powder inhalation formulations

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Abstract

Context: The successful accurate dosing and filling of powders at fill masses of <10 mg is considered to be challenging for the pharmaceutical industry. This is mainly due to the limitations of current powder volumetric dosing technologies, which rely on formulations having 'good' flow properties. This is especially true for dry powder inhaler (DPI) applications where, together with good manufacturability, powders must also exhibit properties that allow acceptable product performance. *Objective*: In this study, the OMNIDOSE® filling technology was investigated for its capability to accurately fill powders suitable for DPI applications, to masses as low as 1 mg. *Results*: Several lactose monohydrate-based powders were successfully dosed at target fill masses of 1 and 5 mg using the current technology at laboratory scale. The filling behavior of the excipients could be related to various aspects of their physical properties. DPI formulations were dosed at masses of 4 and 25 mg at pilot scale to produce capsules that exhibited aerosolization fine particle fractions of ~30% based on label claim. *Conclusions*: Initial studies suggest that the OMNIDOSE® technology is readily adaptable for the dosing of low masses of DPI excipients and formulations and demonstrate the value of thoroughly evaluating powder performance at laboratory scale prior to pilot scale.

Key words: Filling, fine particle fraction, inhalation, lactose, low mass

Introduction

Drug delivery through the respiratory tract is an attractive route for the administration of an active pharmaceutical ingredient (API) for systemic and local applications compared to the current conventional oral, transdermal, and parenteral approaches. Respiratory drug delivery offers numerous potential advantages such as simple, self-administration, large mucosal surface for drug absorption provided by the lungs, nonhepatic drug delivery, and reduced enzymatic and pH degradation of drugs, the latter of which is of particular interest for biological systems[1]. Additionally, the administration of APIs to the lungs has the potential to reduce side effects and improve drug efficacy in the treatment of local disorders such as asthma, chronic obstructive pulmonary disease, and cystic fibrosis because of higher local therapeutic concentrations[2–4].

To deliver an API to the lungs, a delivery system is required. Among such aerosol generation systems, the dry powder inhaler (DPI) offers several advantages, for example, they are small, portable, easy to operate, require short inhalation time, and do not contain propellant[5]. Additionally, DPIs eliminate the problem of poor coordination between actuation and patient inhalation maneuver, as observed for pressurized metered dose inhalers (pMDIs), because the patient inhalation maneuver is used to dispense, and deagglomerate, particles[6]. Moreover, API lung deposition from DPIs is often higher, and less variable, compared with the commonly used pMDI[7,8]. DPIs can be generally categorized as single dose, where the formulation is predispensed in a unit dose capsule or blister, premetered multidose, where the device contains predispensed unit doses, and reservoir-based multidose, where the formulation is metered by the patient before actuation[9]. Premetered DPIs can offer some advantages over the reservoir-based systems, for example the prepacked dose is protected from the environment until use and ensures adequate control of the dose uniformity[10].

The challenge for the successful development of DPI products is, however, to produce a bulk powder formulation that not only exhibits adequate flow and

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(Received 4 Jan 2010; accepted 26 Apr 2010)

stability to allow robust manufacturing, but will also deagglomerate to produce an appropriate API aerodynamic particle size distribution for the delivery of an efficacious dose to the patient[11]. Drug particles suitable for pulmonary applications are typically of micron size range and are usually prepared by milling. However, the high surface area to mass ratio of such particles results in intrinsically cohesive powders that are difficult to meter and deagglomerate[12]. The classical approach to solve this problem is to formulate micronized drugs with inert excipients, commonly lactose monohydrate, to produce the so-called agglomerate and carrier-based systems. Agglomerated systems are typically prepared using finer grades of excipients than those used to produce the carrier-based formulations[13]. Indeed, the overwhelming majority of DPI products in the market contain such formulations[14]. The lactose monohydrate carrier particles play a major role not only in modulating the performance of DPIs but also for manufacturability. A powder must exhibit appropriate flow properties for successful manufacturing, that is, a generally wide and large particle size distribution (PSD). However, for DPI performance, it has been reported that the quantity of fine lactose monohydrate particles, which are in a similar size range as the API, influences the respirable fraction[15]. Such 'fine' materials would be expected to be detrimental to flow and consequently present manufacturing challenges.

Marketed single-dose DPI products generally consist of formulations in blisters or capsules. The masses of such formulations are in the order of milligrams, for example, 5 mg for Spiriva® (capsule) and 12.5 mg for Seretide® (blister). Current capsule-based DPI products can be successfully manufactured using modern capsule-filling technologies. However, such processes are sensitive to the flow properties and the stability of the formulation. Recently, cavity-based filling technologies have become available where detrimental powder flow properties can be minimized using a precompression step. Such technologies may allow the accurate filling of relatively cohesive powders and lower formulation masses. The aim of this study is to evaluate the capability of the OMNIDOSE® filling technology for the filling of low masses of DPI powders of various physical properties. A simple representation of the filling technology is shown in Figure 1 and is based on filling a volume of a precompressed powder into a drum cavity. The drum cavity is then rotated and the powder is dispensed using pressurized air into a vehicle, such as a capsule. In view of the sensitivity of DPI formulations to powder properties, the relationships between powder fill mass and excipient characteristics and fines content were investigated. Additionally, the dosing and aerosol performance of a DPI formulation was studied.

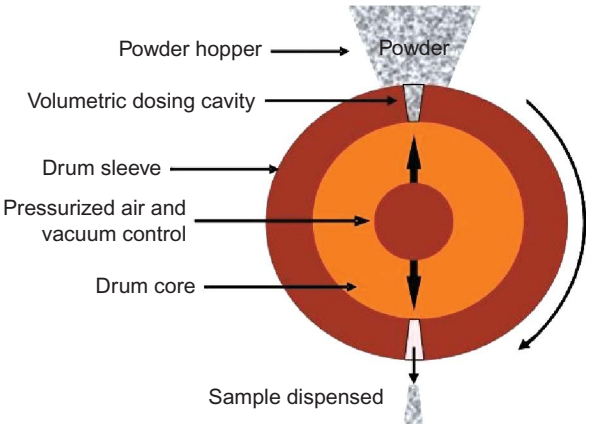

Figure 1. Representation of OMNIDOSE® filling technology.

Materials and methods

Materials

The lactose monohydrate excipients (see Table 1), Respitose® ML001 (batch no. S0017), Respitose® ML002 (batch no. 10286298), and Respitose® ML003 (batch no. 10308574) from DMV-Fonterra Excipients, Goch, Germany; Lactohale® LH201 (batch no. 609925/5) from Friesland Foods Domo, Noord-Nederland, The Netherlands; SorboLac400® (batch no. 10506) from Molkerei Meggle Wasserburg GmbH & Co. KG, Wasserburg Germany; and Lactosphere® MM3 (batch no. 6050318) from Microsphere SA, Via Cantonale, Switzerland, were used as supplied. All materials in placebo studies were initially sieved through a 250-µm sieve. To evaluate the potential of the technology for DPI applications, a suitable model drug, named 'API,' was used in this trial, which was obtained from Novartis Pharma AG, Basel, Switzerland. The micronized API exhibited a volume mean diameter of 1.99 µm and

Table 1. Details of the excipients and formulations used in the study.

Excipient placebo	Excipient blend	Formulation
Respitose® ML001	–	1.2% (w/w) API
Respitose® ML002	1.0% (w/w) Lactosphere® MM3	1.2% (w/w) API
	5.0% (w/w) Lactosphere® MM3	7.5% (w/w)API
Respitose® ML003	1.0% (w/w) Lactosphere® MM3	1.2% (w/w) API
	5.0% (w/w) Lactosphere® MM3	7.5% (w/w) API
Lactohale® LH201	–	–
SorboLac 400®	–	–
Lactosphere® MM3	–	–

geometrical standard deviation (GSD) of 1.8, as measured by Sympatec laser scattering technique (Sympatec GmbH, Clausthal-Zellerfeld, Germany). A modified Aerolizer® inhaler (with comparable device characteristics, such as low resistance, to the Aerolizer®) named 'Inhaler' was used for testing the aerosolization performance of the formulation from size 3 hypromellose capsules (Qualicaps Europe S.A., Alcobendas, Spain).

Preparation of excipient blends and formulations

The API or micronized lactose monohydrate (Lactosphere® MM3) was blended with the carrier lactose monohydrate (see Table 1) using a low-shear blending process. All materials were initially sieved through a 250-µm sieve. The API or the micronized lactose monohydrate was preblended with the lactose monohydrate carrier in a Turbula® 2B blender (Willy A. Bachofen AG, Basal, Switzerland) at 25 rpm for 18 minutes with 30% of the excipient using a sandwich technique. The preblend was then sieved through a 250-µm sieve and blended with the remaining excipient using a Bohle® blender at 15 rpm for 30 minutes (L.B. Bohle Maschinen and Verfahren GmbH, Ennigerloh, Germany). The formulations with API were evaluated for homogeneity using an Antaris® near-infrared online monitoring system (Thermo Fisher Scientific, Walldorf, Germany). Moreover, the drug blend uniformity was confirmed by analyzing appropriate samples from each batch using a validated high-performance liquid chromatography (HPLC) method. The batch sizes were 100 g for laboratory scale and 1 kg for pilot scale.

Powder filling at laboratory scale

Powder was filled into capsules (batch size of 200 capsules) using an OMNIDOSE® TT laboratory scale drum filler (Harro Höfliger Verpackungsmaschinen GmbH, Allmersbach, Germany). The drum used for the laboratory scale machine has only one cavity per drum. Two different cavity volumes 1.33 mm^3 (target 1 mg filling) and 6.25 mm^3 (target 5 mg filling) were used in this study. The corresponding fill mass for the predefined dosing volumes is based on the powder physical characteristics and can be estimated from the powder-tapped density. The precision of the balance used was 0.5% and 0.1% for 1 and 5 mg masses, respectively. The excipient Lactosphere MM3 was dosed twice into the capsule because of its low bulk and cavity density.

Powder filling at pilot scale

Powder was filled into capsules (batch size of 1000 capsules) using an OMNIDOSE® DF1 pilot scale automated filling machine (Harro Höfliger Verpackungsmaschinen GmbH, Germany). The drum used for the pilot scale machine has six cavities per drum. Two different drum cavity sizes were selected based on the powder physical properties. Cone-shaped cavities with sizes of 4.72 mm^3 (target 3.5–4 mg fill mass) and 32.65 mm^3 (target 25 mg fill mass) were machined into the drum sleeve, three pores per size. The precision of the balance used was 0.5% for 1–4 mg masses and 0.01% for 25 mg masses.

Powder bulk and tapped densities

Bulk and tapped densities ($n=5$) were determined according to the procedure described in the European Pharmacopoeia[16]. An Engelsmann tapping volumeter (J. Engelsmann AG, Germany) was used to determine the tapped density. One hundred grams of powder was weighed into a 250-mL graduated cylinder and the bulk volume recorded. The powder was tapped (1250 times) and the tapped volume was recorded. The compressibility index (CI) was calculated according to the following equation:

$$\text{Compressibility index} = \frac{\rho_T - \rho_B}{\rho_T} \times 100,$$

where ρ_B is the bulk density of the powder and ρ_T the tapped density of the powder[17,18].

Cavity density

The powder density in the filling drum cavity was calculated from the volume of the cavity in the filling drum and the mean fill mass, hereafter denoted as cavity density[19].

Dynamic vapor sorption

Water sorption was used to determine the amorphous content ($n=3$, 120 ± 1 mg) of the excipients using a DVS-1 (Surface Measurement Systems, UK) using a qualified method, based on the quantification of amorphous lactose in amorphous lactose/lactose monohydrate blends, which enables the quantification of amorphous lactose content to a limit as low as 0.5% (w/w)[20]. The method utilizing a software-controlled sequence was run which allowed the samples to be exposed to a range of humidities (water activities). The sample was initially maintained at 0% RH for 4 hours to remove any surface moisture, followed by humidity steps from 0% to 90% RH in 10% RH increments. The sample was allowed to reach a near-equilibrium state (% dm/dt, 0.0002%/min) with a maximum allowed time of 120 minutes at each humidity stage before progressing to the next step. This program was then repeated to evaluate any hysteresis.

True density

The true density of the materials ($n=10$) was determined using a Pycnomatic helium pycnometer (Porotec GmbH, Hofheim, Germany).

Particle size distribution by laser diffraction

Particle size distribution (PSD) (n = 3) was determined using a Sympatec HELOS® laser diffraction system (Sympatec GmbH, Germany) equipped with a RODOS®

unit. During the measurement time of 5 seconds, the powder was dispersed with an air pressure of 3 bar. The optical concentration is approximately 1%, with lens number 2 (range 0.45–87.5 μm).

Specific surface area

The specific surface area (SSA) (n = 3) was determined using a Micromeritics Gemini system (Micromeritics Instrument Corp., Norcross, GA, USA) using a Brunauer, Emmet, and Teller (BET) multipoint method. Samples were initially out-gassed at 30°C under vacuum for 12 hours.

Aerodynamic particle size distribution

The fine particle fraction, as percent of declared content (FPF_{DC}), the mass median aerodynamic diameter (MMAD), and the GSD were determined using a Next Generation Impactor (NGI) (n = 3) with a preseparator according to the European Pharmacopoeia[21]. The fine particle mass represented the mass of drug less than 5 μm in size. All measurements were performed using a total volume of 4 L of air volume through the device and impactor at 90 L/min.

HPLC analysis of the API

Quantitative analyses were performed using HPLC with a validated method using a Shimadzu® LC2010C HT system, which was adapted with a Photo-diode Array detector (Shimadzu Schweiz GmbH, Reinach, Switzerland).

Results and discussion

Three general studies were undertaken, namely, the characterization of powders in terms of their bulk and material properties, the applicability of the OMNIDOSE® filling technology for a range of placebo lactose monohydrate excipients, with and without added fines, at low fill masses of 1 and 3.5–5.0 mg, and the aerosolization of a model drug from formulations.

Powder characterization

It is well known that the characteristics, such as powder density, electrostatic charge, PSD, surface texture, hydrophobicity, and water solubility, can significantly affect the in vitro pharmaceutical performance of a DPI formulation. The powder characteristics are also crucial for the manufacturability and fillability of such powders and have to be taken into consideration during the early preformulation development phase.

The powder and material properties of the lactose monohydrate placebo excipients and excipient blends are presented in Tables 2 and 3. It can be seen from Table 2 that the excipients, as expected, exhibited a wide range of powder properties, which were typical for inhalation grade lactose. For example, particle size X50 ranged from 7.3 to 48.4 μm, with specific areas reflecting the PSD. The amorphous content of various lactose monohydrates was in agreement with previous literature data[20] and was generally low. The highest observed amorphous content was, as expected, for Lactosphere® MM3 with an amorphous content of ~1.4%. This relatively high amorphous content could be attributed to the high-energy micronization process used for the preparation of this excipient grader. Additionally, differential thermal calorimetry studies produced typical endothermic thermal events for α-lactose monohydrate, with an endothermic peak at 120–150°C for α-lactose monohydrate dehydration and a melting endotherm at ~205°C with no apparent differences observed between the various α-lactose monohydrate grades (data not shown). The water content of all lactose monohydrate grades was within the pharmacopoeial requirements (data not shown).

Table 2. Physicochemical characteristics and filling behavior of lactose excipients (5 mg target fill mass).

Lactose grade	Lactosphere MM3	SorboLac 400	Lactohale LH201	Respitose ML002	Respitose ML003	Respitose ML001
Bulk density (g/cm^3)	0.21	0.32	0.43	0.51	0.55	0.55
Tapped density (g/cm^3)	0.31	0.52	0.66	0.74	0.78	0.79
Cavity density (g/cm^3)	0.25	0.51	0.67	0.78	0.79	0.79
Compressibility index (%)	32	38	35	31	29	30
X10 (μm)	1.79 ± 0.08	2.19 ± 0.05	3.91 ± 0.06	4.54 ± 0.14	4.14 ± 0.05	5.73 ± 0.44
X50 (μm)	7.26 ± 0.57	9.91 ± 0.11	23.50 ± 0.32	31.25 ± 0.41	38.01 ± 0.44	48.36 ± 3.37
X90 (μm)	14.69 ± 1.67	22.68 ± 0.27	56.31 ± 0.79	82.85 ± 1.32	107.55 ± 2.04	146.04 ± 2.58
Q3 (10.5 μm) (%)[a]	78.5	47.8	42.4	21.2	20.5	20.5
GSD	2.86	3.22	3.79	4.27	5.09	5.00
Amorphous content (%)	1.4	0.8	Not detectable	<0.5	<0.5	0.6
True density (g/cm^3)	1.49	1.51	1.53	1.54	1.54	1.54
Specific surface area (m^2/g)	4.56	3.87	1.17	0.90	0.64	0.60
Mean fill mass (mg) (RSD)[b]	4.64[c] (9.2)	3.20 (7.0)	4.59 (2.7)	4.85 (1.4)	4.97 (2.7)	4.91 (2.8)

[a]Fraction of particles which has a volume diameter of less than 10.5 μm; an indication for the fine particle level. [b]n = 50. [c]The mass is a result of two doses.

Table 3. Powder characteristics and filling behavior (5 and 1 mg target fill mass) of Respitose® ML002 and ML003 blended with 1% and 5% Lactosphere® MM3.

	ML002			ML003		
Lactose grade	0% MM3	1% MM3	5% MM3	0% MM3	1% MM3	5% MM3
Bulk density (g/cm^3)	0.51	0.48	0.44	0.55	0.52	0.48
Tapped density (g/cm^3)	0.74	0.75	0.71	0.78	0.78	0.76
Cavity density (g/cm^3)	0.78	0.77	0.74	0.80	0.79	0.78
Compressibility index (%)	31	36	38	30	33	37
X10 (μm)	4.54±0.14	3.42±0.02	2.27±0.04	4.14±0.05	3.76±0.05	2.52±0.02
X50 (μm)	31.25±0.41	14.73±0.07	13.38±0.21	38.01±0.44	29.52±0.16	23.33±0.01
X90 (μm)	82.85±1.32	52.92±0.81	47.75±0.70	107.55±2.04	77.41±0.89	52.45±0.92
Q3 (10.5 μm) (%)[a]	21.2	23.4	27.8	20.5	22.3	25.2
GSD	4.27	3.93	4.59	5.09	4.54	4.56
Specific surface area (m^2/g)	0.90	1.01	1.31	0.64	0.96	1.19
Mean fill mass (mg)	1.06 4.85	1.03 4.79	1.06 4.61	1.03 4.97	1.07 4.94	1.05 4.93
RSD[b]	4.9 1.4	4.4 2.1	6.3 1.7	3.8 2.7	5.3 3.2	3.8 1.5

[a]Fraction of particles which has a volume diameter of less than 10.5 μm; an indication for the fine particle level. [b]$n = 50$.

The bulk and tapped densities together with the CI were used to give an insight into the powder flow properties[17]. In general, a low bulk and tapped densities indicate poor powder flow. In terms of flow, the powders would be classified as poor to very poor flowing[18]. The bulk and tapped densities and CI generally reflect the PSD of the powders. Additionally, a linear correlation between the fine lactose monohydrate content, represented as Q3 (10.5 μm) (%), and both tapped density (R^2, 0.97) and bulk density (R^2, 0.95) could be established but there was a poor linear correlation with CI (R^2, 0.20). As expected, increases in the fine lactose monohydrate content resulted in a decrease in the bulk and tapped densities and particle size descriptors and an increase in the SSA.

Laboratory scale placebo filling trial: 5 mg target fill mass

The laboratory scale filling behavior of the six lactose monohydrate grades is presented in Table 2. The filling behavior of Respitose® ML001 and Respitose® ML002 are shown in Figure 2. It can be seen from Figure 2 and Table 2 that all the excipients could be successfully filled into capsules; however, the two excipients, SorboLac® 400 and Lactosphere® MM3 (not shown), which exhibited the smallest PSD descriptors and lowest bulk and tapped densities, exhibited filling relative standard deviations (RSDs) of 7.0% and 9.2%, respectively, suggesting that, in the present configuration, these powders would produce capsules with poor content uniformity. In general, there is a linear correlation between the tapped density and cavity density (R^2 = 0.99) and powders that exhibit low tapped density and low cavity density display higher fill mass variability (R^2 = 0.90). Interestingly, there was no apparent simple linear correlation between powder CI and filling RSD (R^2 = 0.18). However, a clear linear correlation could be established between lactose monohydrate PSD descriptor (X10, X50, and X90) and

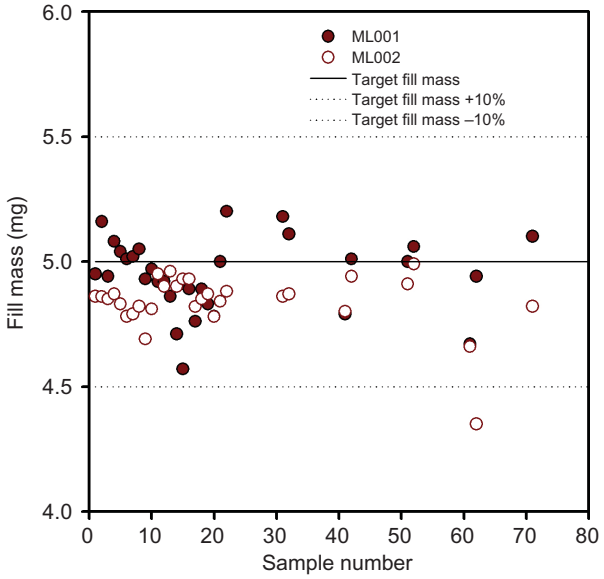

Figure 2. Laboratory scale filling behavior of Respitose® ML001 and Respitose® ML002 using the OMNIDOSE® TT filling technology at target fill mass of 5 mg.

filling RSD (R^2 = 0.99) with the R^2 increasing from 0.57 for relationship with the X90 descriptor to 0.77 for the X10 descriptor suggesting that fines have a stronger influence on such relationships. Additionally, the R^2 for the relationship between Q3 (10.5 μm) (%) and filling RSD was 0.83, suggesting again that the fines content is a key factor in the filling variability of such excipients.

To attempt to directly correlate, and predict, the filling variability of the excipients a correlation between a PSD descriptor, X90, GSD, and filling variability was used. The relationships between these factors are shown in Figure 3. These correlations suggested that optimal filling regimes could be identified based on such parameters. In general, powders with small PSD, in combination with low GSD, produce unacceptable filling performance.

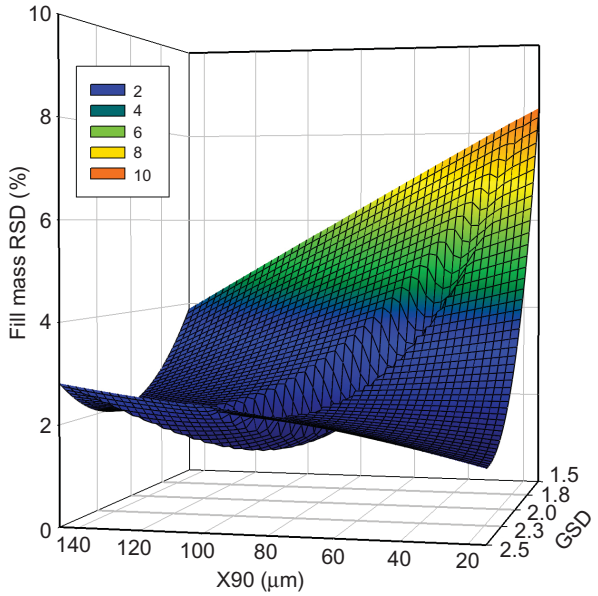

Figure 3. Relationships between lactose particle size descriptor X90, geometrical standard deviation (GSD), and powder filling performance as determined with the OMNIDOSE® TT filling technology at target fill mass of 5 mg. Data points: 7 × 7 × 7.

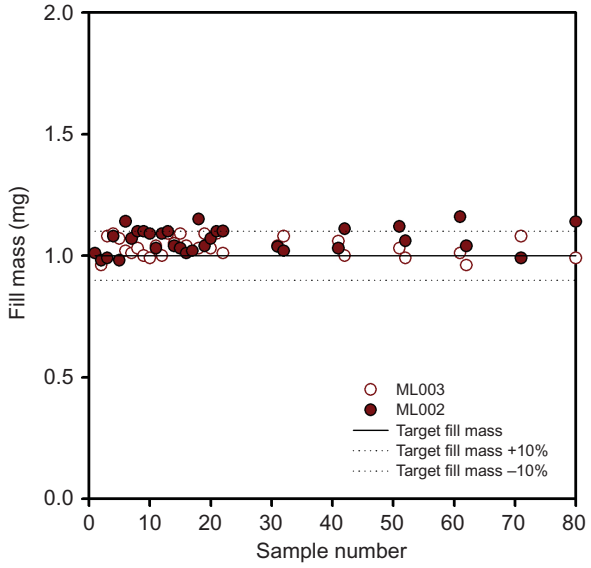

Figure 4. Laboratory scale filling behavior of Respitose® ML002 and Respitose® ML003 using the OMNIDOSE® TT filling technology at target fill mass of 1 mg.

This is mainly due to poor flowability and poor compressability (e.g., Lactosphere® MM3). Accordingly, Respitose® ML002 and Respitose® ML003, which possess powder physical properties in the proposed optimal region, were selected for further studies.

Laboratory scale placebo filling trial: 1 mg fill mass

To evaluate the possibility of filling lower masses of powder, as well as to challenge the previously defined optimal powder properties, attempts were made to fill Respitose® ML002 and Respitose® ML003 at a target fill mass of 1 mg. The results are presented in Figure 4 and Table 3. The two Respitose® powder grades were successfully filled at a target 1 mg powder fill mass with RSD values of 4.8% and 3.8% for Respitose® ML002 and Respitose® ML003, respectively. However, it can be seen from Figure 4 that there are several data points beyond the arbitrary ±10% range for ML003. This is because the difference in powder properties between ML002 and ML003 results in a slightly higher fill mass for ML003 (which has a slightly higher tapped density) when using the same drum cavity showing that the powder properties, including precompression, should be matched to drum cavity size when studying different powders. In contrast, the filling performance (not shown) of Lactosphere® MM3 at this fill mass produced an RSD of 8.9%. These data confirm the previously found optimal powder characterization design space and demonstrate the correlation between filling performance and powder characteristics and suggest that if the powder properties and drum cavity volume can be matched, and controlled, it should be possible to fill capsules at target masses with acceptable filling RSDs.

Effect of adding fine lactose monohydrate on filling performance

In pharmaceutical processes the level of fines in a formulation can have dramatic effect on the properties of a powder. This is particularly true for DPI formulations where fines affect not only the manufacturing process but also the product performance[15]. To investigate the effect of fines on powder filling, micronized lactose monohydrate (Lactosphere® MM3) was added to the previously selected excipients, Respitose® ML002 and Respitose® ML003, at 1% and 5% levels. The resulting blends were filled at target fill masses of 1 and 5 mg. The powder physical characteristics and filling performance are shown in Table 3.

In terms of powder properties, the addition of 5% micronized lactose monohydrate fines to Respitose® ML002 and Respitose® ML003 caused an increase of fine particle content [Q3 (10.5 μm)] by 6.6% and 4.7%, respectively. The increase in fine content also resulted in an expected decrease in bulk density and cavity density and an increase in CI. However, the effect on tapped density was less pronounced. This suggests that the powders containing additional fines are less compressed during filling compared to unadulterated Respitose® ML002 and Respitose® ML003. This observation correlates with the powder X90 and GSD data, which indicates that the higher the coarse particle fraction in the powder and the wider the PSD, the higher the powder compactibility.

The fill mass of the Respitose® ML002 and Respitose® ML003 with 5% Lactosphere® MM3 at 5 mg target fill mass is shown in Figure 5 and the fill mass of Respitose® ML002 with 1% and 5% Lactosphere® MM3 at 1 mg target fill mass is shown in Figure 6. It can be seen from Table 3

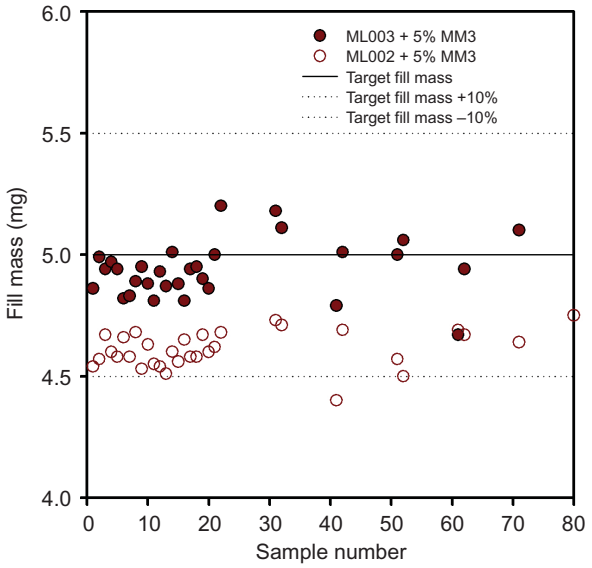

Figure 5. Effect of adding 5% fine lactose monohydrate to Respitose® ML002 and Respitose® ML003 on filling behavior using the OMNIDOSE® TT filling technology at a target fill mass of 5 mg.

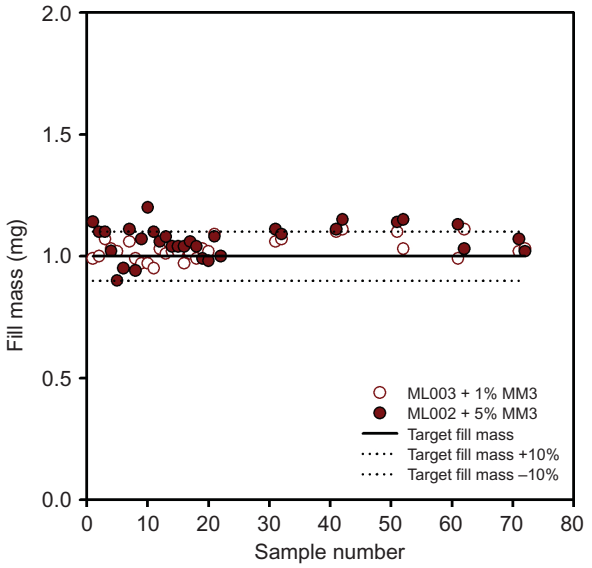

Figure 6. Effect of adding 1% and 5% fine lactose monohydrate to Respitose® ML002 on filling behavior using the OMNIDOSE® TT filling technology at a target fill mass of 1 mg.

and Figures 5 and 6 that variations in the level of fines do not dramatically impact the filling RSDs of the excipients within the range studied. However, it is clear that for lactose combinations which result in large changes in bulk and cavity densities the cavity volume may require modification to achieve a target fill mass. For example, the cavity volume for the Respitose® ML002 with 5% Lactosphere® MM3 blend may have to be modified to achieve the target fill mass of 5 mg, compared to Respitose® ML002. This is reflected in the relatively greater changes in the bulk and tapped densities and CI for this blend

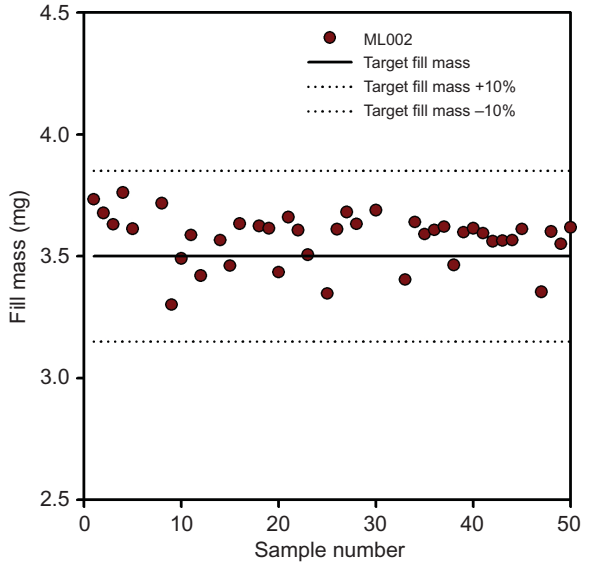

Figure 7. Pilot scale filling behavior of Respitose ML002 at a target fill mass of 3.5 mg.

confirming the effect that changes in powder density can have on the filling of powders in pharmaceutical operations. All powders gave acceptable filling variability except Respitose ML002 with 5% fines at 1 mg fill mass, where interestingly the X90 is below the proposed acceptable threshold of 50 µm.

Pilot scale placebo filling trial: 3.5 mg fill mass

In view of the initial success at filling lactose monohydrate excipients at laboratory scale, an initial pilot scale filling trial using the OMNIDOSE® DF1 was performed at a target fill mass of 3.5 mg using Respitose® ML002 with a batch size of 1000 capsules. The results are presented in Figure 7, for an example of 50 fill consecutive masses. It can be seen from Figure 7 that the filling of Respitose ML002 at a target fill mass of 3.5 mg is readily achievable with a filling RSD of 2.9%.

Aerodynamic assessment of the powder blends: pilot scale filling

As initial investigations have demonstrated that typical inhalation lactose monohydrate excipients can be readily filled at target masses of 1–5 mg, the possibility of filling a formulation was investigated at pilot scale. Two formulations were manufactured containing API concentrations of 1.25% and 7.5% (w/w) and Respitose® ML002. The formulations were homogenous with mean API contents of 101.3 ± 2.9% and 100.6 ± 2.2%, respectively. The 1.25% formulation was filled into size three hypromellose capsules with target fill masses of 4 and 25 mg and the 7.5% formulation was filled at a target fill mass of 4 mg. The batch size was set to 1000 capsules per fill mass. All powders were filled to acceptable target fill mass and exhibited fill mass variabilities of <5%. The API content uniformity in the capsules was determined

Table 4. Aerodynamic particle size distribution data of DPI formulations generated using an NGI at 90 L/min.

Formulation	FPF < 5.0 μm (% DC)	MMAD (μm)	GSD
1.25% API blend/4 mg fill mass	27.0 ± 0.7	3.30 ± 0.07	1.93
1.25% API blend/25 mg fill mass	32.2 ± 0.9	2.95 ± 0.03	1.96
7.5% API blend/4 mg fill mass	35.0 ± 1.1	2.95 ± 0.02	1.81

as 92.7 ± 2.1%, 94.2 ± 2.6% and 97.8 ± 3.18% of declared content for the 1.25% blend/4 mg fill mass, 1.25% blend/25 mg fill mass and 7.5% blend/4 mg fill mass samples, respectively. The aerosolization performance of the filled capsules is shown in Table 4. It can be seen from Table 4 that all the formulations produce FPF_{DC} values of 27–35% suggesting that acceptable fine particle doses could be achieved using this filling technology. An increase in the capsule fill mass from 4 to 25 mg using the same API 1.25% blend resulted in a 5% increase in FPF_{DC} and a decrease in MMAD from 3.30 to 2.95 μm. Moreover, increasing the API concentration per capsule at a fixed fill mass of 4 mg, resulted in a 7% increase in FPF_{DC} and a decrease in MMAD. The high fines/coarse particle ratio in the powder which contains the higher API concentration may allow the formation of agglomerates, which are more easily detached during the inhalation maneuver. It is also important to consider that the 1.25% API formulation filled at 25 mg/capsule and the 7.5% API formulation filled at 4 mg/capsule have similar API dose strengths per capsule; however, only a 2.8% increase in FPF_{DC} could be observed.

Overall these initial investigations suggest that the filling of typical carrier lactose monohydrate excipients at target masses of 1 and 5 mg is readily achievable using the OMNIDOSE® platform at laboratory and pilot scale. Two model DPI formulations were successfully filled into capsules at pilot scale. The formulations exhibited good aerosolization performance. Additionally, and importantly, any small changes in the fines content can be readily accommodated providing there is no significant affect on the tapped and cavity densities that may allow for any supplier variations in excipient batches. However, lactose monohydrate excipients with smaller PSD showed increased filling RSD, because fines are known to affect the bulk properties of powders. An additional advantage of the drum-based technology is that the drums can also be readily produced to contain cavities that can be used for a wide range of powder properties which may allow a wider range of excipient blends to be successfully used in DPI formulations.

Conclusions

The results of this initial study provide a useful insight into the potential of the OMNIDOSE® technology for the laboratory and pilot scale filling of powders which are typically used in DPI applications. At laboratory scale, masses of 5 and 1 mg of a range of DPI excipients could be successfully filled, with acceptable filling mass RSDs. Additionally, an initial pilot scale study of the filling of a DPI formulation showed that capsules which exhibited acceptable aerosolization performance could be produced at a target mass of 3.5 mg. In particular, and importantly, this investigation confirmed the benefit of studying the filling behavior of DPI formulations in laboratory scale equipment as indicators for formulation development and scale-up.

Acknowledgments

The authors thank Prof. Hartwig Steckel of the Christian Albrecht University, Kiel, for his assistance in powder physical characterization. They also thank Dr. Karlheinz Seyfang for his assistance in scaling up the OMNIDOSE® filling process.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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