Understanding DPI blends behaviour during high speed capsule filling

S. Abdrabo*, M. Fridez, T. Eggimann & R. Müller-Walz

Skyepharma AG, a member of the Vectura Group of companies, Eptingerstasse 61, 4132 Muttenz, Switzerland

* Corresponding author : sameh.abdrabo@vectura.com

Summary

Introduction: It is important to investigate the particle-particle interactions taking place in DPI formulations. These are cohesive (drug-drug), and adhesive (drug-carrier) interactions that play an important role in DPI performance during downstream processing such as capsule filling. Understanding such interactions helps in predicting problems such as aggregation or powder segregation, and controlling drug product quality. **Aim:** Understanding interparticulate interactions to predict DPI behaviour during high speed capsule filling for ensuring uniformity of weight and content. **Materials and Methods**: Three different powder blends of either a bronchodilator (X) or an ICS, Inhaled Corticosteroid (Y) or both (X plus Y) were manufactured with inhalation grade lactose as a carrier. All blends were characterized by dynamic testing (Basic Flowability Energy and Specific Energy), bulk measurements (Permeability and Compressibility), shear testing (Cohesion/Adhesion). Capsules of the three blends were filled by a high speed capsule machine dosator type. Fill weights and content uniformity were assessed. **Results and Discussion:** Capsule fill weight achieved was consistent for all blends, however slightly different content uniformity at higher filling speeds was found, which can be related to different drug-drug particle interactions and drug-carrier particle interactions. **Conclusion:** Similar DPI blends could react differently depending on the particle-particle interactions, therefore applying dynamic and bulk measurements as a characterization tool is valuable in understanding the behaviour of these blends in downstream process steps, and selecting the appropriate processing conditions accordingly to ensure that quality and robustness are built-in.

Introduction

Powders are considered a dispersion of solids in air with highly complex interparticulate interactions. In dry powder blends for inhalation, an active drug should be less cohesive and optimally adhesive to the carrier (usually inhalation grade lactose monohydrate) to allow both weight and content uniformity during DPI capsule filling, and also later during aerosolization from the device [1]. It is usually difficult to investigate the effect of individual physical properties such as surface free energy, mechanical interlocking, particle size, shape, surface roughness, particle deformation, and relative humidity on powder performance during processing or aerosolization one at a time [2,3]. Measurement techniques such as dynamic testing (Basic Flowability Energy and Specific Energy), bulk measurements (Permeability and Compressibility), and shear testing (Cohesion/Adhesion) can help to put these impactful physicochemical parts of the puzzle together to enable a better understanding about powder performance in downstream processing steps and during drug delivery [4,5]. The aim of this study was to investigate the effect of powder physical properties on capsule filling uniformity by a dosator type, high speed capsule filling machine. By investigating the physical properties, it will be feasible to apply the appropriate conditions in capsule filling of the DPI powder blends, to avoid problems such as aggregation, segregation, poor flow, adhesion, and cohesion in downstream processing. Measuring such physical properties should be routine for DPI powder blends characterization in line of QbD principles which require the elucidation of critical material attributes.

Experimental Methods

Manufacture of powder blends

Three powder blends were prepared at 2kg scale with lactose monohydrate as a carrier, one blend was a combination of a bronchodilator (X) and an inhaled corticosteroid ICS (Y), and the other two were mono product blends of the respective APIs (X) and (Y), respectively at the same individual API dose concentration as the combination blend. Dose concentration of X was 27 times higher than dose concentration of Y.

Capsule Filling

Capsule filling was performed with the continuous motion Planeta capsule filling machine (MG2; Italy), fitted with 4 dosators, and enabled 100% net weight check (MultiNett system), and statistical gravimetric net weight control. A high-speed capsule filling process for cohesive powder blends was developed using this pilot scale equipment which is easily and fully scalable to commercial batch sizes. The target fill weight was set to 25 mg/capsule with automatic rejection limits at ±5% (23.75 – 26.25 mg), and automatic adjustment of the dosator chamber to reach the target fill weight. Two different sets of dosators with an internal diameter of 2.8 mm and 3.4 mm were used. The machine speed was varied from 6'000 to 12'000 capsules/hour (25-50 rpm), with a run time of 1 hour. Stratified sampling of the capsules was performed throughout the filling process per batch, and capsule API assay was analysed by UPLC on these samples, to assess a potential effect of high speed capsule filling on API content and content uniformity.

Powder blends characterization

The three powder blends were tested for blend content uniformity and characterized by FT4 Powder Rheometer (freemantechnology; UK) in terms of the following (samples were measured in duplicate):

- Dynamic Testing: Basic Flowability Energy, Stability Index, Flow Rate Index, Specific Energy, Conditioned Bulk Density, and Aeration Ratio / Aerated Energy
- Bulk Measurements: Permeability and Compressibility
- Shear Testing: Shear Stress, Cohesion, Unconfined Yield Strength, Flow Function, Wall Friction Angle

Results

Powder blends characterization

All blends met the acceptance criteria of the content uniformity test (API Assay ≥ 95%; RSD ≤ 3%). Table 1 shows the results of dynamic, bulk property, and shear measurements.

Dynamic Measurements	**Blend Y**	**Blend XY**	**Blend X**
	Average± SD (n=2)		
Basic Flowability Energy, BFE (mJ)	79.2(±1.6)	123(±4.5)	103(±6.1)
Stability Index, SI	1.1(±0.01)	1.3(±0.01)	1.3(±0.04)
Flow Rate Index, FRI	1.9(±0.002)	5.3(±0.31)	3.3(±0.006)
Specific Energy, SE (mJ/g)	4.37(±0.05)	10.3(±0.32)	9.1(±0.42)
Conditioned Bulk Density, CBD (g/ml)	0.803(±0.006)	0.675(±0.01)	0.697(±0.01)
Aeration Ratio, AR_5	3.7(±0.2)	2.2(±0.2)	2.2(±0.03)
Aeration Energy, AE_5 (mJ)	20.1(±1.8)	36.5(±2.2)	30.8(±0.27)
Bulk Property Measurements	**Blend Y**	**Blend XY**	**Blend X**
Pressure Drop, $PD_{15,2}$ (mbar)	17.3(±0.22)	37.1(±0.33)	32.0(±0.5)
Permeability, $k_{15,2}$ x10^9 (cm^2)	3.4(±0.01)	1.4(±0.02)	1.6(±0.04)
Compressibility, CPS_{15} (%)	16.8(±0.3)	26.8(±0.2)	25.2(±0.6)
Shear Measurements	**Blend Y**	**Blend XY**	**Blend X**
Shear Stress, $\tau_{7,9}$ (kPa)	4.1(±0.11)	6.1(±0.01)	6.0(±0.2)
Shear Stress, $\tau_{3,9}$ (kPa)	2.1(±0.006)	3.5(±0.05)	3.4(±0.2)
Flow Function, FF	6.7	3.0	3.0
Wall Friction Angle, $WFA_{1.2\mu m}$ (°)	19.5	26.4	23.3

Table 1 - Powder blends characterization by FT4 Powder Rheometer

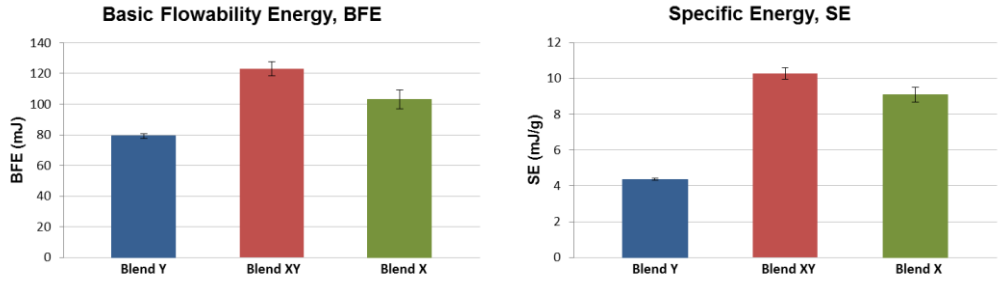

Figure 1 – Basic Flowability Energy and Specific Energy of the DPI blends

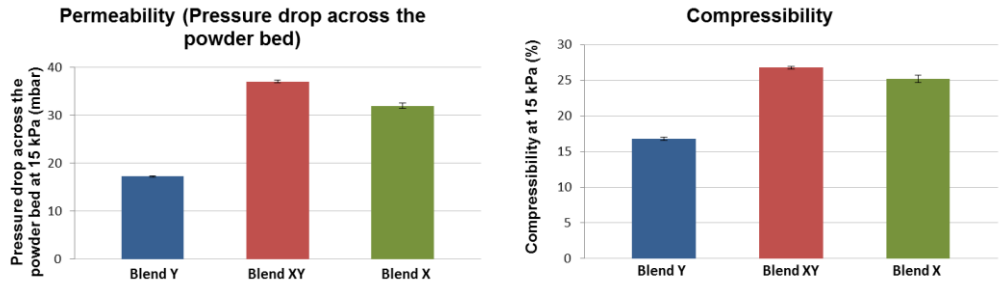

Figure 2 – Permeability and Compressibility of the DPI blends

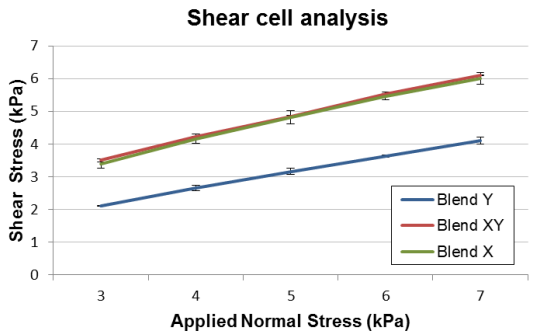

Figure 3 – Shear cell analysis of the DPI blends

As shown in Table 1 and Figures 1-3, the blend comprising Y differs significantly ($p<0.05$) from the powder blends containing drug substance X either alone or in combination with Y in terms of Basic Flowability Energy BFE, Specific Energy SE, and Flow Rate Index FRI, Aerated Energy AE, Compressibility, Permeability and Shear Stress values.

Capsule Filling

Table 2 shows capsule filling results in terms of fill weight accuracy. Overall, all powder blends showed good capsule filling performance in terms of fill weight and RSD. The larger dosators (diameter 3.4 mm) were used only once and resulted in a higher variability in fill weight compared to the smaller dosators with 2.8mm diameter (batches 1B to 1A). For all three blends, slightly smaller fill weight variability was seen for the batches filled at higher speed. All fill weight distributions showed a Normal distribution.

Batch	**1A**	**1B**	**3A**	**3B**	**4A**	**4B**	**5A**	**5B**
Active ingredient	Y	Y	Y	Y	X	X	XY	XY
Dosator diameter [mm]	2.8	3.4	2.8	2.8	2.8	2.8	2.8	2.8
Filling speed [caps/hr]	12,000	12,000	6,000	10,000	6,000	10,000	6,000	10,000
Conforming capsules filled	9,974	8,509	5,838	9,539	4,073	9,626	4,070	9,638
Non-conforming capsules	22	798	115	19	287	83	135	182
Non-conforming capsules [%]	0.22	9.38	1.97	0.20	7.05	0.86	3.32	1.89
Fill weight average [mg]	24.98	25.04	24.80	24.96	25.02	25.02	25.03	25.03
Fill weight RSD [%]	1.57	2.15	1.85	1.65	2.17	1.69	2.09	1.83

Table 2 – Capsule filling parameters and results. The fill weights shown were measured from the 100% capacitive weight control system (MultiNett). Rejection limits were set at ±5% (23.75 – 26.25mg)

The API content in the capsules was analysed for batches 3, 4 and 5. For batch 3 (single API, Y), very stable assay results were obtained, the initial higher value for batch 3A can be linked to a higher fill weight at the start of filling. Batch 4 (single API, X), showed more variability in the results, especially at a speed of 10'000 capsules/hour (time 0 and 60 minutes), see Figure 4. For the combination batch (batch 5), slightly variable assays were obtained for both actives, see Figure 5.

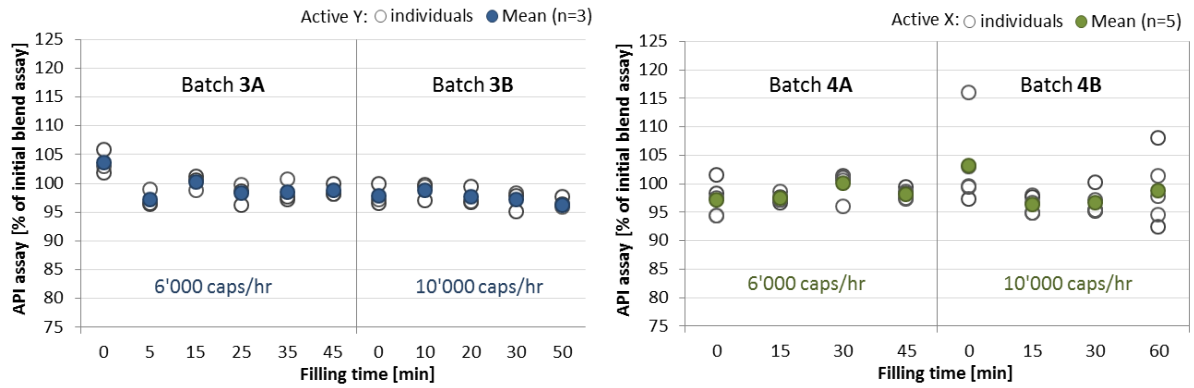

Figure 4 – Capsule content results of the single API batches filled with the 2.8mm Ø dosators at different speeds

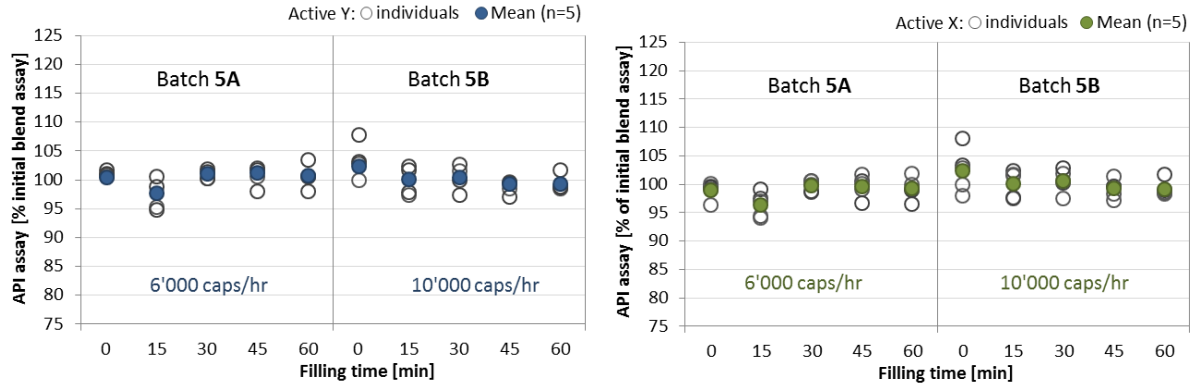

Figure 5 – Capsule content results of the combination batch filled with the 2.8mm Ø dosators at different speeds

Discussion

Blend Y showed a significantly lower Specific Energy (SE) ($p<0.05$) indicating less mechanical interlocking and friction, Figure 1; the lower Aerated Energy (AE), ($p<0.05$), in comparison to blends containing X (Table 1) indicates that this blend has the lowest cohesion, hence better flow resulting in more uniform capsule filling. The lower Compressibility and Permeability values ($p<0.05$), Figure 2; also indicate a denser particle packing, a characteristic of free-flowing powders. Also, blend Y showed a lower shear stress value in comparison to blends containing X ($p<0.05$), Figure 3, confirming the better flowability of the Y blend. On the other hand, the combination blend containing X and Y showed the highest Basic Flowability Energy (BFE), Figure 1, and the highest Flow Rate Index, as shown in Table 1 indicating the highest resistance to flow, which is characteristic for cohesive powders. Moreover, as shown in Figure 2, this blend together with the mono blend containing X had the highest Pressure Drop across powder bed i.e. the least permeability, and the highest Wall Friction Angle (WFA), Table 1, which further confirms the cohesiveness of blends containing X. It can be assumed that active X having a higher concentration in the blend; it dominates the properties of the blend. All these results explain why blends containing X as mono blend or in combination showed larger variability in capsule content (Figures 4, 5).

Conclusion

Dynamic, bulk property, and shear measurements using the FT4 Powder Rheometer correlated well with the results from the capsule filling process, and can be used as a predictive tool in the formulation screening of blends for high speed capsule filing. The results showed clearly that the cohesiveness of blends containing the active drug X resulted in slightly more variable filling into capsules mainly at higher speeds, while a more uniform content was found for the powder blend with drug Y due to better flow.

Acknowledgment

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