DPI inhalation performance optimization through API micronization design

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Summary: The inhalation performance of a Dry Powder Inhaler (DPI) are strictly correlated to the critical quality attributes (CQA) of the Active Pharmaceutical Ingredient (API). Particles typically need to be within the 1-5 µm aerodynamic diameter range in order to reach the airways [1]. Such dimensions are usually targeted by means of micronization of the crystalline API. A widely used micronization equipment is the jet-mill apparatus in which micronization is achieved by air or nitrogen at very high pressure. The two main Critical Process Parameters (CPP) which directly affect the API particle size are the micronization pressure and the feed rate. This was demonstrated by a Principal Component Analysis (PCA) that took into consideration four of the main API CQAs affecting the DPI Fine Particle Fraction (FPF) (particle size distribution, particle specific surface area, Cohesion Adhesion Balance (CAB) and amorphous content), micronization pressure and feed rate. As a consequence, a direct correlation between DPI FPF with both API CQAs related to particle dimension (particle size distribution and specific surface area) and CPPs of the micronization process was observed. The two CPPs were studied by means of a Design of Experiment (DoE) approach to obtain a validated model able to directly predict the DPI FPF resulting from the formulation manufactured starting from the obtained micronized API. An equation correlating the DPI FPF with the micronization pressure and feed rate was obtained, demonstrating the possibility to modulate the desired DPI inhalation performance by directly controlling the micronization parameters.

Introduction: DPIs use in clinical practice is increasing. However, the development of a formulation for inhalation is challenging. Obtaining the API in the proper size range and identifying the CQAs that could affect its aerodynamic behavior is one of the challenging steps during development. API size reduction is usually obtained by micronization which is recognized as the standard and the most common process to obtain particles with dimensions suitable for inhalation (about 1-5 µm) [2]. The main CPPs that could influence the efficiency of API particle size reduction are the feed rate and milling pressure. By modulating these CPPs it is possible to obtain micronized APIs with very different characteristics, including particle size distribution (PSD), cohesiveness, specific surface area and amorphous content. These are all API CQAs that can influence the manufacturability of the formulation (e.g. API homogeneity within the blend), and the aerodynamic behavior of the resulting formulation (e.g. consistent and efficient API de-aggregation). If we were able to associate the micronization CPPs range with the DPI aerodynamic behaviour, we could define the operational space in which to obtain the optimal DPI inhalation performance. Quality by Design (QbD) approach can be successfully applied to optimize and shorten formulation feasibility studies.

Methods: The tested DPIs were prepared mixing the selected API with a carrier (lactose) and a ternary agent to reach a final API concentration of 0.5 %. The API was micronized by means of Jet Milling (chamber diameter=10 cm) and twin screw feeders as the feeding device [3], [4]. The API particle size distribution was obtained by means of a Mastersizer 2000 instrument equipped with a Hydro 2000µP measurement cell (Malvern, Malvern, UK) using cyclohexane containing SPAN 85 as dispersant. The API specific surface area was measured using the B.E.T. algorithm by means of a Tristar analyzer equipped with a Flow Prep 060 sample degas system (Micromeritics, Norcross, GA, USA). The API amorphous content was quantified by means of isothermal gas perfusion calorimetry (IGPC) using a 2277 Thermal Activity Monitor (TA Instruments Ltd, New Castle, DE, USA). The API cohesiveness value with respect to lactose and ternany agent was evaluated by means of a Nanoscope Atomic Force Microscope using the colloid probe measurement technique [5]. The inhalation performances were obtained using a Fast Screening Impactor (FSI) equipped with a 100L/min insert and an additional pre-separator (Copley Scientific, Nottingham, UK) and a validated RP-HPLC/UV isocratic method (HPLC/UV 2690/2695 Alliance equipped with a chromatographic column Atlantis C18, 3.0 µm, 100x2.1 mm, Waters, Milford, MA, USA). For the DoE approach, the results were elaborated using programs written for the Matlab environment (MathWorks, Natick, MA, USA). The DoE approach [6], [7], [8], creates a model which correlates the experimental responses with the investigated variables and can be used to predict the outcome of the experiments that were not performed. The PCA converts a set of responses of possibly correlated variables into a set of values of linearly uncorrelated variables called Principal Components. PCA defines a new orthogonal coordinate system that optimally describes the experimental variance in a single dataset [9].

Results:
The API micronization process was investigated by means of a DoE approach in order to obtain a model able to correlate the API CQAs and the DPI FPF with the two main micronization CPPs: the feed rate and the micronization pressure. API PSD was represented only by d(v, 0.9) as the most representative value of the complete API particle population. A full factorial design 2^2 was considered with a validation point performed in triplicate. The feed rate ranged from 6 to 10 g/min, while the micronization pressure from 2.5 to 7 bar. The Uncoded and Coded matrixes of the performed experiments with the obtained results are reported in Table 1 and

2, respectively. In the Uncoded matrix the actual CPPs values are shown, while in the Coded matrix the actual CPPs values are re-scaled in the range from -1 to +1.

Exp. Nr	Micron. Pressure (bar)	Feed rate (g/min)	d(v, 0.9) (µm)	Specific surface area (m^2/g)	Amorphous content (%)	CAB *vs* lactose	CAB vs ternary agent	FPF (%)
1	2.5	6.0	8.0	4.4	1.0	1.0	0.4	49.0
2	7.0	6.0	3.0	6.8	8.2	0.9	0.6	76.4
3	2.5	10.0	8.7	3.9	5.0	0.7	0.6	46.0
4	7.0	10.0	3.6	6.3	9.6	1.2	0.3	75.3
5	4.0	7.4	4.8	5.0	9.0	1.9	1.2	64.3
6	4.0	7.4	5.1	5.1	8.0	1.2	1.1	64.2
7	4.0	7.4	5.2	5.2	5.3	0.7	0.3	67.5

Table 1: Uncoded matrix of the experiments

Exp. Nr	Micron. Pressure (bar)	Feed rate (g/min)	d(v, 0.9) (µm)	Specific surface area (m^2/g)	Amorphous content (%)	CAB *vs* lactose	CAB vs ternary agent	FPF (%)
1	-1	-1	8.0	4.4	1.0	1.0	0.4	49.0
2	+1	-1	3.0	6.8	8.2	0.9	0.6	76.4
3	-1	+1	8.7	3.9	5.0	0.7	0.6	46.0
4	+1	+1	3.6	6.3	9.6	1.2	0.3	75.3
5	-0.3	-0.3	4.8	5.0	9.0	1.9	1.2	64.3
6	-0.3	-0.3	5.1	5.1	8.0	1.2	1.1	64.2
7	-0.3	-0.3	5.2	5.2	5.3	0.7	0.3	67.5

Table 2: Coded matrix of the experiments

The obtained data were initially elaborated by a PCA in order to verify the correlation between the micronization CPPs, the API CQAs and the DPI FPF. As highlighted in Figure 1, the DPI FPF appeared strongly correlated to the micronization pressure, specific surface area (FPF is very close to micronization pressure and BET in the PCA loading plot) and to d(v,0.9) (opposite positions with respect to the plot centre of the PCA loading plot), it showed a little correlation with the feed rate (feed rate is very close to the centre of the PCA loading plot), while it was not correlated with CAB and amorphous content (orthogonal positions with respect to the plot centre of the PCA loading plot).

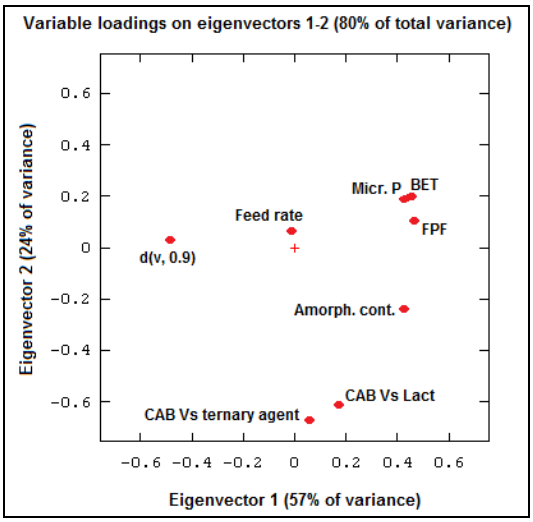

Figure 1: PCA loadings of the API CQAs, micronization CPPs and DPI FPF

Considering the observed correlation of the CPPs, with the d(v,0.9) and BET CQAs, a mathematical relationship to describe such correlation could be written. A linear equation was verified for both CQAs. The model reported in eq. 1 was postulated:

$$d(v,0.9) \text{ or } BET = b_o+b_1*X_1+b_2*X_2+b_{12}*X_1*X_2 \quad \text{(eq. 1)}$$

Where:
b_0 = constant
b_1, b_2, b_{12} = variable coefficients
X_1 = micronization pressure (coded value)
X_2 = feed rate (coded value)

Applying a Multiple Linear Regression Analysis (MLRA) to the data of the experiments 1-4, the following equations were obtained (eq. 2 and 3):

$$d(v0.9)\ (\mu m) = 5.83 - 2.53*X_1 \quad \text{(eq. 2)}$$

$$BET\ (m^2/g) = 5.45 + 1.27*X_1 - 0.25*X_2 \quad \text{(eq. 3)}$$

Since from the PCA the two CQAs BET and d(v,0.9) are correlated to the DPI FPF and the two CQAs are also correlated to the micronization CPPs, a mathematical model able to directly correlate the DPI FPF with the micronization CPPs could be obtained.
At the beginning, a linear correlation between DPI FPF and the micronization CPPs was verified. The same model reported in eq. 1 for BET and d(v,0.9) was postulated.
Applying a MLRA to the data of the experiments 1-4, the following equation was obtained (eq. 4)

$$FPF = 61.68 + 14.18*X_1 - 1.03*X_2 + 0.48*X_1*X_2 \quad \text{(eq. 4)}$$

By using the data of the validation point (experiments 5-7), the model resulted not validated; in spite of a DPI FPF predicted value of 57.2% by the model, the DPI FPF experimental value of 65.3 ± 1.9% was obtained.
It was therefore decided to use the validation point to build a quadratic model. The model reported in eq. 5 was postulated:

$$FPF = b_o+b_1*X_1+b_2*X_2+b_3*X_1*X_2+b_4*X_1^2+ b_5*X_2^2 \quad \text{(eq. 5)}$$

Where:
DPI FPF = DPI Fine Particle Fraction
b_0 = constant
b_1, b_2, b_3 ,b_4, b_5 = variable coefficients
X_1 = micronization pressure (coded value)
X_2 = feed rate (coded value)

Applying a Multiple Linear Regression Analysis (MLRA) to the data of the experiments 1-7, the following equation was obtained (eq. 6)

$$FPF = 69.98 + 14.18*X_1 - 1.03*X_2 + 0.48*X_1*X_2 - 4.15*X_1^2 - 4.15*X_2^2 \quad \text{(eq. 6)}$$

The model was used in the routine API micronization process during the product development and provided the expected results allowing the delivery of the desired DPI FPF by directly modulating the micronization pressure and the feed rate of the jet milling machine.

Conclusion: Performing the feasibility experiments by using a DoE approach and elaborating the obtained results by means of MLRA, a mathematical equation able to calculate the DPI FPF starting from the API micronization CPPs was achieved. This approach allowed to deeply understand the effect of the micronization process parameters on the DPI inhalation performance and to speed up the product development.

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