Powder Technology 301 (2016) 830–838

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Multivariate data analysis to assess dry powder inhalers performance from powder properties

Andrea Elia [a,b], Marina Cocchi [a,*], Ciro Cottini [b,*], Daniela Riolo [b], Claudio Cafiero [b], Roberto Bosi [b], Emilio Lutero [b]

[a] Department of chemical and Geological Sciences, Via Campi 103, 41126 Modena, Italy
[b] Chiesi Farmaceutici S.p.A., Dept. of Chemistry, Manufacturing & Control, Largo F. Belloli 11/A, 43122 Parma, Italy

ARTICLE INFO

Article history:
Received 19 February 2016
Received in revised form 1 July 2016
Accepted 2 July 2016
Available online 4 July 2016

Keywords:
Dry powder inhaler
PLS regression
VIP
Powder characterization tests
DUSA
NGI

ABSTRACT

The study aimed at investigating the correlations among the physical and bulk properties of carrier based dry powder inhaler formulations and the performance of the powder inhaler device estimated by in-vitro tests for a specific active pharmaceutical ingredient (API), and at obtaining predictive models for the in-vitro performance. Samples from scale-up process batches having different formulations, process settings and bulk size, were characterized by rheological, density and particle size tests. In vitro performance was evaluated by several parameters obtained by a dosage unit sampling apparatus (DUSA) and a next generation impactor (NGI). Correlations between powder properties and performance properties were established using partial least square (PLS) regression analysis. Variable importance in projection (VIP) was used in order to assess the most influential powder characterization variables to estimate the analytical ones. Particle size, density and rate of flowability are significant for modeling the Delivered Dose of the API and the total quantity of powder related to each dose. Powder characterization variables, describing the degree of cohesiveness and the flow properties of powder, are related to the total amount of the active ingredient for different formulations. DUSA test variables were satisfactory predicted on the basis of powder characterization variables, while NGI performance variables were predicted with higher error.

1. Introduction

Dry powder inhalers (DPI) are devices that deliver a dry powder formulation of drug to the lungs [1–3]. Their development was initially promoted as an alternative to pressurized metered dose inhaler (pMDI), following the Montreal Protocol [4] of the 1987, which provided for the non-use of ozone reducer propellants in medicinal products. In addition of being propellant free, DPIs possess higher stability with respect to the liquid state [4]. Moreover, DPI based on passive devices are directly activated by the patient's respiratory airflow, so provide a general optimization between actuation and inhalation [5–7]. DPI formulations are mainly mixtures of drug and coarse particles of lactose based excipients. α-lactose monohydrate sugar is the most used and FDA approved and it is used as the main excipient. It is able to fluidize and disperse the drug whose particles are in the breathable size range, while it is not delivered to the lungs. Other components, such as fine particle lactose and magnesium stearate, can be used in the formulation in order to optimize the de-agglomeration of drug particles from the large carrier particles. The active ingredient can be designed as a target for a generic or specific respiratory disease, such as asthma and COPD (chronic-obstructive-pulmonary-disease). It has to adhere to the carrier's surface during the manufacturing process and keep this status during the shelf-life of the product, but it has to de-aggregate during the delivery phase, to follow the inspiratory flow and to reach the deposition site. As powder is transported from the device to the lungs of the patient as an aerosol, it becomes important to understand how it flows under gravity when consolidated, unconsolidated, aerated or even fluidized, and how readily it will entrain air and release it again. Important powder properties include particle size, shape, density, cohesion, aeration, dynamic flow and shear properties [8]. Several studies have shown that physico-chemical carrier properties and cohesive-adhesive force balances between drug and carrier have an influence on the in-vitro aerosol deposition [9,10]. In particular, performance was optimized when the drug-carrier cohesion–adhesion balance ratio was slightly cohesive. Moreover, aerosol performance resulted dependent also on the device's design and patient's inspiratory force. Devices with greater aerosol resistance resulted in greater FPF values. In this sense, tuning of the resistance to airflow in the design of a dry powder inhaler may improve the drug deposition in the respiratory tract, as in the case of passive devices [11]. Understanding powder flowability, fluidization, de-agglomeration and in general all physico-chemical powder

* Corresponding authors.
E-mail addresses: A.Elia@chiesi.com (A. Elia), marina.cocchi@unimore.it (M. Cocchi), C.Cottini@chiesi.com (C. Cottini).

http://dx.doi.org/10.1016/j.powtec.2016.07.002
0032-5910/

properties, leads to a better knowledge of the overall delivery system [12].

It is also important to understand how these properties may be affected by process parameters, especially during the scale-up of a product [13,14]. Mixing, sieving, filling, granulation and in general all process operations can modify powder characteristics, and their effects should be taken into account in order to obtain a reliable process and a product with the required characteristics [15–18]. In this sense, measuring powder properties within or at the end of the manufacturing process, can give information on the quality of the product, before executing in-vitro analytical tests of performance. These tests are essential and mandatory before proceeding to the subsequent phases of the drug development, but are very time-consuming. NGI (next generation impactor) and DUSA (dosage unit sampling apparatus) analysis can take few days of execution and, even more important, can be preceded by a quarantine period of samples storage. Consequently, other scale-up batches may have been already manufactured during this period, without taking advantage of the suggestions that the previous results can give.

Powder characterization tests [19] require a shorter time of execution. Some tests, such as aeration, density and flowability tests require less than 15–20 min of execution, while others, such as Shear Cell Test, usually last less than 1 h. All tests employed in this work can be performed in a half-day work per sample, ideally at the end of the production of powder bulk. Gathering information in a shorter time can bring benefits in scale-up activities, which often require shortcuts.

Most of the research undertaken in this area has emphasized the influence of some chemical-physical properties on the DPI performance, mainly by studying one property at time, i.e. using a univariate approach [20,21]. However, studying the properties altogether can lead to a better understanding of the performance in term of the overall behavior of the powder as determined by the inter-play of several physico-chemical properties. It is well recognized that a multivariate approach improves data analysis efficacy and process understanding [22–25]. Here, we apply multivariate data analysis to the data arising from several powder characterization tests and in-vitro performance tests. In particular, principal component analysis (PCA) is used as an explorative data analysis tool in order to extract salient traits of the studied batches and the correlation structure of measured variables, and partial least square (PLS) regression is used in order to establish correlations among one or more performance variables and the powder characterization variables with the aim of obtaining predictive models. In order, to assess which are the most relevant features to estimate the performance variables and to improve the overall interpretability of the models, the Variance Importance in Projection (VIP) parameter has been used [26,27]. To the best of our knowledge this is the first study attempting to predict DPI performance from powder characterization tests in scale-up phase.

2. Materials and methods

2.1. Samples

The study is undertaken at the scale-up step of drug development, i.e. at the phase where, after laboratory scale optimization the product is tested at pilot plant level before passing to plant manufacturing. A total of 27 samples were taken at the end of pilot manufacturing process of batches of powder. Formulations consisted of excipient and one active ingredient. The excipient used was alpha-lactose monohydrate based. The active pharmaceutical ingredient (API) was a target molecule designed for a generic or specific respiratory disease, such as asthma and COPD (chronic-obstructive-pulmonary-disease). Five different formulations were used, respectively named A, B, C, D and E, increasing the amount of active ingredient from A to E. The batches differed for bulk size, process parameters and starting materials. The manufacturing process consisted in the excipient mixing, the addition of the active principle, mixing and sieving step. Process parameters were set according to the batch size and the information derived from the scale-up process. The formulation, as well as the process, is under development, so that any additional detail cannot be provided at the moment. Despite of this, the manufacturing procedure was optimized for each formulation, and all the results in terms of blend uniformity analysis were satisfactory. In particular, the expected quantity of active ingredient (as mean of 40 samples of 20 mg each taken from the bulk) was inside the acceptance criteria (90.0–110.0%), with a relative standard deviation of no more than 5.0%.

The resulting powder was placed into a generic dry powder inhaler either manually (22 samples) or using an instrumental filling procedure (5 samples).

Each sample consisted of 500 g of powder and two devices taken at the end of the manufacturing process. The 500 g were characterized by powder characterization tests within one–two days from production, while the two devices were analyzed for the in-vitro performance by DUSA and NGI tests in a period that ranges from fourteen to twenty days, this is due to the higher time required for the in vitro tests and the internal organization of the laboratory at the company. All tests were performed in controlled conditions of humidity and temperature. The different time periods between characterization and in-vitro tests support the aim of this study, which is to obtain predictive information on DPI performance as soon as possible during the scale-up activities. As mentioned before, this work is about the investigation of all possible correlations between the properties of the powder and its inhalation performance. To this aim, having collected batches that well span the manufacturing variability is an advantage in order to obtain a general correlation model.

The evaluation of the effects of the parameters and materials on performance is not reported here, and it will be dealt in a coming study.

2.2. Powder characterization tests

2.2.1. Density

Poured Density and Tapped Density of powder samples were measured using the jolting Stampf Volumeter STAV 2003 (from Engelsmann, Germany). A measured amount of powder was introduced into a cylinder of 250 ml. Poured Density refers to the initial mass/volume ratio. Tapped Density was measured by mechanically and vertically tapping the cylinder under its own weight and considering the final volume obtained.

2.2.2. Particle size distribution

Particle size determination of powder samples was performed with the Vibratory Sieve Shaker AS 200 Control (from Retsch, Germany) on the powder samples. The powder was fractionated according to the different sieves: 425 μm, 355 μm, 300 μm, 250 μm, 212 μm, 200 μm and 180 μm. The achievement of full sieving was assured with a sieving time of 25 minutes, as tested in our laboratory. The corresponding variables are the percentage of powder with particle size under these sieve size values.

2.2.3. Stability & Variable Flow Rate

FT4 Powder Rheometer (from Freeman Technology, UK) was used in order to measure dynamic flow and shear properties of powder.

Stability & Variable Flow Rate properties were determined by combining seven conditioning and test cycles (for the Stability test: test1–test7) and four conditioning and test cycles (for the Variable Flow Rate: test8–test12). Measurements were performed in triplicates. The used vessel size was 25 mm. Blade tip speed was 100 mm/s for the Stability test cycles, while 100, 70, 40 and 10 mm/s for the variable flow rate test cycles. The measured parameters were the Basic Flowability Energy BFE (mJ), the Stability Index SI, the Flow Rate Index (FRI), the Specific Energy (SE) (mJ/g) and the Conditioned Bulk Density (CBD) (g/ml). BFE is the energy required to move a conditioned and stabilised powder at a given speed of rotation of the blade. SI is a factor describing