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High shear mixing of lactose and salmeterol xinafoate dry powder blends: Biopharmaceutic and aerodynamic performances

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ABSTRACT

This work aimed to investigate the effect of a high shear mixer on the biopharmaceutics and aerodynamic performances of salmeterol xinafoate/lactose blends for inhalation. The influence of mixing energy during blending on powder bulk properties, aerosolisation and *in vitro* dissolution rate of drug was studied. There was a clear dependence of the blends bulk characteristics on the mixing rate and time that affected the emitted dose. The fine particle dose or respirable fraction of salmeterol xinafoate was favored by the mixing intensity leading to the disaggregation of the drug particles. An important dependence of the extra-fine drug particles on the mixing conditions was determined. The effective dispersion on the carrier particles of the salmeterol xinafoate improved the dissolution rate of the drug from the blend. This was due to the drug particle size distribution in the blend. When the fine particle dose of different blends was dissolved, no differences among the dissolution rates were observed.

1. Introduction

Dry powder inhalers (DPIs), developed to avoid coordinated inhalation act and chlorofluorocarbons propellant issues of Metered Dose Inhalers, are still object of intense studies [1,2]. Several drugs to treat asthma or chronic obstructive pulmonary disease, such as β-agonist, corticosteroids and muscarinic receptor antagonists, are delivered from DPIs at very low dose (2–600 μg). As a consequence, in order to prepare a product mass facilitating the uniform filling of devices and the efficient delivery of drug, in most cases their formulation with bulking excipients is mandatory [3]. DPI formulations are often blends of a small quantity of micronized active ingredient with a larger amount (between 5 and 20 mg) of coarse lactose used as carrier. Due to the different drug and carrier characteristics, the blending process requires numerous operative steps and is time consuming. In order to disperse the drug onto the carrier, the cohesive forces between drug microparticles have to be broken up using mechanical energy [4]. In inhalation technology the blending process has to construct an ordered mixture in which drug microparticles are stuck on the larger carrier surface. The ordered mixture guarantees homogeneity and stability of the formulation but, at the same time, the detachment during aerosolisation of fine drug particles should not be hindered. During inhalation, the air turbulence strips off the drug microparticles from the carrier surface and drags them into the lungs, according to their aerodynamic size [5]. Delivering a homogeneous and stable ordered mixture with high respirable fraction of drug is the requirement of a high quality inhalation product.

Frequently, the preparation of ordered powder blends for

Abbreviation: ED, emitted dose; DPI, dry powder inhaler; FPD, fine particle dose; FPF, fine particle fraction; MMAD, mass median aerodynamic diameter; NGI, next generation impactor; SX, salmeterol xinafoate.

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inhalation is carried out by low shear tumbling mixing, such as with the Turbula® apparatus, known for shaking-mixing in a closed container small quantities of powders. Recently, the quick and intense process of high shear mixing was proposed as an alternative to the low shear blending process, with the objective of reducing the mixing time and improving the dispersion of fine material in the coarse particle bed [6]. It was shown that a high shear blending process could induce changes in the morphology and water sorption characteristic of lactose [7]. Moreover, the formation of high-energy sites could affect the formulation physicochemical properties [7–9]. A previous publication on the aerosolisation of undisclosed drug/lactose blends obtained with DIOSNA high shear mixer showed that the fine particle dose of formulations decreased as the mixing energy increased [10]. However, few data exist on drug/lactose blends focusing on the effect of mixing not only on the aerodynamic aspects but also on the *in vitro* availability of drug.

Since the high shear mixing could produce, in a very short time, homogeneous dispersion of micronized drug on the carrier surfaces, the aim of this work was to investigate how the process energy of a high shear mixer could influence the aerodynamic and biopharmaceutical performances of blends for inhalation. In particular, the influence of "energy input" during dry powder blending on bulk properties, aerosolisation and *in vitro* dissolution rate of powder blends containing salmeterol xinafoate (SX) and lactose was studied.

The research hypothesis was that a different high shear mixing mechanism might positively affect the respirability and *in vitro* availability of salmeterol xinafoate from lactose blends for inhalation. Four blends of micronized salmeterol xinafoate and α-lactose monohydrate were prepared with a mixer combining high shear and high impact forces. The effect of different mixing speeds and times was investigated through the *in vitro* aerodynamic behavior and dissolution rate of SX.

A pre-metered capsule-based device and a multi-dose metering device were employed for the aerosolisation of SX blends, in order to provide different de-agglomeration capabilities. The results of mixing procedures, i.e., the adhesion between drug and carrier, were quantified as drug respirability from the formulations. In addition, the dissolution rate of SX in the different blends was performed before and after the aerosolisation with two inhalers.

2. Materials and methods

2.1. Materials

Salmeterol xinafoate was obtained by Midas Pharma GmbH (Ingelheim am Rhein, DE) and micronized at dv_{50} of 1.99 μm. α-lactose monohydrate (Respitose® SV003, particle size 30–100 μm) was received from DFE Pharma (Goch, DE). All solvents used were of analytical grade. Water was purified by reverse osmosis (MilliQ, Millipore, Guyancourt, FR).

Two types of Dry Powder Inhalers having different de-agglomeration properties were used. The RS01® inhalation device was a gift of Plastiape S.p.a. (Osnago, LC, IT). It is at medium resistance (air flow rate 60 L/min), single dose capsule device characterized by high de-agglomeration power [11]. Hydroxypropylmethylcellulose (HPMC) capsules (size 3) were a gift from Capsugel (Colmar, FR). Easyhaler® (Orion Corporation, Espoo, FI) (air flow rate 45 L/min) is a multiple dose powder inhaler that can deliver up to two hundred doses [12].

2.2. Blend preparation

The blends were obtained with the Picomix high-shear batch mixer for dry powders (Hosokawa Alpine, Augsburg, DE). The mixing element rotates in a conical vessel for blending of very small powder batches. The composition of the blends was designed to match the commercially available formulation of Serevent® Diskus® that is 72.5 μg of salmeterol xinafoate in 12.5 mg of formulation with lactose monohydrate. Micronized SX and the carrier α-lactose monohydrate (SX content at 0.58% w/w) were mixed with four different mixing programs. The mixing time and speed were adjusted to provide different "energy input" during the mixing process. Operating parameters for the manufacture of the powder blends using Picomix® high shear mixer are illustrated in Table 1.

Each blend was analyzed after 1 week of storage in sealed glass vials at room conditions to avoid relaxation effect of the materials.

2.3. Drug content uniformity of blends

Twelve samples for each blend were randomly taken from the mixtures removed from the mixer and the SX content was quantified. Briefly, 20 mg of powder samples, accurately weighed, were dissolved in 25 ml of water:methanol mixture 25:75. The solutions were filtered (0.45 μm, PTFE, Sartorius, Germany) before injection. Quantitative determination of SX was carried out by HPLC. The chromatographic system used was an Agilent 1200 series (St Claire, CA, USA). A SymmetryShield™ Reverse Phase C8, 5 μm 3.9 × 150 mm column (Waters corp., USA) maintained at 40 °C was used. The analyses were carried out under the following operating conditions: the eluent was acetonitrile:methanol:water solution (30:30:40) with the addition of 0.1% of tetrabutylammoniumhydrogen sulphate and adjusted to pH 3.0 with ammonium acetate M solution. The flow rate was 1 ml min^{-1} and the injection volume 50 μl. The UV detector was set at wavelength of 228 nm. In these conditions the retention time of salmeterol free base was about 6 min. Detector signal processing was performed using Chemstation Agilent software. The linearity of salmeterol xinafoate response, evaluated with standard solutions, gave a R^2 correlation coefficient >0.99, in the concentration range between 0.04 and 13 μg/ml. The precision of the method was 0.90%.

2.4. Morphological analysis

The morphology of the powders was determined by Scanning Electron Microscopy (SEM) (Sigma HD, Carl Zeiss, DE), at extra high tension of 1.00 kV. SX blends were placed on a double-sided adhesive tape pre-mounted on an aluminium stub and analyzed after a 30 min depressurization.

2.5. Aerodynamic assessment

The aerodynamic assessment of the SX blends was *in vitro* performed on aerosols obtained with two different devices, namely RS01® and Easyhaler®. In the first device, the powder was preloaded in a capsule and aerosolized using an airflow rate of 60 L/min, whereas in the second device, the powder, metered by the inhaler, was aerosolized at 45 L/min. The air volume drawn through the inhalers was 4 L.

Using RS01® device, 12.5 mg of the powder blend, accurately weighed, were introduced into a size 3 hard HPMC capsule. The capsule was inserted into the holder chamber of RS01, pierced and its content was aerosolized at 60 L/min for 4 s. The air flow rate, correspondent to 4 kPa pressure drop over the inhaler was controlled by flow meter DFM 2000 (Copley Scientific, UK).

In the case of Easyhaler®, the device reservoir was loaded with 1 g of blend and sealed with its cap. This inhalation device was operated at 45 L/min for 5.3 s. The inhaler was primed wasting the first three doses before the actuation in the NGI. Pressing the