The Influence of the Formulation and Delivery Approach on the Aerodynamic Performance of Salmeterol Xinafoate

Cláudia Moura[1,2], Sofia Silva[1], Filipe Neves[1], Ana Aguiar-Ricardo[2] & Eunice Costa[1]

[1] Hovione SA, Loures, 2674-506, Portugal

[2] Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Caparica, 2829-516, Portugal

Summary

Dry powder inhaler (DPI) systems are conventionally formulated using a carrier-based (CB) approach. The powder performance is highly influenced by the lactose properties, which can be variable, and frequently lead to blend uniformity issues or poor Active Pharmaceutical Ingredient (API) aerosolization. Some of these challenges can be overcome by using alternative technologies such as spray-drying (SD) for preparing inhalable formulations of composite particles (CMP) with enhanced aerodynamic performance (ADP).

Salmeterol xinafoate (SX), a cohesive inhalation API that usually presents poor ADP through the CB approach, was formulated using two DPI strategies, a CB approach where the SX was size reduced by jet milling (JM) until a median particle size (Dv50) of 2.6 µm and blended at 0.4% (w/w) with coarse (Respitose ML001) and fine (Lactohale 300) lactose excipients with a label claim of 50 µg of SX/actuation and a CMP approach in which a water/ethanol solution with 2% (w/w) of solids concentration composed of trehalose(80%), leucine(20%) and SX(0.4%) was SD to generate a dry powder with a label claim of 50 µg of SX/actuation. The ADP was assessed by a Next Generation Impactor (NGI) using a Plastiape HR model 7 device at 60 L/min for both DPIs. The deposition profiles were also compared to a SX suspension metered dose inhaler (MDI) formulation, with a label claim of 36.3 µg of SX/actuation, by NGI at 30 L/min.

The ADP of the two DPI powders showed that although a similar emitted dose (ED) was obtained, the CMP presented a fine particle fraction < 5 µm relative to the ED (FPF_{ED}) of 90%; three times higher than the CB powder and 1.5 times higher than the MDI formulation. It was concluded that the production of CMP by SD clearly shows a superior performance relative to the other classical approaches. This strategy is especially advantageous for potent APIs that can be difficult to formulate as DPIs.

Introduction

Drug delivery to the lungs can be performed using three different devices: dry powder inhalers, pressurized metered-dose inhalers and nebulizers. Each of them have their relative strengths and weaknesses thoroughly described in the literature [(1)(2)]. More recently, an increased interest has arisen around DPIs due to its propellant-free formulation (environmental friendly), processing (one phase), stability, low cost, among other factors [(1)(2)]. Typically inhalation APIs are highly potent and require subsequent formulation for adequate metering, consistent dosing and aerosolization. The drugs for the DPI systems are conventionally formulated using a CB approach. In this approach, the API previously size-reduced to 1 to 5 µm (inhalable range) is blended with one or more excipients, usually lactose monohydrate [(3)]. Nevertheless, this strategy presents several drawbacks such as blend uniformity issues and poor aerosolization due to limited control and potential variability over API and carrier interactions [(3)]. To overcome these constraints, several particle engineering technologies have been developed and optimized such as SD [(3)(4)(5)]. This technology can produce inhalable particles with controlled particle size, morphology and density by manipulating formulation composition and process parameters such as solute concentration, atomization, feed flow rate, drying gas rate and solvents type, among others. This increased control over the powder properties allows the optimization of the powder aerosolization behaviour and dispersability, which potentially allows for the reduction of the API dose while maintaining the amount delivered to the target site [(5)(6)].

In an attempt to develop inhalation powders with advantageous features, the manufacture of “special” particles has recently gained momentum with several patents protecting the production of such particles including Pulmosol™ and PulmoSpheres® technology developed by Nektar Therapeutics, Technosphere® by MannKind Corporation, and AIR®/ARCUS™ technology by Alkermes, among others [(3)].

The main goal of this work was to perform a fair ADP comparison between a standard CB approach and an emerging technology for the production of composite particles by SD. For that, SX was chosen as the model drug due to its known cohesivity and poor aerosolization performance.

Experimental methods

Particle Engineering and Formulation

The SX API was formulated using two different DPI approaches and as a suspension MDI:

A) **Carrier-based (CB) approach**: The SX raw material provided by Hovione SA was size reduced by jet milling until a Dv50 of 2.6 µm was reached as determined using a laser diffraction method. A detailed API characterization was previously performed [7], comprising, among other techniques modulated differential scanning calorimetry (mDSC) and X-ray powder diffraction (XRPD). A geometric addition strategy was used to blend 0.4% (w/w) of the micronized SX with 4% (w/w) of fine lactose (Lactohale 300; DFE Pharma) and 95.6% (w/w) of coarse lactose (ML001; DFE Pharma) in a Turbula mixer (Glen Mills). The blend uniformity was further assessed by high performance liquid chromatography (HPLC) [7]. After blending, the powder was analysed by scanning electron microscopy (SEM).

B) **Composite particles (CMP) approach:** An ethanol(20% w/w):water(80% w/w) solution with 2.% (w/w) of solids concentration of which 79.8% (w/w) is composed of trehalose, 19.8% (w/w) of leucine and 0.4% (w/w) of SX were spray-dried using a BUCHI model B-290 unit. The solution was SD at a feed flow of 7 g/min, drying gas flow of 35±5 kg/h, atomization gas flow of 50 mm in the rotameter and drying gas outlet temperature of 95 ºC. After SD, the powders were characterized by mDSC, XRPD and SEM.

C) **MDI approach:** To perform a simple comparison between the two DPI approaches and another marketed formulation strategy, a MDI suspension formulation was also prepared. The JM SX was provided by Hovione with a Dv50 of 2.6 µm as determined by laser diffraction. The required amount of API was placed inside a pressure resistant glass vial and filled with HFA-134a (1,1,1,2 – tetrafluroethane) propellant having a label claim of 36.3 µg of SX/actuation.

In-vitro impaction measurements

The ADP of both DPI formulations (CB and CMP) was assessed by NGI with 12.5 mg of formulation (SX label claim of 50 µg/actuation) filled in hydroxypropyl methylcellulose (HPMC) size 3 capsules using a Plastiape HR model 7 device at 60 L/min, at a pressure drop of 4 kPa. For the CB blends the optimized NGI method was performed with 10 capsules, while for the CMP particles 4 capsules were actuated. On the other hand, the performance of the MDI formulation was tested using a NGI at 30 L/min (n=10 shots per NGI; for each analysis the first 3 shots were discarded). The uniformity of the delivered dose was assessed as described in [8]. For all *in-vitro* impaction measurements, the SX mass deposited in each stage was determined using an appropriate HPLC method.

Results and Discussion:

For supporting the CB DPI formulation, SX was firstly size-reduced by JM to the inhalable range. After JM, the SX crystalline particulates were in the polymorphic form I with trace seeds of polymorphic form II as determined by XRPD and mDSC, being compliant with the starting raw material [7]. The CB DPI formulation prepared with JM SX had acceptable uniformity as determined by HPLC (6.9% of RSD).

On the other hand, through the CMP approach, partially amorphous particles were obtained. The observed crystalline peaks were due to the presence of leucine, which, given its hydrophobicity, most likely precipitated/recrystallized on the particle surface during SD [3]. For this DPI formulation, there was no need to assess uniformity since SX is dispersed within the excipients matrix, comprising 0.4 % w/w of the total formulation.

The SEM micrographs of both DPI formulations are presented in **Figure 1**. The differences observed between the two powders are clear: on the left side of the figure, coarse lactose particles covered by fine lactose particles and SX particles (which can potentially aerosolize upon device actuation) are observed; while on the right side, small inhalable composite particles containing SX with a narrow particle size distribution were obtained.

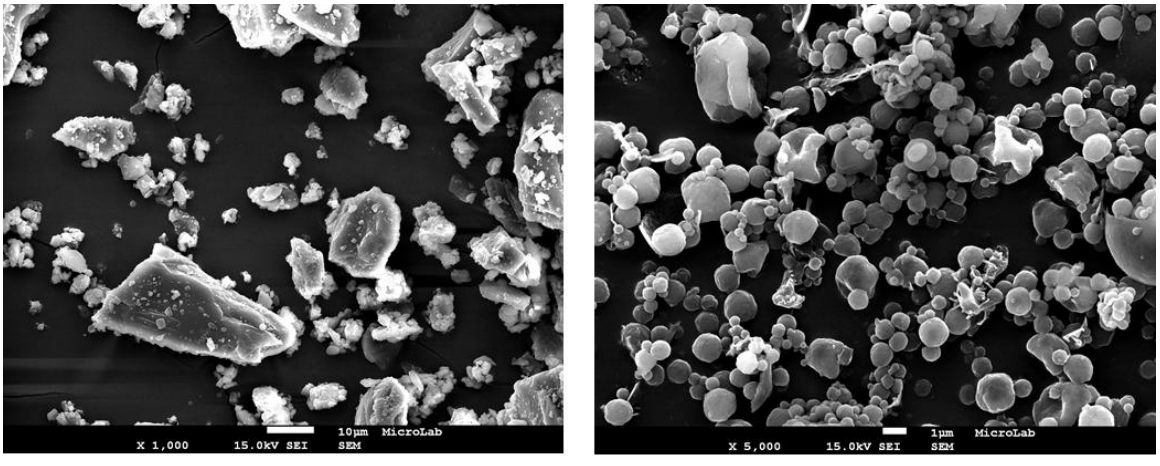
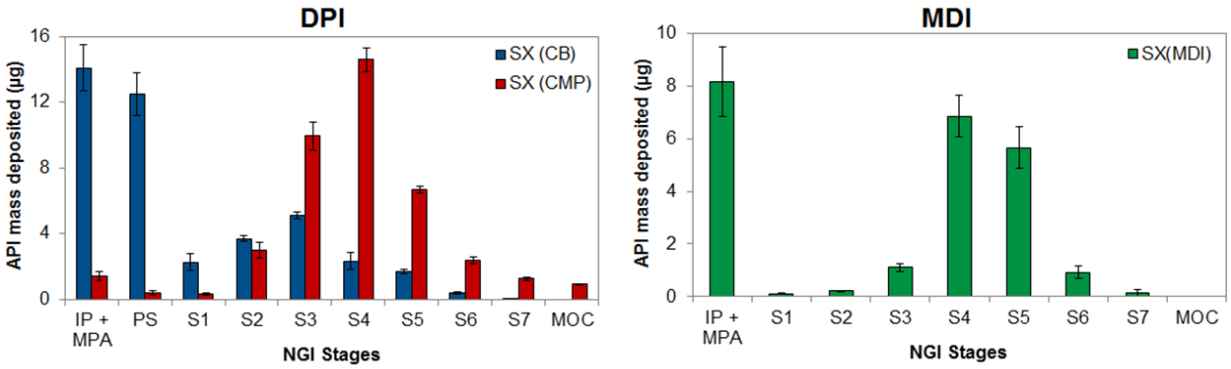


Figure 1 – SEM micrographs of the CB approach powder (1000x) and the CMP (5000x).

The *in vitro* impaction measurements by NGI of both DPI formulations are presented in **Figure 2**. A clear difference in the deposition profile of the formulations is observed. While in the CB approach the API mostly deposited in the mouthpiece adaptor (MPA), induction port (IP) and pre-separator (PS), presenting a low FPF_{ED} of 28.2%; the CMP approach mostly deposited on the lower stages, achieving FPF_{ED} values of approximately 90% (**Figure 2 – left**).

The comparison between these two DPI formulation approaches clearly shows the superiority of the CMP approach in regards to performance. However, additional characterization and stability testing of both formulations would be required to complement the benchmarking of the approaches. This is particularly important for the CMPs since these are composed of partially amorphous materials.



	DPI		MDI
	SX (CB)	SX (CMP)	SX
ED (µg)	42.2 ± 0.9	41.0 ± 2.3	23.1 ± 2.2
FPD (µg)	11.9 ± 0.4	36.9 ± 1.9	14.2 ± 1.5
FPF_{ED} (%)	28.2	90.0	61.6
MMAD (µm)	3.8	2.2	2.4

Figure 2 - (left) Aerodynamic performance of the CB and CMP powders by an NGI at 60L/min using a Plastiape HR device model 7 operated at 4 kPa; (right) Aerodynamic performance of the MDI by an NGI at 30L/min. The error bars represent the standard deviation.

The performance of the DPI formulations was also benchmarked against a model suspension MDI formulation. For the MDI, the delivered dose uniformity across actuations was assessed and has indicated that the suspension was uniform (RSD of the ED of 7%; data not shown).

The NGI deposition profile of the MDI is shown in **Figure 2**. An overall comparison of the three formulation approaches, CB, CMD (both DPIs) and MDI shows that the FPF_{ED} obtained for the CMP particles was three times higher than the CB approach and 1.5 times higher than the MDI (**Figure 2 – right**).

It is however important to highlight that the direct comparison of the MDI and DPIs aerodynamic performances is rather limited by the different aerosolization mechanisms inherent to DPIs and MDIs, formulation dosages, API particle sizes and flow rates used during NGI testing. The main goal of the work was to assess which formulation approach could potentially provide the best ADP for SX.

Conclusions:

Based on a comparison between the DPI formulation approaches, it was concluded that the CMP approach was the most suitable for a model API that is hard to formulate and that typically presents very low delivery efficiencies by the conventional lactose blending approach, while minimising variability and blend uniformity issues. An improved aerodynamic performance was observed for the CMP that presented FPF_{ED} values three times higher than the conventional CB approach and 1.5 times higher than a model suspension MDI. The CMP powders also have the advantage of being produced by SD, which is a one-step process, and readily scalable. The CMP powders can potentially enable a reduction of the API concentration in the formulation while maintaining the desired drug dose at the site of action, potentially reducing the adverse side effects for the patients. Future studies to further benchmark both strategies will address stability upon storage and capsule / device filling activities in order to guide formulation scientists on the relative advantages and disadvantages of these DPI formulations.

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