

De Novo Engineering of Crystalline Low Dose Combination Inhalation Particles of a Long-acting β_2 -agonist and Corticosteroid

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Summary:

Previously, we have demonstrated that the SAX process may be utilised to produce individual particulates of two active ingredients, which will allow the delivery of combination medicaments effectively and independently of dose variation. In this study, we extend this concept into the development of co-processed particles of low-dose preparation. SAX particles of budesonide and formoterol were successfully co-processed into individual crystalline properties, which resulted in better *in-vitro* performance than that of a blended equivalent. This approach presents itself as novel means to produce inhaled combination of low dose drug which may lead to offer the potential for enhanced clinical efficacy for synergistic interaction.

Introduction:

Delivery of combined inhaled drug delivery systems has been useful in the management of asthma (Barnes, 2002). The recommended strategy for the control of asthma is combined inhalation therapy with inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABA). It has been demonstrated that addition of a long-acting β_2 -agonist (LABA) to an inhaled corticosteroid (ICS) is superior to ICS alone in achieving asthma control (Matz, Emmett et al., 2001). Additionally, for the preclinical work, co-administration of ICS and LABA has a mechanism of action with synergistically interacting effect. It is crucial to have synergistic actions of LABA and ICS at the cellular, receptor and molecular level (Theophilus, Moore et al., 2006).

Recently, the global initiative for asthma has endorsed the use of budesonide/formoterol (Symbicort SMART[®]) for both maintenance and relief therapy in asthma. Budesonide/formoterol is usually available in two strengths for maintenance and reliever therapy (100 μ g/6 μ g and 200 μ g/6 μ g), which are typically delivered using a dry powder inhaler (DPI). The preparation of combination DPI formulations containing low concentrations of active can pose significant challenges during product development. Current combination therapies are commonly prepared by blending both the micronised LABA and ICS together with coarse lactose. These preparations are then loaded into a DPI device and actuated by the patient to receive both medicaments. However, owing to means in which the products are prepared there is very little control to ensure that both drugs are delivered together and in adequate concentrations. Furthermore, there is a greater likelihood of variations in dose delivery of the actives as a function of product storage conditions. Hence, there is requirement of processes that may enable production of low dose combination inhaled products that will allow both drugs to be delivered more effectively and independent of dose variations. Hence, there is requirement of processes that may enable production of low dose combination inhaled products that will allow both drugs to be delivered more effectively and independent of dose variations.

Aim:

The aim of the present study was to employ the solution atomisation and crystallisation with sonication (SAX) process to generate individual particles that consisted of both the ICS (budesonide) and LABA (formoterol). The aerosolisation efficiency of these novel particles was also assessed.

Materials:

Micronised budesonide (BUD) and formoterol fumarate dehydrate (FFD) were obtained from Sicor (Santhia, Italy). All organic solvents were of at least analytical grade and were supplied by Fisher Chemicals (Loughborough, UK). Water was prepared by MilliQ from reverse osmosis (Molsheim, France). Etched lactohale was produced from coarse carrier α -lactose monohydrate (Friesland Foods Domo – Pharma, Zwolle, The Netherlands).

Methods:

SAX-produced BUD-FFD particles were prepared from 1.5% w/v of BUD:FFD in the ratio 36:1 in methanol. The solution was sprayed through a co-axial two-fluid atomiser (Büchi, Labortechnik, Flawil, Switzerland) at a sprayed rate of 4 ml.min⁻¹ with air pressure at 2.5 bar including positive pressure 30 L.min⁻¹ via SAX process. The resulting particles were then collected in hexane at 5°C and exposed to sonic energy to induce nucleation and crystal growth. The particles were isolated from the non-solvent using supercritical CO₂ solvent extraction. The materials were characterised to determine particle size using laser diffraction (Sympatec, Clausthal-Zellerfeld, Germany) and morphology using scanning electron microscopy (SEM, Jeol, Japan).

Formulations containing 1.6% w/w combined SAX BUD/FFD particles, was prepared by geometric blending with 63 - 90 μm sieve fractions of surface-etched lactose as described elsewhere (El-Sabawi, Price et al., 2006). In order to compare the *in-vitro* inhalation performance of SAX BUD/FFD and micronised BUD/FFD, a combination formulation containing 1.56% w/w micronised BUD and 0.04% w/w micronised FFD was prepared by geometric blending with 63 - 90 μm sieve fractions of surface-etched lactose. Formulations were aerosolised from ten 25 mg capsules (size 3, HPMC) using a *Cyclohaler*[®] at 60 L.min⁻¹ into a Next Generation Impactor (NGI) to assess the formulation performance. Drug concentrations were determined by HPLC system (Jasco, Japan) with a 4.6 mm x 250 mm C18 5 μm Hypersil column (Thermo Electron Corporation, Waltham, MA, USA), and mobile phase consisted of 60% acetonitrile, 40% of 5 mM Sodium dihydrogen orthophosphate (set to pH 3). The flow rate was 1.5 ml.min⁻¹, column temperature was 30°C and injection volume 200 μl . Drug retention times were 3.2 minutes for BUD and 9.8 minutes for FFD. UV detection wavelength used to detect for both BUD and FFD was set at 214 nm.

Results and discussion:

SEM analysis showed that the median equivalent volume diameter of micronised BUD and FFD were 2.21 ± 0.01 and 2.42 ± 0.02 μm , respectively. Particle size analysis of SAX BUD/FFD exhibited a monomodal particle size distribution presenting a median equivalent volume diameter of 4.17 ± 0.04 μm . SEM analysis of the combined SAX BUD/FFD demonstrated particles with uniform shape and morphology (Figure 1).

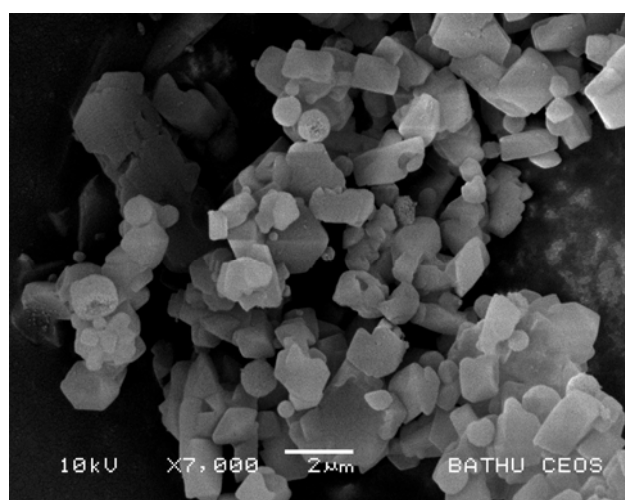


Figure 1. Scanning electron micrograph of combined SAX particle of BUD/FFD.

The fine particle fraction of the emitted dose (FPF_{ED}) of combined BUD/FFD from micronised and SAX formulations is shown in Figure 2. The FPF_{ED} of the formulation comprised of micronised BUD and FFD was 14.75 ± 0.63 % for BUD and 6.19 ± 1.87 % for FFD. In comparison, the formulation of SAX processed BUD/FFD showed significantly (one way ANOVA, $p < 0.05$) greater FPF % of BUD (21.78 ± 1.4 %) and FFD (14.19 ± 0.92 %). The increased fine particle delivery of the SAX particles may be related to the morphology of the material, which may minimize contact between the carrier and the drug particles and therefore, corresponded to increased fine drug particle liberation.

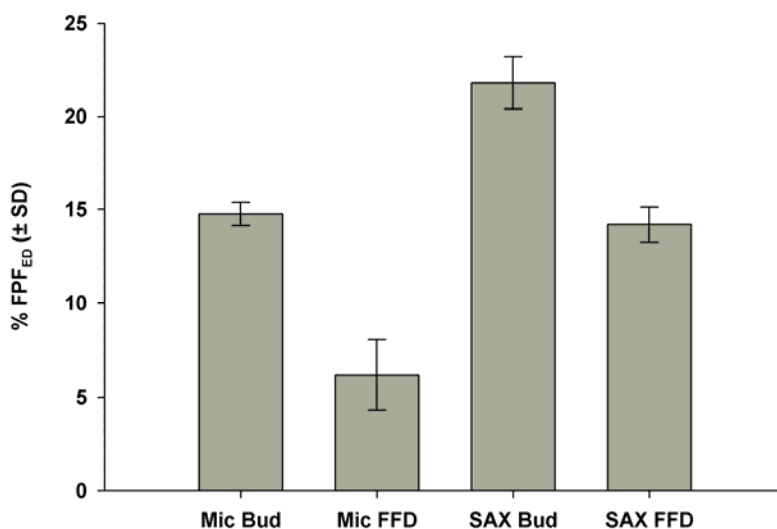


Figure 2. The fine particle fraction of the emitted dose (FPF_{ED}) of Bud and FFD following aerosolisation of combinations comprising of micronised Bud/FFD and SAX Bud/FFD.

The ratio of BUD:FFD on stages 2-5 of micronised BUD:FFD is compared with SAX-produced Bud:FFD in Figure 3. As can be seen from this figure, stage-by-stage analysis suggested that the SAX processed BUD/FFD formulations were delivered consistently, whereas the micronised BUD and FFD delivered more BUD than FFD in the lower stages of the NGI. Such results show the fact that the combination particles of Bud:FFD engineered from SAX process were successfully co-processed into individual particles and resulted in consistent drug deposition on to the lower stages of NGI of the *in-vitro* study.

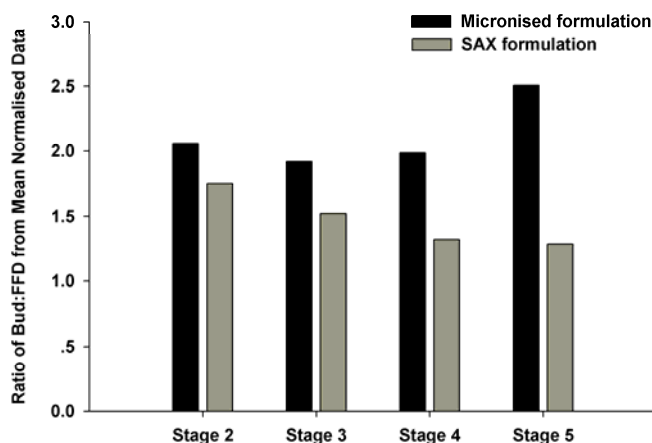


Figure 3. The ratio of Bud:FFD on stage 2 – 5 of the NGI following aerosolisation of formulations containing micronised Bud/FFD and SAX Bud/FFD at 60 L.min⁻¹

Conclusion:

In conclusion, the SAX process shows great promise in developing individual particulates of two active ingredients, which will allow the delivery of combination medicaments effectively and independently of dose variation.

References:

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