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# Optimized particle engineering of fluticasone propionate and salmeterol xinafoate by spray drying technique for dry powder inhalation

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ABSTRACT

Asthma is one of the most common respiratory diseases that can be efficiently managed through combined treatment of fluticasone propionate (FP) and salmeterol xinafoate (SX). In this study, we challenged the use of both spray drying and mixing techniques in sequential combination of lactose or mannitol with FP and SX as two steps in development of inhalable powder formulation of the drugs. Leucine was used as a dispersibility enhancer. The formulations were optimized using the Design-Expert software. The effects of three independent variables namely the type of carrier, percentage of spray-dried carrier and the amount of leucine were investigated on in vitro deposition. The results showed that the maximum fine particle fraction (FPF) and the minimum particle size was belonged to formulation in which the percentage of leucine was 20% with respect to the total solid content and 50% of mannitol was used during spray drying, while the remaining 50% of it was applied in the physical mixing process. This study showed that not only the choice of carrier and additives for every drug combination, but also an optimized ratios of them during both spray drying and physical mixing can be crucial in developing suitable inhalable dry powder formulations.



## 1. Introduction

Asthma and COPD are complex disease conditions of the airways that both are characterized by air flow limitation and airway inflammation [1]. In order to manage these respiratory complications, therapies are required to control symptoms, reduce exacerbations and improve health status in patients. The first-line treatment for both conditions is long-acting β2-agonists (LABA) and inhaled corticosteroids (ICS), which are employed to aid bronchodilation and reduce inflammation, respectively [2,3].Inhalation dosage forms containing a LABA and ICS are available in both pressurized metered dose inhaler (pMDI) and dry powder inhaler (DPI) platforms [4]. Due to the concern about ozone depleting effects of chlorofluorocarbons used in pMDIs, the DPIs are emerging as an important noninvasive delivery approach in the new decade and beyond [5]. DPIs are currently used by an estimated 40% of European patients to treat asthma and COPD [6]. Among the inhalation products available for such diseases, the combination of salmeterol xinafoate (SX, LABA) and fluticasone propionate (FP, ICS) (Seretide®/Advair®, GlaxoSmithKline, UK) has achieved widespread acceptance among physicians and patients and is listed in the top ten best-selling pharmaceutical products of recent years [7]. This combination therapy shows greater efficacy compared to monotherapy treatments with the individual components [8], and reduced mortality rates in COPD beyond that achieved by single therapies [9].

The delivery efficiency of dry powder products through inhalation is dependent on drug formulation, the inhaler design, and the inhalation technique. Successful drug delivery depends on the interaction between the powder formulations and the device performance to generate a suitable aerosol. To achieve deep lung penetration, drug particles are often micronized to sizes between 1 and 5 μm [10]. However, small drug particles generally have poor flow properties and hindered dispersibility due to their highly cohesive nature. In other words, they tend to adhere and remain in the DPI device during the emission process which lead to low aerosol generation and unreliable dosing [11,12].Therefore, to improve flow and dispersion, a population of coarse particles (50–100 μm) is incorporated into the DPI formulation to serve as carriers onto which the drug particles adhere during blending [13]. Such blends provide the essential improvement in powder

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flow properties to enable adequate metering and fluidization of the highly cohesive fine drug particles. Moreover, the drug particles must detach from the surface of the carrier during the process of aerosolization in order to reach their site of action [13]. This is the key process that governs the performance of such formulations, and is dependent upon the balance between the cohesive and adhesive forces between drug and carrier particles and the aerodynamic drag forces acting against them during aerosolization. It is, therefore, unsurprising that numerous studies have shown the influential role of carrier material on fine particle delivery and subsequent formulation performance, as such a change will also lead to different levels of drug-carrier adhesion [14,15].

Spray drying has been routinely employed for the production of pharmaceutical particles for decades [13]. The compound is fed as a solution or suspension in a liquid medium and atomized into a hot drying environment. Particles produced by spray drying are usually amorphous, more spherical and possess a lower density compared to other methods [16].

The addition of various amino acids to DPI formulations obtained by spray drying has the potential to significantly improve the in vitro deposition profile of drug particles [13]. In particular, addition of leucine usually results in less cohesive particles with smaller sizes which is due to the surfactant behavior of leucine that leads to the reduction of droplets' size during atomization and decreases particles adhesion [17].

In this study, we demonstrated how a rational approach to experimental design of a DPI formulation could generate highly respirable powder, which offered simultaneous and efficient in vitro delivery of SX and FP to the lungs. To this aim, we optimized the type of carrier, percentage of spray-dried carrier and the amount of leucine using the Design-Expert software (version 7.0.0, Stat-Ease, Inc., Minneapolis, MN, USA). To the best of our knowledge, this is the first systematic research investigating the combined use of spray drying and mixing techniques in sequential addition of common used carries to micronized drugs in development of dry powder inhalers and trying to optimize the partial amounts of co-processed carriers added in each step of the formulation process. Development of such optimization methods as an alternative to traditional ones offers better investigation of the influencing factors on the response(s) as well as the interaction effects between them, through usually less number of experiments. After spray drying, the formulations were physically blended with the remaining amount of the same coarse carrier, which was initially used in the feed solution. Particle size properties as well as in vitro aerosol performance were examined in different formulations in order to find the optima with desirable DPI attributes.

## 2. Materials and methods

### 2.1. Materials

Micronized FP and SX were supplied from Cipla (India).α-lactose monohydrate was purchased from DMV International (The Netherland). Mannitol and l-leucine were from Crester (France) and Merck (Germany), respectively. The HPLC grade methanol, ammonium acetate, and absolute ethanol were all supplied from Merck (Germany).

### 2.2. Quantitative sample analysis by high pressure liquid chromatography (HPLC)

Quantitative analysis of the sample was done using HPLC system (Waters 6006, USA). The column used was a Hypersil ODS (4.6 mm × 150 mm), which was packed with 5 μmC18 stationary phase. The mobile phase was a mixture of methanol and0.8% (w/v) ammonium acetate buffer in the ratio of 72:28 v/v. The buffer was made by dissolving ammonium acetate in reverse osmosis water. The mobile phase was freshly made before each analysis, followed by filtration through 0.45 μm nylon filter and degassing. The flow rate was 1.00 ml/min at 40 °C and an ultra violet (UV) detector (Waters M486, USA) was set at the wavelength of 228 nm. The injection volume of the sample was 20 μL that was determined by means of a loop. Each sample was analyzed in triplicate using a run time of 10 min. All solvents used were HPLC grade. SX was detected as two distinct peaks; one belonged to xinafoic acid (XA) and the other to the salmeterol free base [18]. The HPLC method was validated throughout the SX and FP concentration range of 0.5–50 μg/ml and was found to be linear, accurate, precise and reproducible for both analytes.

### 2.3. Content uniformity analysis

Upon blending, the drug content uniformity of all the formulations was assessed. Each formulation was spread evenly over a clean surface and ten samples of 10 ± 1 mg were taken from random positions. Each sample was dissolved in a suitable solvent containing methanol and 0.8% (w/v) ammonium acetate (75:25 v/v) to final volume of 10 ml and drug concentration was assessed using HPLC. The portion of drug in each sample was calculated and the content uniformity was expressed as the relative standard deviation (RSD) from the mean. All the formulations had to meet the relevant USP standard prior to further investigations. According to the USP, acceptable DPI formulations are the ones in which the drug content of 9 out of 10 samples is in the range of 75–125% from the assigned average mass and no formulation is outside the range of 65–135% [19].

### 2.4. Experimental design

An optimization process based on a D-optimal design was applied for the preparation of combinatory DPI formulation of SX/FP. This design offers a statistical model to describe the effects of preparation conditions on the formulation properties especially when categorical variables are involved along with numerical ones. Table 1 shows the three independent variables and their levels. The nominal variable was the type of carrier and numerical variables included the percentage of spray dried carrier with respect to the total amount of carrier and the percentage of leucine relative to the total formulation. The generated experimental matrix is shown in Table 2, wherein the effects of independent variable were evaluated on in vitro aerosol performance as well as the size of spray-dried microparticles. Data of all dependent variables was collected as the mean of triplicate measurements. The significance of the effects of independent variables on the responses was assessed by ANOVA and the best fitting statistical model to the test data was analyzed by the software. Finally, the response surface plots were used to determine the optimum conditions for formulation development.

### 2.5. Preparation of spray dried particles

Different amounts of both drugs, carrier (lactose or mannitol) and leucine were dissolved in the mixture of ethanol:water at the ratio of 70:30 v/v to prepare feed solutions for spray drying. The amounts of FP and SX in all formulations were constant and equivalent to 27.5 and 5.5 mg, respectively. The amount of carrier (lactose or mannitol) and leucine varied according to Table 2. Spray drying was performed using a B-191 mini spray dryer (Büchi-B191, Switzerland) under following conditions: 110 °C inlet temperature, 60–65 °C outlet temperature, 2.5 ml/min feed rate, 90% aspiration,