Assessment of the Effects of Drying Methods on Powder Properties: A Comparative Study of Spray Drying from Solution and Suspension

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Introduction

Dry powder inhalers (DPIs) offer a promising approach for delivering medication directly to the lungs, particularly for managing localized respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD). Advantages encompass drug stability and the absence of propellant gases, yet attention is directed toward enhancing DPI characteristics through particle engineering, mainly using the spray-drying method [1]. By adjusting liquid composition and drying parameters, DPI development and optimization can be achieved, leading to improved aerodynamic performance and dispersibility, ultimately enhancing effectiveness [2,3].

The objective of this research is to develop a dry powder suitable for inhalation, incorporating two anti-asthmatic medications: ciclesonide (CIC), classified as an inhaled corticosteroid (ICS), and indacaterol (IND), a long-acting beta agonist (LABA), using spray drying technology. Due to CIC's high hydrophobicity and previous studies demonstrating the beneficial effects of a deflated morphology for aerosolization performance, cyclodextrins are employed to enhance API solubility [4]. Additionally, the potential for suspension atomization will be investigated owing to the drug's hydrophobic nature. The primary goal of this study is to investigate and compare the drying outcomes of solutions and suspensions on the final properties of the dry powders, while assessing the influence of variations in solid content. In addition, attention is also directed towards formulating a dry powder with an improved lung deposition profile.

Methods and Materials

Spray-drying: A 5 and 10 % (w/w) atomized liquids containing CIC, IND, and cyclodextrins are formulated. The suspension contains hydroxy-propyl-β-cyclodextrin, which does not allow the solubilization of a high quantity of CIC, along with a surfactant agent (Tween® 80). Solubilization of the API is facilitated using Crysmeb, a methyl-β-cyclodextrin, chosen based on the results of a phase-solubility test. Both solution and suspension are subjected to spray drying using a Procept 4 M8-Trix Formatrix spray-dryer (Procept, Zelzate, Belgium) with a bi-fluid nozzle (0.4 mm) under the following parameters: inlet temperature of 160°C, feed flow rate of 3.85 g/min, nozzle gas pressure of 3 bar, cyclone gas pressure of 0.4 bar, and an inlet gas flow of 0.4 m^3/min. These conditions were determined based on previous experiments [2].

Dried Powders Characterization: Analyses include determination of yield process, particle size distribution measured by laser diffractometer Mastersizer 3000, moisture content via thermogravimetric analysis (TGA), and particle morphology characterized by scanning electron microscopy (SEM) after metallization with Au. Homogeneity of CIC and IND is assessed by collecting 10 samples from the powder bed, and drugs recovery rates post-drying process in each sample is determined using an HPLC method. Raman hyperspectral imaging (R-HSI) experiments were conducted using a Labram HR Evolution (Horiba Scientific).

Aerodynamic Properties Characterization: The pulmonary deposition profiles of the powders were determined using a Next Generation Impactor (NGI, Copley Scientific, UK) at airflow rates of 100 L/min, employing a low resistance device, as per European Pharmacopoeia guidelines. The fine particle fraction (FPF) was calculated by comparing the ratio of particles within the 1-5 µm range to the recovery dose and compared to Onbrez® FPF, a DPI formulation on the Belgian market composed of lactose as a carrier and IND.

Results and Discussion

Developed Powders Properties:

The engineered spray-dried powders obtained with optimal parameters enabled the production of dried particles characterized by a deflated morphology, with particle sizes below 5 µm and a water content approximately at 5 %, representing properties suitable for inhalation delivery (Fig. 1) [3]. The major difference between the suspension and the solution is the particle size since larger particles are obtained once suspensions are dried.

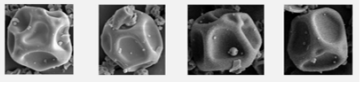
	Solution		*Suspension*	
	5% (w/w)	**10% (w/w)**	**5% (w/w)**	**10% (w/w)**
Spray-drying yield (%)	77.60 ± 1.03	76.37 ± 1.08	77.39 ± 2.82	66.30 ± 4.80
Particle size d50 (µm)	2.94 ± 0.04	2.94 ± 0.11	3.45 ± 0.21	4.11 ± 0.28
Water content (%)	6.46 ± 0.54	4.56 ± 1.40	4.34 ± 0.21	4.06 ± 0.27
Particle Morphology				

Figure 1: Morphology and characteristics of the spray-dried powders.

Powders homogeneity and drug recovery:

The evaluation of active ingredients homogeneity in powders from solutions and suspensions showed consistent distribution, represented by a coefficient of variation less than 5 %. However, CIC recovery rates after suspension drying were notably lower due to its non-solubilized state, resulting in decreased recovery rates (Fig. 2A). The non-solubilized drug is probably lost on the walls of drying chamber. This is proven by Raman hyperspectral imaging: while spray-dried solutions revealed a singular signature for each pixel, indicating homogeneous distribution of excipient and API due to their solubilization before atomization (Fig. 2B), suspensions unveiled distinct CIC signatures (Fig. 2C) signifying non-uniform distribution of excipient and CIC post-drying due to varied API solubilization.

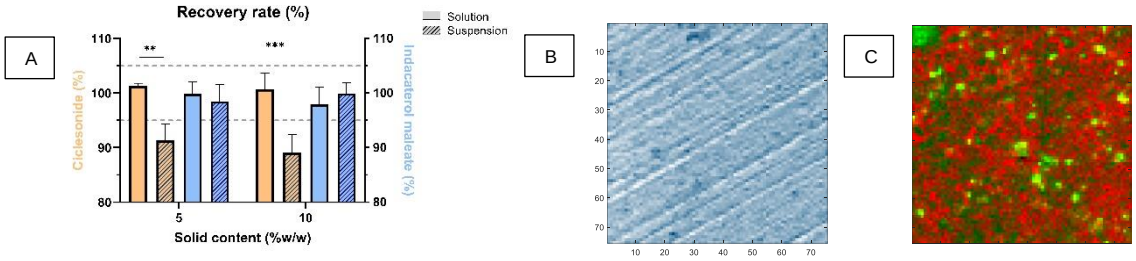


Figure 2: Recovery rate post-drying (A). Raman hyperspectral imaging results from spray-dried solutions (B) and suspensions (C).

In vitro Aerosolization Performance:

The *in vitro* aerosolization performance of the produced powders derived from solutions demonstrates high FPF values of 58.27 ± 7.49 % and 56.25 ± 1.24 % for CIC, at concentrations of 5 and 10% (w/w) respectively, and 54.25 ± 2.99 % and 53.27 ± 4.17 % for IND (Fig. 3). These findings indicate uniform deposition of both APIs. Additionally, the dried particles obtained from solutions lead to a significant enhancement in the FPF of IND by nearly 15 % at both solid content levels compared to the specialized product Onbrez®, resulting in a heightened lung deposition profile, attributed to the absence of carrier and optimized powder properties. Nevertheless, atomized suspensions led to lower FPF values of 35,16 ± 4,68 % and 26,86 ± 4,59 % for CIC, at concentrations of 5 and 10% (w/w) respectively, and 42,88 ± 7,96 % and 36,28 ± 5,53 % for IND. This phenomenon may be attributed to the larger particle size and less homogenized distribution of API within the powders when atomizing suspensions, resulting in increased impaction in the upper respiratory stages.

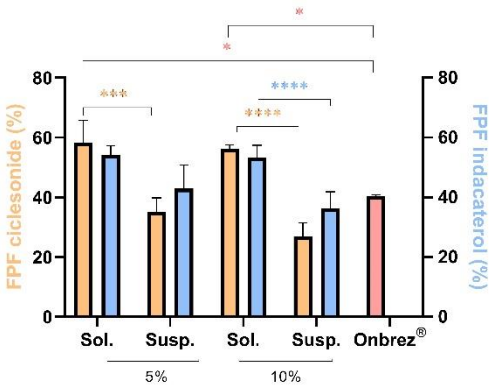


Figure 3: CIC and IND FPF from solution and suspension at both solid content of 5 and 10% (w/w) compared to FPF of Onbrez®.

Conclusion

In conclusion, the variation in solid content from 5 to 10 % exhibited negligible influence on powder properties and lung deposition profiles. This study demonstrated that atomized solutions produced powders with improved properties for inhalation, including particle size and powder homogeneity, resulting in significantly higher lung deposition of the drug. Moreover, laboratory-produced powders derived from dried solutions using spray drying technology achieved an augmented pulmonary deposition, surpassing the commercially available Onbrez® product by nearly 15 %. These findings underscore the significance of the solubilization state of active ingredients and the role of particle engineering in enhancing the pulmonary deposition of drugs (compared to carrier-based powder), thereby augmenting their therapeutic efficacy.

The perspectives of this study focus on improving the powder flowability, currently deemed poor, by investigating possibilities such as lactose-mixture or self-agglomeration while evaluating the stability of active ingredients in the powders over time [5].

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