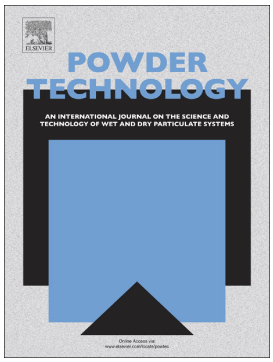

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Enhancement of inhaled micronized powder flow properties for accurate capsules filling

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KEYWORDS

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Capsule filling
Lung delivery
Adhesive mixture
Inhalation powder
Interparticle Interaction Forces

ABBREVIATION

API, Active Pharmaceutical Ingredient; BUD, Budesonide; COPD, Chronic Obstructive Pulmonary Disease; DPI, Dry Powder Inhaler; ED, Emitted Dose; FPD, Fine Particle Dose; FPF, Fine Particle Fraction; FOR, Formoterol fumarate dihydrate; HPB, Hydroxypropyl-β-Cyclodextrin; HPLC, High Performance Liquid Chromatography; HR, High Resistance; Lac70, Inhalac® 70; Lac230, Inhalac® 230; LEU, L-leucine; LOD, Limit of Detection; LOQ, Lower Limit of Quantification; LR, Low Resistance; MOC, Micro-orifice Collector; NGI, Next Generation Impactor; PIF, Peak Inhalation Flow; pMDI, pressurized Metered-Dose Inhaler; PSD, Particle Size Distribution; RAF, Raffinose pentahydrate; RD, Recovery Dose; RSD, Relative Standard Deviation; SD, Spray-Dried; SEM, Scanning Electron Microscopy; SMI, Soft-Mist Inhaler.

1. Introduction

Dry powder inhalers (DPI) are gaining popularity in the field of pulmonary treatments due to their numerous advantages. Compared to pressurized metered-dose inhalers (pMDI), soft-mist inhalers (SMI), and nebulizers, which utilize liquid formulations, DPIs employ solid-state formulations, thereby conferring increased drugs and microbial stability [1,2]. Furthermore, DPIs offer several benefits, including propellant-free operation, elimination of the need for hand-mouth coordination and the ability to deliver high doses of drug, making them an appealing option for pulmonary drug administration [3,4]. To achieve therapeutic efficacy, particles or droplets must have an aerodynamic diameter within the range of 1-5 μm, enabling deep lung deposition while minimizing impaction in the upper respiratory tract or diffusion [5,6]. However, concerning specifically powders, the requirement for small particle size leads to interparticulate interactions characterized by cohesive and adhesive forces, such as van der Waals or electrostatic forces, resulting in reduced powder flowability [7]. Apart from particle size, powder flow properties are influenced by other particle characteristics, including shape, surface roughness, and size distribution, all of which contribute to the handling challenges and can pose limitations in industrial processes such as capsules or container filling [8,9].

To enhance the bulk properties of powder formulations used in DPIs, a common approach involves combining micronized active pharmaceutical ingredient (API) with a carrier, typically a coarse particle ranging in size from 50 to 200 μm, commonly lactose monohydrate [10]. Generally, more than 90% of the mixture consists of the carrier. This results in an ordered mixture, also known as an adhesive blend, which consists of a mixture of micronized particles and significantly larger particles (>100 μm) [5,11,12]. Within the blend, adhesive forces facilitate interactions between API particles and the carrier surface, resulting in their attachment [13]. For effective deposition in the deep lung, micronized particles must detach from coarse particles [12,14]. Achieving a balance between formulation stability and uniformity through interactions and ensuring adequate separation of the API from the carrier is essential to obtain a high lung deposition [12,13,15]. The dissociation process is influenced by factors such as the formulation itself, including particle size distribution and particle interactions. The deagglomeration of the powder also depends on external factors, such as the type of inhaler used and its resistance and the patient's inspiratory flow rate [2,16]. During inspiration, the separation of the mixture results in carrier impaction in the upper respiratory tract, making API particles available for deposition to the target site [10]. However, the interaction forces between the carrier and APIs are complex, and developing inhalation powders with high pulmonary deposition remains a significant challenge, even with the addition of fines. Indeed, currently available DPIs typically achieve a fine particle fraction (<5 μm) of approximately 20-30%, resulting in a considerable loss of API in the throat-mouth region and within the device [15,17,18].

In recent decades, extensive research has been conducted on particle engineering in the context of developing inhalation powders, including both carrier-based and carrier-free formulations. Particle engineering allows the design of particles with desirable properties to achieve optimal pulmonary deposition [19]. Various particle properties, such as size, density, shape, drug stability, surface properties, crystallinity and hygroscopicity, significantly impact powder aerosolization [3,20]. Among the diverse methods available for developing such complex particles, spray-drying is currently the most commonly employed approach [21]. Spray-drying is a pharmaceutical manufacturing process wherein solution, emulsion or

suspension containing the desired API is atomized into fine droplets and subsequently dried using hot gas, resulting in the formation of dry particles [22]. This method is frequently used due to the ease of modification of various parameters, such as atomization and drying conditions, liquid formulation, and equipment design [13,23]. Spray-drying allows the precise control of the attributes of the particles, enabling modification of several properties, thereby enhancing the aerosolization performance of the resulting powder [13].

Particle engineering involves the production of a wide range of particle types, including Pulmosphere® and deflated particles. The Pulmosphere® process, employed in the production of TOBI® Podhaler, a commercially available DPI, involves the generation of porous low-density particles through emulsion atomization [22]. The distinct porous morphology and hydrophobic surface result in the development of a carrier-free formulation that exhibits reduced interparticle cohesive forces [24]. Consequently, this formulation demonstrates enhanced aerodynamic performance, ultimately improving the overall efficiency of the powder [25].

Besides investigating porous particle shapes, deflated morphologies are also under investigation. Cui *et al.* [26] have synthesized Netilmicin-based particles with a corrugated surface, while Mangal *et al*. [27] have investigated the effect of L-Leucine concentration on the deflated morphology of the particles. Dufour *et al*. [28] successfully developed deflated particles by spray-drying a solution containing hydroxypropyl-β-cyclodextrin (HPB) and budesonide [28]. Impaction tests revealed significantly superior aerosolization performance compared to Miflonide®, a carrier-based formulation [28]. In addition, Lechanteur *et al*. [29] demonstrated the impact of the composition of the spray-dried liquid feedstock on the morphology of the particles. The authors defined a new deflation ratio as the product of the number of dimples and their depth, which exhibited a discernible correlation with the aerosolization performance of the resulting powder [29]. Subsequently, employing a Design of Experiment methodology, the intricate relationship between specific spray-drying parameters and powder performance was explored [30]. These analyses led to the identification of optimal powder formulation and drying parameters in our group.

This formulation comprises two carbohydrates (HPB, 50% *m/v*; raffinose, 50% *m/v*), an amino acid (L-leucine, 5% *m/v*), and two drugs (budesonide, 0.66% *m/v*; formoterol fumarate, 0.02% *m/v*). HPβCD was chosen for its ability to produce particles with desirable aerodynamic properties, facilitating effective aerosolization. The addition of raffinose aimed to optimize the formulation's cost-effectiveness, while leucine was included to provide moisture protection. Consequently, the optimized powder demonstrates a deflated morphology and exceptional aerosolization performance, achieving a fine particle fraction of nearly 60% for both drugs. These results hold significant promise in the context of inhaled powder development. However, the suboptimal flow characteristics resulting from the small particle size (d0.5 = 2.56 µm) underscore the need to address this challenge, as it is crucial for enhancing the flowability of the spray-dried (SD) powder and enabling reproducible and accurate capsule filling. Conventional methods such as dry and wet granulation are impractical for inhalation powders [31]. Furthermore, the process of creating soft pellets remains poorly understood from a physical standpoint, leading to inadequate control [32]. For these reasons, this research aims to explore an alternative option, which involves combining micronized atomized powder with larger lactose particles. Two different types of lactose, namely Inhalac® 70 and Inhalac® 230, were used in order to evaluate their size and surface properties (roughness, area…) on blend

homogeneity, blend flowability, and aerosolization performance. Five adhesive mixtures with varying lactose proportions, ranging from 0% to 100%, were prepared and studied. Moreover, a capsule drum filler was employed to assess the reproducibility of filling, considering an industrial perspective. Finally, the dissociation of the powder during inhalation was investigated using different inhaler resistances.

Overall, this study aims to improve the flow characteristics of the micronized powder, enhancing processability while preserving the superior performance achieved through particle engineering. The findings presented herein contribute valuable insights to address critical issues in the pharmaceutical manufacturing of inhalation powders.

2. Materials and methods

2.1. Materials

Budesonide (BUD) micronized and formoterol fumarate dihydrate (FOR) were used as model APIs and were supplied from Minakem (Dunkerque, France) and CHEMO Industriale chimica (Saronno, Italy), respectively. Hydroxypropyl-β-cyclodextrin (HPB) was kindly provided by Roquette (Lestrem, France). Raffinose pentahydrate (RAF) was obtained from Acros Organics (ThermoFisher Scientific, Geel, Belgium). L-Leucine (LEU) was purchased from Tokyo Chemical Industry (Tokyo, Japan). Inhalac® 70 (Lac70) and Inhalac 230® (Lac230), inhalation grades of α lactose monohydrate, were procured from Meggle (Wasserburg, Germany).

HPLC grade methanol and acetonitrile were purchased from J.T Baker (Deventer, The Nederlands), HPLC grade ethanol absolute from ThermoFisher Scientific (Geel, Belgium), ammonium acetate and ammonia solution 25% from Sigma-Aldrich (St. Louis, MO, US). Water was purified via a Millipore system (18.2 MΩ/cm resistivity, Milli-Q) before filtration through a 0.22 µm Millipore Millipak – 40 disposable filter units (Millipore Corporation, USA).

Inhalation grade hydroxypropyl methylcellulose capsules size 3 were obtained from Capsugel® (Lonza, Colmar, France). Capsules were used with low resistance (LR) (code: 239700001AB) and high resistance (HR) (code: 239700002AA) Plastiape RS01 monodose devices (Berry, Evansville, IN, US).

2.2. Spray-drying

Pulmonary particles were prepared by spray-drying a 15.75% (*w/v*) solution using the Procept 4M8-Trix Formatrix spray-dryer (Procept, Zelzate, Belgium) with a bi-fluid nozzle. The solution before atomization was prepared by dissolving HPB and RAF separately in Milli-Q water. The two carbohydrates were used at a ratio of 50:50 (*w/w*). After complete dissolution, BUD and FOR were added to HPB and RAF, respectively, at concentrations of 0.656% and 0.020%. After agitation and dissolution, the two liquid phases were combined, and 5% (*w/v)* LEU were added. The different components of the solution were chosen following a design of experiments previously conducted by Lechanteur et al [30]. The solution was spray-dried under the following conditions: inlet temperature 180 °C, outlet temperature 95 °C, feed flow rate 1.8 g/min, nozzle gas pressure 4 bar, inlet gas flow 0.4 m^3/min, nozzle diameter 0.4 mm. The above conditions were selected by preliminary experiments [29,30]. The process yield is calculated for each formulation according to the following equation (Eq (1)).

$$\text{Process yield (\%)} = \frac{\text{Mass of powder collected after atomization (g)}}{\text{Mass of total diluted powder before atomization (g)}} \times 100 \quad (1)$$

2.3. Preparation of powder blends

Five mixtures composed of different proportions of SD powder and Lac70 were prepared under ambient conditions (Table 1). The mixtures contain decreasing amounts of atomized powder, and the fifth mixture contains the API in micronized form, in the same percentages as in the SD powder alone, namely 0.66% of BUD and 0.02% of FOR. SD powder was sieved through a 315-µm sieve to break up large aggregates prior to blending. The mixtures were prepared

by initially mixing the SD powder or the micronized APIs and the coarse lactose manually using a sandwich layer technique. Mixing was then continued with a Turbula® blender (T2A; Willy A. Bachofen, Switzerland) operated at 66 rpm for 45 minutes [33,34]. Moreover, a blend with Lac230 was also prepared using the same procedure and consists of 50% SD powder and 50% Lac230 to compare the properties of lactose. All prepared blends were stored in opaque glass containers under ambient conditions.

Table 1: Composition of the five Lac70-mixtures (w/w).

Mixture	SD powder	Micronized APIs	Lac70	Lac230
1	100	0	0	0
2	80	0	20	0
3	50	0	50	0
4	20	0	80	0
5	0	0.68	99.32	0
6	50	0	0	50

2.4. Evaluation of powder blends homogeneity

The homogeneity of each powder mixture was evaluated by taking 10 samples from different positions in the powder bed right after the preparation of the blends. The 50:50 mixtures were stored at room temperature and protected from light. The homogeneity of each blend was also assessed after 2, 4, 6 and 8 weeks of storage. To do so, each sample contained the equivalent of 20 ± 2 mg of SD powder and was dissolved in 35% water – 65% methanol. Both the BUD and the FOR content of the samples were quantified using high performance liquid chromatography (HPLC) following a method reported in section 2.5. Recovery rate was calculated using the following equation (Eq (2)). The blend homogeneity was evaluated based on the relative standard deviation (RSD) across 10 sample points. This measure is the ratio of the standard deviation to the mean expressed as a percentage. Blends showing ≤ 5% RSD of the mean BUD and FOR recovery rate were considered as homogeneous [35–37].

$$Recovery\ rate = \frac{Measured\ drug\ content}{Theoretical\ drug\ content}\ x\ 100 \quad (2)$$

2.5. High-Performance Liquid Chromatography Analysis

Quantification of BUD and FOR was performed using an Agilent 1100 Series HPLC (Santa Clara, USA). A 3x50 mm column filled with 3,5 μm C18 (X Bridge BEH C18 Column) was used, along with a UV detector operating at 243 nm. The mobile phase consisted of ammonium acetate buffer at pH10 / methanol with the following gradient mode: 0min – 55/45 (v/v); 1 min - 55/45 (v/v); 2 min - 35/65 (v/v); 7 min - 35/65 (v/v); 8 min - 55/45 (v/v); 20 min - 55/45 (v/v). The flow rate was 0.7 mL/min, and the column temperature was set at 30 °C while the sampler was set at 10 °C.

The validation of the process was conducted using total error as the decision criterion. Acceptance limits were established at 10% within the range of 100 µg/ml - 1 µg/ml for BUD and 10 µg/ml - 0.1 µg/ml for FOR. Accuracy profiles for both BUD and FOR were constructed utilizing their respective selected calibration models: weighted quadratic regression ($1/X^2$) for BUD and weighted linear regression ($1/X^2$) for FOR. In the case of BUD, the limit of detection (LOD) and lower limit of quantification (LOQ) were determined to be 0.2899 µg/ml and 4.395

µg/ml, respectively. For FOR, the LOD was measured at 0.1161 µg/ml, with an LOQ of 0.9282 µg/ml. All validation outcomes were computed using the Enoval software (Arlenda, Liege, Belgium).

2.6. Solid state characterization

2.6.1. Particle size distribution (PSD)

The particle size distributions of the powders were determined by laser diffraction using the Malvern Mastersizer 3000® (Malvern Instruments, Worcestershire, UK) equipped with an AeroS unit. The high-energy venturi was used to ensure the dispersion of agglomerates. Samples of approximately 150 mg were dispersed in air using 4 bar pressure. A micro-tray was used due to the small quantity of powder employed, with a feed rate set at 30% to achieve an obscuration range of 0.5-8%. The particle size of the powders was analyzed using Malvern Mastersizer software. The average PSD was measured from three replicates of each sample.

2.6.2. Water content

The residual water content of all powders was chemically quantified by coulometric Karl Fischer titration on a Mettler Toledo V30 Volumetric Titrator. Approximately 40 – 80 mg of powder was added to the titration cell containing Hydranal® Composite 5K and the water content was measured. All powders were analyzed in three replicates.

2.6.3. Particle morphology

The particulate morphology was examined through scanning electron microscopy (SEM) using either a Philips XL30 ESEM or a FEI Quanta 600, following metallization with Au (~50 nm). Representative micrographs were acquired, and a dozen particles were randomly selected from each powder for morphological characterization.

2.6.4. Bulk density and tapped density

The bulk and tapped densities were measured using the Granupack (Granutools, Awans, Belgium). This instrument is an automated tapped density measurement method characterizing the packing dynamics of a powder. At the beginning of the measurement, the powder is placed in a metallic tube. The diameter and the length of the tube used are D = 26 mm and L = 70 mm. Afterwards, a light hollow cylinder is placed gently on top of the powder to keep it flat during the compaction process. The cylindrical cell containing the powder performs a succession of free falls, called “taps”. In this study, measurements were performed with 35 mL of powder subjected to 500 taps. After each tap, a distance sensor measures the position of the hollow cylinder. From this distance, the height and the volume of the powder bed are computed. As the powder mass is known, the bulk density, which is the ratio between the mass and the volume of the powder, is calculated after each tap. The Hausner ratio is defined as tapped density divided by initial bulk density. This ratio is used to evaluate powder flowability.

2.6.5. Cohesive index

The cohesive index was measured using the Granudrum (Granutools, Awans, Belgium). This automated powder flowability-measuring instrument allows for the assessment of a powder's flowability and its cohesion index. A transparent-walled drum, horizontally oriented and hermetically sealed, is partially filled with a sample of powder. During the measurement, the drum rotate with an angular velocity ranging from 2 RPM to 60 RPM. Snapshots are taken during each rotation, and an edge detection algorithm identifies the air/powder interface in each image. Following the image capture process, the average position of the air/powder interface and the corresponding fluctuations are computed. The dynamic cohesive index is measured using the interface fluctuations. The values presented in this article are expressed for a rotation speed of 6 RPM.

2.7. Capsules filling

The capsules used in the impaction tests (see section 2.8) were filled using two different methods: manual and semi-automatic filling.

2.7.1. Manual filling

Size 3 HPMC capsules filled manually with a spatula contained the equivalent of 15 ± 1 mg of SD powder content. The powder is weighed directly into the capsule on an analytical balance (AT261 DeltaRange®, Mettler Toledo, Switzerland). Capsules were filled just before the impaction test and were stored in an opaque glass container.

2.7.2. Semi-Automatic filling

The Drum TT (Harro Höfliger, Allmersbach im Tal, Germany) is a compact volumetric filling machine used to simulate the industrial process of filling capsules. This machine consists of a drum dosing system for minimal quantities and a pneumatic unit to control vacuum and compressed air. The vacuum is set in order to change the compaction of the powder. A representation of the filling process is shown in Figure 1. Firstly, 2 g of powder were filled into the powder hopper for a series of 24 capsules. The stirrer was rotated 360° for each filling. For this study, a vacuum of – 0.55 bar was adjusted for the filling step and a 15,215 mm^3 dosing bore was used. The ejection pressure was set to 0.45 bar. After saturating the 1 μm filter, each capsule was filled with several pellets of powder in order to have the equivalent of 15 mg of SD powder content per capsule. The filling tests were performed under a controlled humidity of 30 ± 5%.

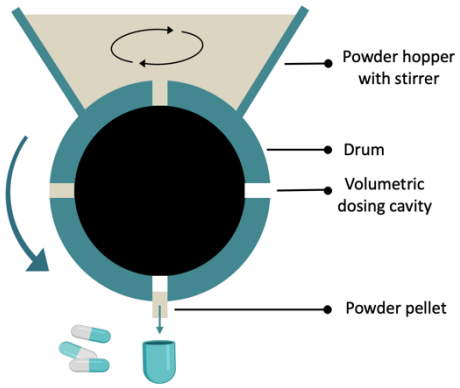

Figure 1: Representation of Drum TT.

2.7.3. Mass uniformity of dosage units

To verify the reproducibility of capsule filling using Drum TT, a mass uniformity test was performed. The filling weight variation was determined by individually weighing 200 capsules before and after drum filling using an analytical balance (AT261 DeltaRange®, Mettler Toledo, Switzerland). The net weight of fill content was determined by subtracting the weight of a capsule filled with powder from the weight of the same capsule when empty. The average mass, mass deviations from the average mass and percentage deviation were calculated. These deviations were compared to the tolerated limits specified in the European pharmacopoeia. Based on the table in procedure 2.9.5, a maximum deviation of 10% around the average mass is accepted. According to this procedure, a maximum of 2 units can deviate from this percentage to be compliant, and no unit can deviate by more than twice this percentage.

2.8. *In vitro* lung deposition evaluation

The *in vitro* aerosol performance was determined by a *Next Generation Impactor* (NGI; Apparatus E, Copley, Nottingham, UK), as per European pharmacopoeia. This 8 stages impactor is equipped with a pre-separator and the induction port is connected to the device with a suitable mouthpiece adapter. The air flow rate was adjusted to 30 or 100 L/min by a flow controller (TPK; Copley, Nottingham, UK) for a duration of 2.4 s at both flow rates. Plastiape RS01 high- and low-resistance inhalers were used in this study and a batch of 12 capsules were shot in each run. The powder deposited at each level was recovered with an appropriate volume of 65% v/v methanol in water mixture and subsequently analyzed by HPLC. The recovery dose (RD) represents the total mass of the API recovered from the capsules and the device to the last stage of the NGI. The percentage of drug released from the inhaler is defined as the emitted dose (ED) and is calculated from the cumulative amount of powder from the induction port to the last stage of the NGI. The fine particle dose (FPD) is the mass of drug with aerodynamic diameter lower than 5µm and the fine particle fraction (FPF) is calculated using the following equation (Eq (3)).

$$FPF = \frac{Mass\ of\ particles{<}5\mu m}{Recovery\ dose\ (RD)}\ x\ 100 \qquad (3)$$

2.9. Statistical analysis

Statistical analysis was performed using One-Way ANOVA and Tukey's tests at a significance level of 0.05 with the GraphPad Prism 9 software.

3. Results and discussion

3.1. Selection of the Ratio of Spray-dried and Lactose in Mixtures

To improve the flowability of the micronized SD powder [30] and facilitate consistent and precise capsule filling, five adhesive mixtures were prepared with varying proportions of Lac70, ranging from 0% to 99.32%. As shown in Table 1, the mixtures range from 100% SD powder in mixture 1 to 99.32% Lac70 in mixture 5. The first selected lactose grade for optimizing flow properties is Lac70, characterized by an average particle size of 229.28 μm.

Initial experiments were conducted to assess how the flow characteristics of the powder were influenced by the powder blends. Figure 2 illustrates the tapped densities obtained for the 5 blends. A significant enhancement in flow properties becomes evident with increasing Lac70 quantity in the mixtures. Specifically, tapped densities of 0.27, 0.48, 0.63, 0.83 and 0.89 were observed for mixtures 1, 2, 3, 4 and 5, respectively. An increase in tapped density, and consequently, a decrease in the Hausner ratio, results in improved flow properties.

However, the incorporation of Lac70 may adversely affect the efficiency of pulmonary deposition for the atomized powder by hindering the effective detachment of particles and impeding optimal aerosolization of the powder. Consequently, impaction tests were conducted under specific parameters, with a flow rate of 100 L/min and a low-resistance (LR) inhaler device.

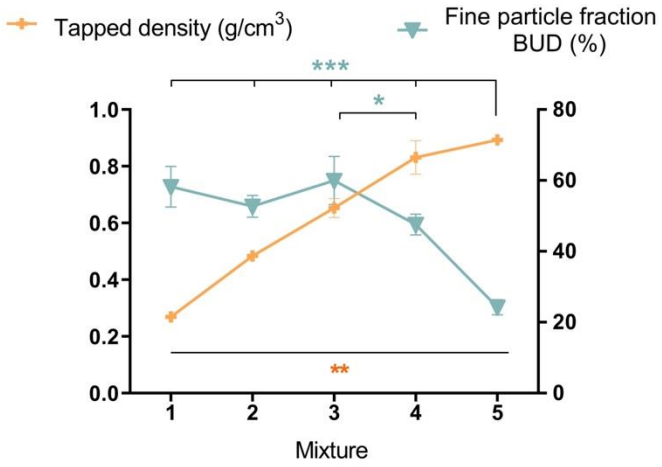

Figure 2 : Tapped density and budesonide (BUD) fine particle fraction of the Lac70-blends ($p < 0.05$). The ratios of SD/Lac70 in the mixtures are as follows: 100:0 for mixture 1; 80:20 for mixture 2; 50:50 for mixture 3; 20:80 for mixture 4 and 0:99.32 for mixture 5.

Figure 2 shows the *in vitro* lung deposition results for the five independently prepared blends, with a specific focus on the FPF of BUD representing the quantity of powder characterized by an aerodynamic diameter ranging from 1 to 5 μm. The results indicate a notably high *in vitro* lung deposition of BUD for blends containing SD powder and Lac70. Indeed, mixtures 1 to 4 exhibit FPF for BUD of 58.23%, 52.69%, 58.64% and 47.59%, respectively. An apparent declining trend in FPF is evident in mixture 4. One hypothesis suggests that lactose particles may exert excessive inter-particle cohesion with SD particles, resulting in a decreased

aerosolization of the inhalation powder [23]. In contrast to blends involving SD powder with different quantities of Lac70 (mixtures 1 to 4), the mixture 5, containing micronized APIs (0.68%) and Lac70 (99.32%), exhibited significantly lower deposition of BUD, with a FPF of 24.23%. This result suggests that the deflated shape of the SD particles, which have an average size of 2.56 µm, may play a crucial role in achieving deep lung deposition.

Based on a compromise between high aerosolization and improved flow characteristics of the blend, the mixture 3 was selected for further in-depth analysis. Indeed, mixture 3, consisting of a 50% blend of SD and Lac70, demonstrates enhanced flow characteristics in comparison to the exclusive use of SD. This enhancement in flow properties is achieved without compromising the remarkably high *in vitro* lung deposition.

3.2. Impact of Lactose Surface Properties on Inhalable Powder Mixtures

To identify the most optimal formulation, the examination of different lactose types within the mixture has been undertaken. The external surface and roughness of the carrier influence the physical interactions between the drug or SD powder and the lactose crystals. These interactions impact critical parameters, including the arrangement of micronized SD particles on the lactose surface, the flow characteristics, the uniformity of the mixture, and the potential for powder aerosol dispersion [38,39]. For these reasons, we employed another type of sieved lactose monohydrate, namely Lac230. Classically, lactose grades are defined based on their respective mesh classifications. Lac230, having passed through a finer mesh sieve, achieves a smaller particle size (d50) of 101.54 µm (± 0.35). In contrast, Lac70, sieved through a coarser mesh, presents a larger particle size (d50) of 229.28 µm (± 0.65). Moreover, the manufacturer evaluated the surface area per mass of samples (m^2/mg) using the BET (Brunauer, Emmett and Teller) theory. The surface area of Lac70 and Lac230 is 0.13 and 0.16 m^2/g, respectively [40].

The spatial arrangement of SD particles and lactose within the blends was evaluated through SEM. Figure 3 presents micrographs illustrating the 50:50 blend with Lac70 in Figure 3a and Lac230 in Figure 3b. As evident in the magnified images, the SD particles are distinguished by their deflated morphology. The micronized particles of atomized powder appear to adhere to the large lactose particles, forming adhesive mixtures [33].

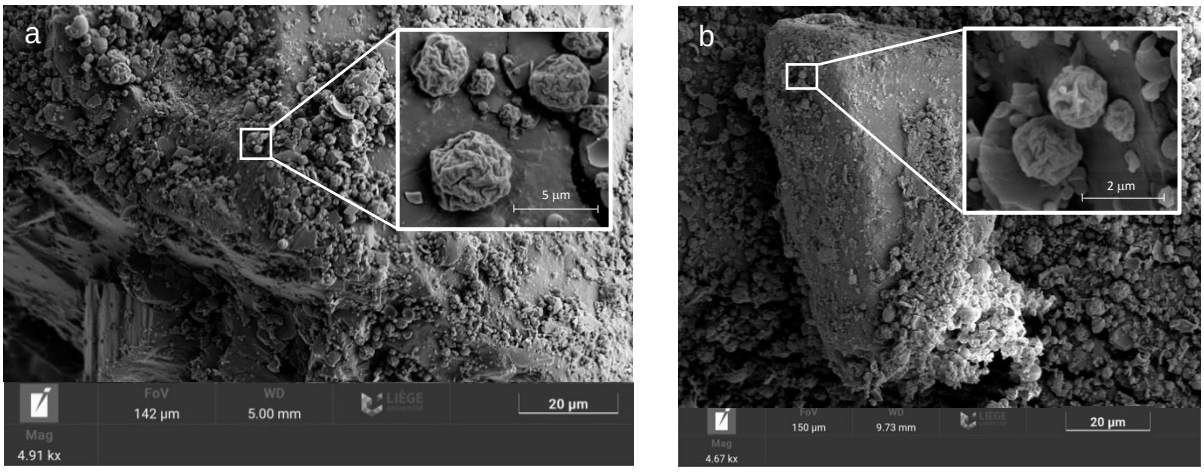

Figure 3 : Scanning Electron Microscopy of 50:50 blends of spray-dried powder and Lac70 (a) and Lac230 (b).

The impact on the flowability of powder blends was initially examined. The inclusion of the coarse lactose particles significantly ($p < 0.05$) improves the Hausner ratio, and thus, the flow properties of the final blends. Indeed, this can be observed in Table 2, with Hausner ratio values decreasing from 1.58 for the SD powder to values of 1.42 and 1.39 for the blends with Lac230 and Lac70, respectively.

These observations are also validated through the assessment of the cohesive index. The cohesive index plays a crucial role in assessing the cohesion of a powder, a parameter that significantly influences powder flow. Intense cohesion within a powder leads to irregular flow, while reduced cohesion results in a more consistent flow. An approaching zero cohesive index signifies minimal cohesion in the powder. Conversely, a highly cohesive powder hinders manipulation as it adheres excessively to the drum walls, preventing the capture of snapshots. Cohesive index of 52.65 and 44.16 were measured for blends containing Lac230 and Lac70, respectively. No results were obtained when manipulating with the SD powder alone. Indeed, due to its strong interparticle forces, the powder adhered to the drum, preventing the assessment of the powder interface in the captured images. This demonstrates the enhancement in powder flow characteristics following the incorporation of lactose. Additionally, it is noteworthy that the flow tends to be more favorable in the Lac70-blend compared to Lac230. A lower cohesion index is obtained with Lac70, suggesting that interparticle interactions within the powder may be less pronounced than in the Lac230-blend. The same trend is observed when examining the Hausner index values (Table 2), with a slightly lower Hausner ratio observed with Lac70. This can be notably explained by the larger particle size of Lac70 compared to Lac230 [41].

Table 2: Particle size, flowability and water content for the SD powder, for the 50:50 mixture of SD and Lac230 and for the 50:50 mixture of SD and Lac70 (n=3).

Material	Particle size (μm)			Flowability			Water content (%)
	d_{10}	d_{50}	d_{90}	Cohesive index	Tapped density (g/cm^3)	Hausner ratio	
SD powder	1.17 ± 0.02	2.56 ± 0.13	5.32 ± 0.41	/	0.27 ± 0.01	1.58 ± 0.06	2.69 ± 0.53
50/50 mixture SD/Lac230	1.585 ± 0.05	13.70 ± 4.43	132.83 ± 4.10	52.65	0.59 ± 0.01	1.42 ± 0.12	5.45 ± 0.51
50/50 mixture SD/Lac70	1.99 ± 0.44	119.32 ± 25.98	294.55 ± 58.99	44.16	0.63 ± 0.01	1.39 ± 0.01	4.83 ± 0.71

In contrast to the API-carrier blends typically present in commercially available inhalation powders, the blends formulated in this study exhibit a significantly higher proportion of micronized particles, accounting for 50% of the total composition. Adhesive blends, also referred as ordered blends, consist of micronized particles (<5 μm) and significantly larger particles (>100 μm) [11,12]. While random blends consist of particles with a similar size distribution, where gravitational forces outweigh interparticular forces, adhesive blends are characterized by adhesive forces that surpass gravitational forces [11]. In these blends, micronized particles adhere to the surface of coarse particles through various interparticular forces [33]. The predominant forces facilitating this adhesion are van der Waals forces, while other forces, such as electrostatic forces and capillary forces, also come into effect [11,33,42].

Achieving a balance between cohesive forces (drug-drug) and adhesive forces (drug-coarse particle) is essential for attaining a stable and homogeneous blend. To achieve this balance, adhesive forces must surpass cohesive forces. The ratio between these two forces impacts the uniformity of the API content in the blend [11,33]. Indeed, the disparity in particle size leads to a risk of segregation, a phenomenon commonly observed in powder mixing processes, resulting in issues related to drug content homogeneity and aerosolization performances [12,37]. The uniformity of the mixture is a determining factor in the effectiveness and robustness of dry powder inhalers. The attractive forces between micronized powder and lactose must be sufficiently robust to sustain blend uniformity over time, but not excessively strong to allow particle detachment and optimize powder aerosolization performance [33,43]. To assess the homogeneity of the BUD and FOR content, powder assays were conducted immediately after the mixture preparation, as well as at 2, 4, 6 and 8 weeks thereafter.

The blends uniformity, represented by RSD, is shown in Figure 4a and in Suppl. Data 1. After 8 weeks of storage, the content variability (RSD) of BUD and FOR within the mixtures remains below 5%, a threshold deemed acceptable for inhalation powders [44]. The adhesion forces between atomized powder and particles of lactose, which spontaneously form during mixing, are substantial enough to maintain the stability of the blends without segregation. This can be explained notably by the small particle size of the SD powder, with a mean geometric diameter of 2.56 μm, as observed in Table 2. Indeed, Saharan *et al*. [33] explained that particles smaller than 5 μm are preferred to achieve a homogeneous adhesive blend with lactose particles. This is attributed to electrostatic charges between the micronized particles and the lactose particles preventing the segregation phenomenon [11]. Indeed, small particle size significantly influences charging behavior, especially in relation to the triboelectric effect. When two

materials come into contact, they initiate a process of charging, known as the triboelectric effect [45]. This process of charge exchange depends on several factors, such as particle size, shape, and surface roughness, all of which collectively impact interactions within adhesive blends [46]. The residual water content of powders also impacts the homogeneity of an adhesive blend. Indeed, an increase in moisture content enhances capillary bridges and adhesion between SD powder and lactose [11,33]. The specific residual water percentages in the blends, measured at 5.85% and 4.83% for the Lac230- and Lac70-blend (Table 2), respectively, might contribute to the stabilization of these blends.

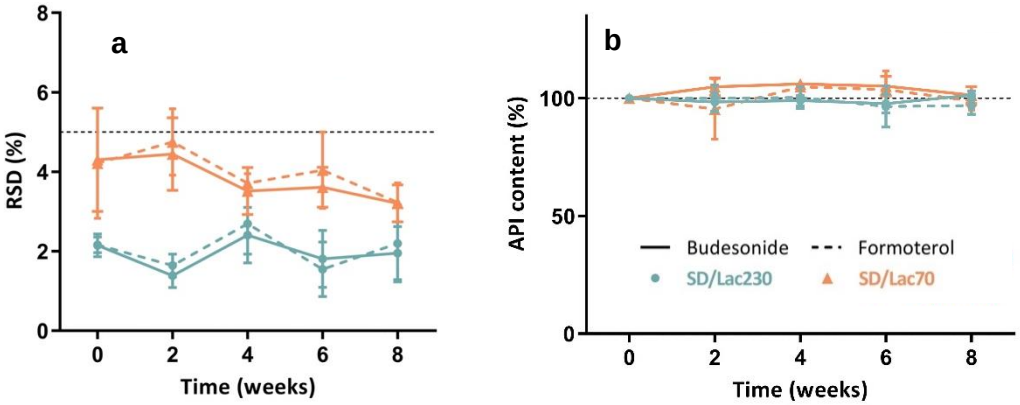

Figure 4: Relative standard deviation (RSD) (a) and content (b) of budesonide and formoterol fumarate within the Lac230- and Lac70-blends after 0, 2, 4, 6 and 8 weeks of storage.

Even if all blends are homogeneous, the Lac230-blend demonstrates superior results, as evidenced by RSD values ranging from 1.38 to 2.41 for BUD and 1.55 to 2.69 for FOR. In contrast, the Lac70-blend demonstrates lower homogeneity, exhibiting RSD values ranging from 3.20 to 4.45 for BUD and 3.23 to 4.75 for FOR. The improved homogeneity with Lac230 can be explained by two hypotheses. The first one relates to the higher surface area (attributed to the smaller size), which could result in increased interparticulate forces. The second hypothesis involves the surface roughness of both lactoses. As explained by Podczeck *et al*., the surface roughness of Meggle products increases with a decrease in particle size [38]. This phenomenon can account for the enhanced interparticular interactions between SD powder and Lac230 [39].

Figure 4b shows the measured content of BUD and FOR after 0, 2, 4, 6, and 8 weeks. The values are presented relative to time 0, wherein the content of BUD and FOR is considered as 100%. After an 8 weeks-storage period, content values approaching 100% are attained for FOR and BUD in both the mixture containing SD powder and Lac70, and the mixture containing SD powder and Lac230. This confirms the high quality and uniformity of the blends.

Mixtures involving SD powder and either Lac230 or Lac70 in a 50:50 ratio have been shown to enhance the flow properties compared to SD powder alone. Despite the differences between the two lactose grades used in the blends, adhesive forces contribute to the sustained homogeneity over time, preventing segregation.

3.3. Aerosolization Performance of 50:50 Blends

The 50:50 blend of SD powder and lactose was selected based on a compromise between flowability enhancement and deep BUD *in vitro* lung deposition. Herein, the homogeneity of deposition for both active ingredients (BUD and FOR) was also evaluated, along with the impact of inspiratory flow rates and the type of lactose used for blending.

Figure 5a presents the FPF measured for BUD and FOR within the SD powder, the 50:50 powder blend of SD and Lac230, and the 50:50 powder blend of SD and Lac70. Impaction tests were carried out with a LR device at two inspiratory flow rates: 100 L/min and 30 L/min. These parameters were compared to assess *in vitro* lung deposition depending on the applied flow rate. This comparison aimed to differentiate between subjects with maximal inspiratory capacity and those with respiratory difficulties, such as asthma patients [47].

At 100 L/min, FPFs depicted in Figure 5a demonstrate that the blends do not compromise the aerosolization of the powder. Specifically, FPFs of BUD obtained for the blend composed of Lac230 and the blend composed of Lac70 are 64.58% (± 2.52) and 58.97% (± 4.65), respectively, while the FPF of the SD powder alone is 58.23% (± 5.71). Similar trends are observed for FOR, with FPF values of 62.12% (± 0.56), 64.59% (± 6.30), and 59.87% (± 6.44) for the Lac230-blend, the Lac70-blend, and the SD powder. These FPF values are high, indicating effective separation of micronized particles from lactose particles within the powder. The interparticle forces that facilitate adequate adhesion between SD particles and lactose particles are not overly strong, thus allowing for a high aerosolization performance of the SD powder [43]. Figure 5a also showcases a uniform deposition of both active ingredients, regardless of the type of powder. This homogeneous deposition is of utmost importance as it ensures dose consistency and uniformity [48–50].

However, a slight downward trend in FPF is observed at a flow rate of 30 L/min compared to the flow rate of 100 L/min. This can be ascribed to variations in the deposition of API across different stages of the NGI depending on the flow rate. Figure 5c and Figure 5d illustrate the deposition of BUD by aerosolized capsule, from the inhaler to the Micro-Orifice Collector (MOC), referred to as stage 8. Capsules contain 15 mg (±1) of SD powder, whether filled with SD powder alone or with one of the blends. The aerosolization of BUD under an airflow rate of 100 L/min is depicted in Figure 5c, and under 30 L/min in Figure 5d. The quantity of recovered BUD at the device level significantly increases with a flow rate of 30 L/min, regardless of the powder. This is also apparent in Figure 5b, which depicts the emitted dose (ED) of BUD, representing the quantity of powder released from the device. A significantly higher ED ($p < 0.05$) is observed when a flow rate of 100 L/min is applied. This can be explained by reduced turbulence in the inhaler at low flow rates, potentially leading to a decrease in the dissociation of micronized powder and lactose particles [51]. Indeed, while the grid present in the RS01 contributes to deagglomeration, it also depends on the turbulence generated by the airflow and the resistance of the device [33,52] The greater the inspiratory airflow increase, the higher the energy available for powder deagglomeration. The LR of the RS01 used requires a high airflow rate, at least 90 L/min, to generate effective deagglomeration from lactose particles [51]. This observation is evident through the decreased powder deposition in the pre-separator when using a flow rate of 100 L/min, indicating a higher probability of the formulation to being deagglomerated [53].

It can also be observed that the amount of powder retained in the device decreases significantly ($p < 0.05$) when the blends are aerosolized, in comparison with the SD powder alone (Figure 5c and Figure 5d). The decline in cohesive forces, either between powder particles or between particles and the inhaler, leads to increased dispersion of the powder outside the capsules and the inhaler [33,54]. This also results in a significant increase ($p < 0.05$) in the ED for the blends compared to the SD powder at 30 L/min. While the achieved ED for BUD in the SD powder is 65.53% (± 1.51), values of 79.32% (± 2.19) and 78.78% (± 6.67) are obtained for the Lac230-blend and the Lac70-blend, respectively, as observed in Figure 5b.

To resume, no reduction in aerosolization is observed when comparing the blends to SD powder alone. Moreover, the *in vitro* lung deposition of both APIs exhibits uniformity. A trend of decreased FPF is observed at a low inspiratory flow rate, corresponding to a decrease in the ED at 30 L/min compared to 100 L/min, using a LR device. However, it is important to highlight that the blend enhances the emitted dose, minimizing the powder retained within the inhaler.

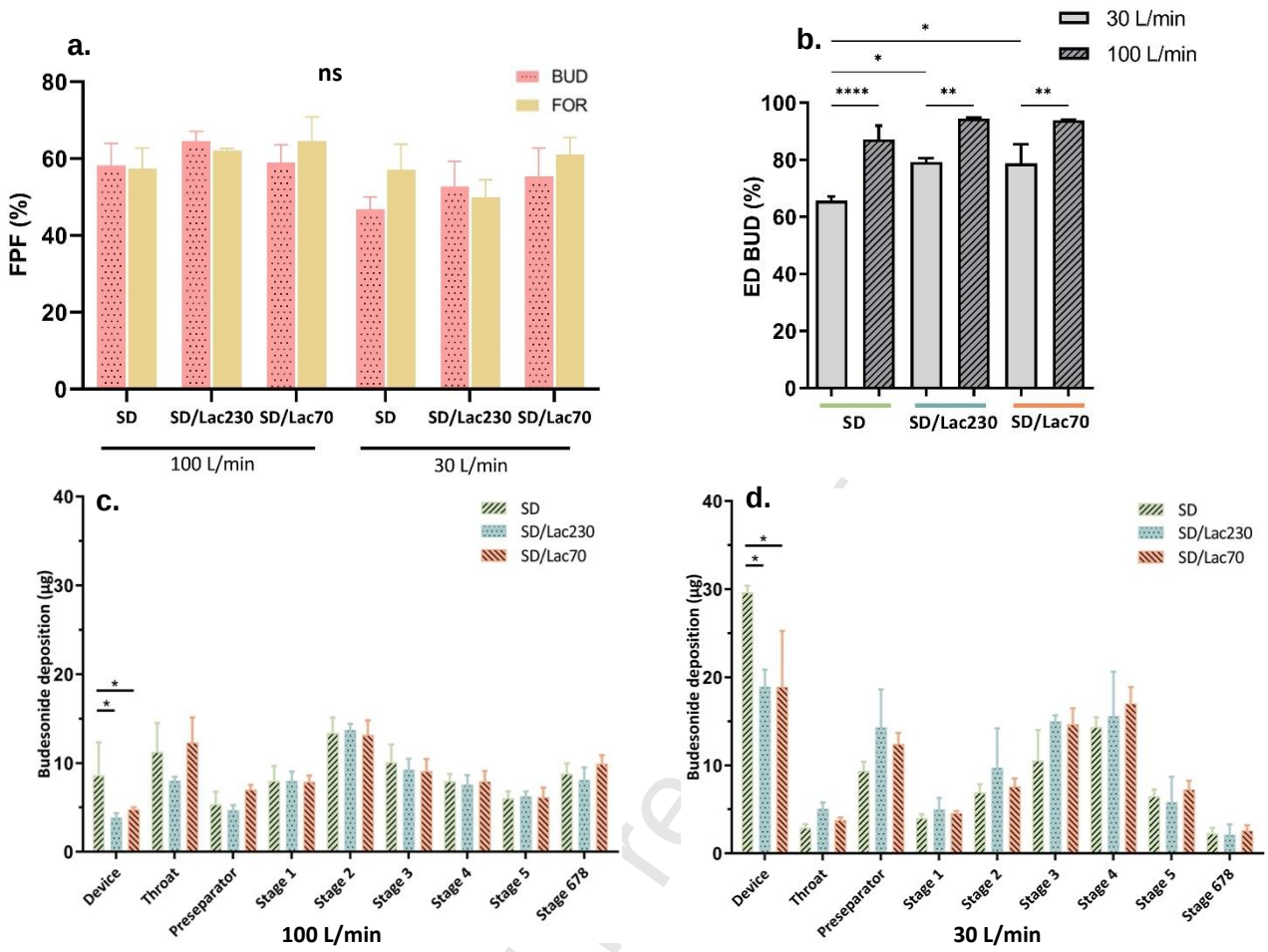

Figure 5: Fine particle fraction of budesonide (BUD) and formoterol fumarate (FOR) contained in the spray-dried powder and in the two blends measured at air flow rates of 100 and 30 L/min using a low resistance RS01 (n=3) (a); Emitted dose of budesonide (BUD) contained in the spray-dried powder and in the two blends measured at air flow rates of 100 and 30 L/min using a low resistance RS01 (n=3) (b); Deposition of budesonide (BUD) after aerosolization of the spray-dried powder (SD), the Lac230-blend (SD/Lac230) and the Lac70-blend (SD/Lac70) into the NGI at an air flow rate of 100 L/min (c) and 30 L/min (d) using a low resistance RS01 ($p < 0.05$).

3.4. Drum filling

The impact of SD powder flowability enhancement on capsule filling was evaluated. The evaluation of industrial powder processing was conducted using SD powder alone and lactose-mixtures with the Drum TT, a compact volumetric filling machine. This equipment facilitates the precise dosing of minimal powder quantities and is used to test and optimize powder formulations in the galenic area. The Drum TT features a borehole that is filled with powder through a vacuum system, followed by the ejection of the resulting powder plug. Ensuring optimal powder flowability is significant to ensure the complete ejection of powder plugs from the dosing bore, thereby ensuring reproducible capsule filling outcomes.

To obtain approximately 15mg of SD powder content per capsule with a vacuum set at -0,55 bar, 2 plugs of SD powder are required, whereas 3 plugs are needed for mixtures containing

lactose. The capsule filling mass using the drum is shown in Figure 6. According to the European Pharmacopeia, among 20 capsules, a maximum of 2 capsules can deviate by 10% from the average mass, and the mass of any single unit cannot deviate by more than twice that percentage.

Out of a total of 200 capsules filled with SD powder, a significant number of capsules have a mass exceeding the established limits, as indicated in Figure 6a. Indeed, the mass of 65 capsules exhibits a fluctuation ranging from 10% to 20% relative to the mean. Additionally, 14 capsules have a mass deviation exceeding 20% compared to the average capsule weight. The SD powder alone adheres within the dosing bore, causing the formation of plugs with varying masses. Ensuring consistent filling with the SD powder alone poses a significant challenge due to its high cohesion, leading to issues such as adhesion to container walls and the occurrence of arching [55]. The substantial cohesive forces of the SD powder may also prevent the ejection of the plug from the drum. This accounts for the higher significant variability observed during the filling process, evidenced by an RSD of 11.35%.

Conversely, blends facilitate reproducible filling, with no capsule mass deviating by more than 10% from the average weight, as evidenced in Figures 6b and 6c. The mass profiles obtained from both blends exhibit considerably higher consistency, presenting a distinct contrast when compared to the profile of the SD powder. RSDs of 3.09% and 2.08% are attained for the Lac230- and Lac70-blends, demonstrating significantly reduced variability compared to the filling process involving the micronized powder alone. This demonstrates a correlation between the improvement of the flowability and the consistency of the filling process. The incorporation of lactose in the mixtures thereby facilitates powder handling and enhances the dosage uniformity though improved flow properties.

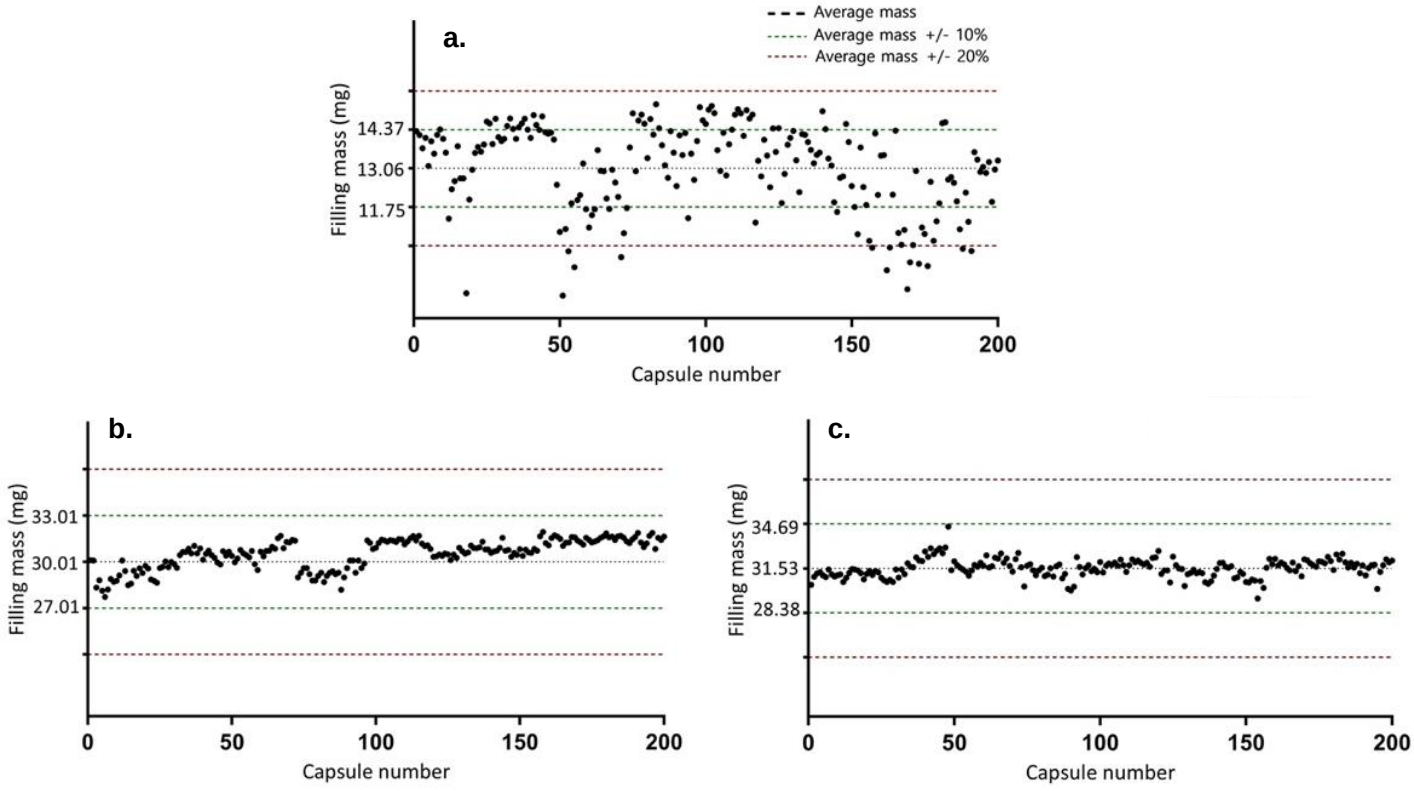

Figure 6: Mass uniformity of capsules filled with the Drum TT with the spray-dried powder (a), with the Lac230-blend (b) and with the Lac70-blend (c).

3.5. Aerodynamic performance of dosed powder plugs

As mentioned in the previous section, during the filling process, the powder is vacuumed into the drum and compacted in various degrees within its cavity, depending on the applied vacuum level and powder properties [56]. Consequently, the capsules are filled with plugs of more or less agglomerated powder, which might reduce the ED from the inhaler and, hence, the FPF [55]. Indeed, powder compaction during filling can hinder effective powder dispersion during aerosolization [55,56].

To compare two filling methods, impaction tests were conducted using a LR RS01 at two air flow rates: 30 L/min and 100 L/min. The results demonstrate similar ED and FPF for BUD between the two filling methods, irrespective of the tested blend, at the same inspiratory flow rate (Table 3).

At 100 L/min, the BUD ED for the Lac230-blend was 94.45% with manual filling and 95.02% with drum filling. Impaction tests showed ED (BUD) of 93.87% and 94.61% for the Lac70 blend, with manual and automatic filling, respectively. Similarly, comparable FPF (BUD) values were obtained for both filling methods. A similar trend was observed for FOR. Thus, it is demonstrated that powder compaction into pellets does not impact powder aerosolization when a high inspiratory flow rate (100 L/min) is applied. Similar to the 100 L/min flow rate, no difference was observed in powder aerosolization at a flow rate of 30 L/min, whether capsules were manually or automatically filled. Indeed, manually filled capsules yielded a BUD ED of 79.32%, while automatically filled capsules achieved an ED of 80.31% for the Lac230-blend. The obtained ED (BUD) for the Lac70-blend were 78.78% and 70.51% for manual and automatic filling. Similarly, no discernible differences in FPF were observed between the two filling methods at 30 L/min. Therefore, lung deposition is not influenced by the filling method at the same inspiratory flow rate.

Table 3: Emitted dose and Fine Particle Fraction of BUD and FOR at air flow rates of 30 and 100 L/min obtained through manual and drum filling methods, for the Lac230- and Lac70-blends.

		Emitted Dose (%)				**Fine Particle Fraction (%)**			
		Lac230-blend		**Lac70-blend**		**Lac230-blend**		**Lac70-blend**	
		Manual Filling	Drum Filling	Manual Filling	Drum Filling	Manual Filling	Drum Filling	Manual Filling	Drum Filling
BUD	30 L/min	79.32 ± 2.19	80.31 ± 5.19	78.78 ± 6.67	70.51 ± 5.28	52.74 ± 6.54	54.18 ± 3.40	55.39 ± 7.35	46.92 ± 3.97
	100 L/min	94.45 ± 0.66	95.02 ± 0.50	93.87 ± 0.28	94.61 ± 0.45	64.58 ± 2.52	62.55 ± 0.76	58.97 ± 4.65	62.25 ± 2.68
FOR	30 L/min	80.62 ± 2.60	80.36 ± 5.85	82.87 ± 7.19	77.43 ± 3.37	49.98 ±4.54	55.59 ± 1.57	61.01 ± 4.46	50.58 ± 2.90
	100 L/min	93.07 ± 1.19	93.43 ± 0.64	96.5 ± 0.70	94.26 ± 1.94	62.12 ± 0.56	58.85 ± 1.53	64.60 ± 6.30	66.44 ± 3.27

Nevertheless, a notable reduction in the ED of BUD occurs when the inspiratory flow rate decreases from 100 L/min to 30 L/min when using the Drum TT filling method, as already observed in Figure 5. This can be observed in Figure 7a, depicting the ED of BUD as a function of air flow rate. The ED decreases from 95.02% to 80.31% for the Lac230-blend, and from 94.61% to 70.51% for the Lac70-blend. A similar reduction is observed for FOR, as shown in Suppl. Data 2a. These results suggest that the powder pellets formed during volumetric filling disperse less effectively when a low inspiratory flow rate is applied with a LR device. Consequently, the aerosolization performance of lactose blends will be decreased in patients with reduced inspiratory capacity.

To enhance the dispersion of compacted powder pellets at a low inspiratory flow rate (30 L/min), a high-resistance (HR) inhaler was used. The objective was to assess whether increased resistance has an impact on the dispersion of powder pellets. Indeed, the performance of a DPI is influenced by the patient's inspiratory flow, the formulation characteristics, and the intrinsic resistance of the device [57]. Resistances are categorized from low to high based on the peak inhalation flow (PIF) required to generate a pressure drop of 4 kPa [16,58]. Specifically, the LR RS01 necessitates an inspiratory flow rate close to 100 L/min to achieve a 4 kPa pressure drop, signifying that a flow rate of approximately 100 L/min is required to generate the requisite turbulent energy for effective powder disaggregation [16,51]. Conversely, the HR RS01, characterized by a reduced inlet size, generates sufficient turbulent energy for proper powder dispersion at a flow rate of about 65 L/min [16].

A significant improvement in ED is observed when a HR inhaler is used at a low inspiratory flow rate (30 L/min), compared to a LR inhaler. This can be observed in Figure 7b, depicting the BUD ED obtained for Lac230- and Lac70-blends at a flow rate of 30 L/min, as a function of the inhaler resistance. Notably, there is an increase in the ED from 80.31% to 88.98% for the Lac230-blend, while corresponding values of 70.51% and 87.68% are observed for the Lac70-blend. Similarly, the FPF for the Lac230-blend increases from 54.18% to 62.83% for the LR and HR inhalers, and from 46.92% to 63.25% for the Lac70-blend (Suppl. Data 3a). A similar trend is observed for FOR, with an improvement in both ED and FPF when using a HR inhaler at a low inspiratory air flow rate (Suppl. Data 2b and 3b).

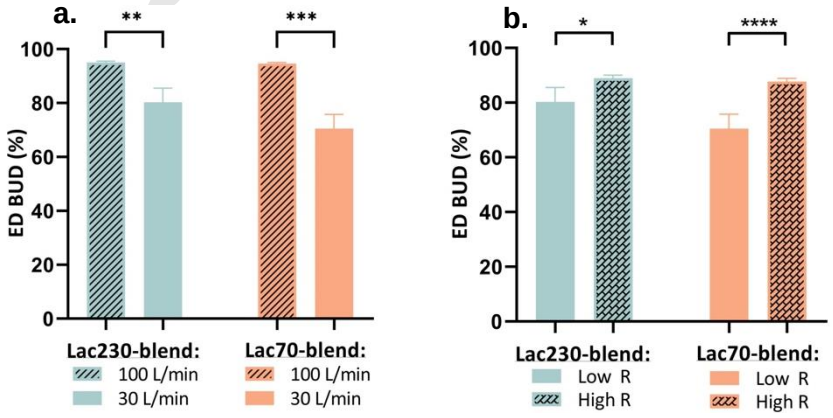

Figure 7: Budesonide (BUD) Emitted dose of Lac230- and Lac70-blends at air flow rates of 100 and 30 L/min with a low resistance RS01 (a) and at 30 L/min with a low- and a high-resistance RS01 (b) ($p < 0.05$).

These results can be explained, firstly, by the increase in the tangential inlet velocity achieved with the HR inhaler. This effect induces increased rotation of the capsule, facilitating a greater release of powder from the capsule and, consequently, leading to an improved ED [16,51]. Secondly, the rise in shear forces amplifies turbulence within the capsule chamber, enhancing the dispersion of SD powder from lactose particles. The intensified turbulent flow associated with the HR inhaler results in a fourfold increase in particle impaction between the particles and the device compared to the use of a LR inhaler [16]. This explains the significant improvement in the ED when using the HR RS01, by enhancing the dispersion of pellets formed during filling with the Drum TT. Moreover, the RS01 demonstrates a need for a lower inspiratory flow to achieve high powder aerosolization efficiency, making it more suitable for patients with reduced inspiratory capacity [59,60].

Finally, the use of a HR inhaler yields comparable FPF to those achieved at an air flow rate of 100 L/min. Specifically, FPF values for Lac230- and Lac70-blends at a flow rate of 100 L/min with a LR inhaler are 62.55% and 62.25%, respectively. In contrast, the HR inhaler produces FPF values of 62.83% and 63.25% at a reduced flow rate of 30 L/min. This demonstrates the advantage of employing a HR inhaler when a patient faces constraints in their inspiratory flow.

4. Conclusion

This study aims to formulate blends of micronized inhalation powder and lactose to enhance processing ease during industrial phases while maintaining high aerosolization performance. A blend consisting of 50% spray-dried powder (SD) and 50% lactose demonstrated improved flow characteristics while preserving high *in vitro* lung deposition of two drugs, budesonide (BUD), and formoterol fumarate (FOR).

The results underscore the importance of adhesive forces between SD particles and lactose in ensuring stability and preventing segregation within the blend. A comparison of lactose grades, particularly Inhalac® 230 and Inhalac® 70, revealed superior homogeneity with Inhalac® 230, likely due to different surface properties. When an industrial prototype filler is used, these blends significantly improved the homogeneity of capsules compared to SD powder alone. This demonstrates that the addition of lactose improved the flow properties of the engineered powder.

Furthermore, impaction tests showed that compacted powder pellets formed during drum filling did not hinder aerosolization. However, at low inspiratory flow rates (mimicking patients with limited breathing capacity), the advantages of high-resistance inhalers were emphasized. Indeed, these inhalers induce a fine particle fraction comparable to higher airflow rates for both drugs.

In conclusion, this study describes an innovative formulation strategy for using highly cohesive micronized inhalation powders on an industrial scale. While these powders exhibit excellent aerosolization properties, handling remains a major challenge for their final use in dry powder inhalers. Therefore, we propose producing a mixture of such micronized powder and coarse lactose, as this study has shown improvements in powder handling, with the potential to optimize inhalation therapies for various patients. The successful enhancements in processing and aerosolization efficacy position these formulations for further development and clinical use.

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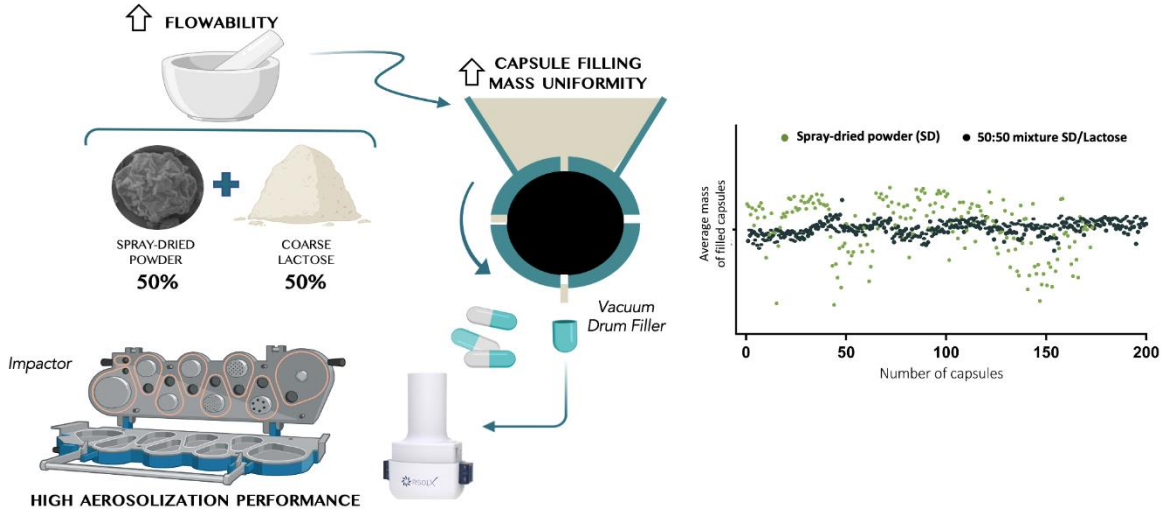
DECLARATION OF INTEREST

The authors declare that they have no known competing financial interests or personal relationship that could have appeared to influence the work reported in this paper.

Graphical abstract



HIGHLIGHTS

- Optimizing inhalation powder flowability enhances industrial processability
- Blend of spray-dried powder and coarse lactose lead to homogeneous ordered mixture
- Mixtures do not reduce aerosolization performance of engineered powder
- Mixtures greatly improve capsule filling mass uniformity (vacuum capsule filler)