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Manufacturing softpellets using triboelectric agglomeration of fine powders on a vibrated inclined plane: Method and application to dry powder inhalion

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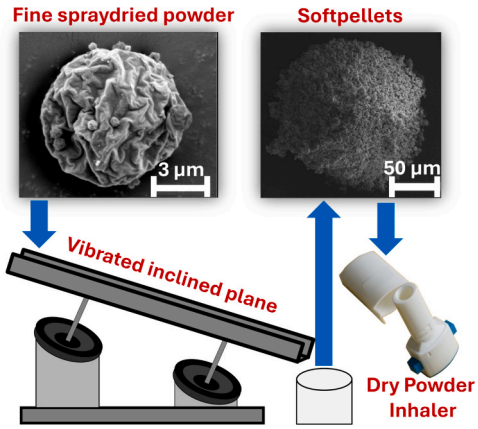
HIGHLIGHTS

- Vibrated inclined plane developement to generate agglomerates from fine powders.
- Electrostatic charges promote the formation of robust but brittle softpellets.
- Softpellets are spherical with a size of 800 μm and improved flow properties.
- During inhalation, the softpellets redisperse into independent particles, resulting in high fine particle fraction close to 60 %).

GRAPHICAL ABSTRACT



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ABSTRACT

Fine powders are required in many industrial applications, but their poor flow properties make handling and processing challenging. In Dry Powder Inhalation (DPI), for instance, inhaled particles must have an aerodynamic diameter between 1 and 5 μm to ensure therapeutic efficiency. However, these fine powders are difficult to manipulate, particularly during capsule or reservoir filling. To address this issue, we propose a set-up to form brittle agglomerates, referred to as softpellets, which exhibit enhanced flowability while maintaining the ability to break up when needed. Our method is based on a vibrating stainless steel inclined plane on which fine

Abbreviation: API, Active Pharmaceutical Ingredient; BUD, Budesonide; DPI, Dry Powder Inhaler; ED, Emitted Dose; FOR, Formoterol Fumarate; FPF, Fine Particle Fraction; FPF, Fine Particle Dose; HR, High Resistance; Lac500, Lactose Inhalac® 500; LOD, Limit of Detection; LOQ, Lower Limit of Quantification; LR, Low Resistance; NGI, Next Generation Impactor; PSD, Particle Size Distribution; RD, Recovery Dose; RH, Relative Humidity; SEM, Scanning Electron Microscopy; SD, Spraydrying; SD powder, Spray-dried Powder.

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particles flow under controlled vibration, leading to agglomeration. The powder is dispensed after being sieved, and the process parameters have been optimized. For that, two powders were used: a fine lactose (Inhalac® 500) and a homemade engineered spray-dried powder. Experimental results suggest that triboelectric charging plays a key role in particle cohesion, driving agglomeration. The resulting softpellets are spherical, approximately 800 μm in diameter, and exhibit significantly improved flowability compared to the initial powder. Their mechanical robustness was assessed using a texture analyzer and laser diffraction under varying pressures. Finally, low-inspiratory flow impactor analyses confirm that the agglomerates are effectively released from the capsule device and dissociate upon inhalation, achieving a fine particle fraction of nearly 60 %. This study demonstrates a promising strategy for enhancing the flowability of micronized powders without the addition of binders or other excipients. While this proof-of-concept was developed for DPI formulations, the approach could be extended to other pharmaceutical or industrial powder applications.

1. Introduction

When two objects are rubbed against each other, electric charges are exchanged at the surfaces. This contact electrification, called triboelectric effect, is an old and fundamental scientific subject. However, despite many studies dedicated to this subject, the fundamental mechanisms behind the triboelectric effect are still being investigated. Even the basic question related to the nature of the transferred charges between two insulating materials (electrons, ions or material) is still debated [1]. This effect is predominant in powders and granular materials which show significant charging due to the high rate of collisions between its constituents [2–4].

Practically, triboelectrification in powders induces cohesive forces leading to agglomeration, adhesion to surfaces, flow fluctuations, blockage or inhomogeneities in mixtures. More dramatically, electrostatic discharges may lead to accidental explosions [5,6]. On the other hand, triboelectrificationis used advantageously in electrophotography [7], powder coating [8] and separation processes [9]. In this paper, we show how agglomeration induced by triboelectric charges to form softpellets can help to optimize processes by improving the material flowability. To illustrate the interest of these softpellets, we will focus on pharmaceutical processes and in particular on dry powder inhaler. However, other applications could benefit from this self-agglomeration process, like cosmetology or composite materials.

To ensure therapeutic efficacy, inhalation powders must have an aerodynamic diameter between 1 and 5 μm. This particle size range facilitates optimal diffusion in the lower airways while reducing the risk of impaction in the throat [10,11]. Particle engineering techniques, such as spray drying, are currently being investigated to improve the aerodynamic properties of inhalation powders. These methods not only optimize particle characteristics—such as size, density, shape, surface area, crystallinity, and stability—but also enable the effective delivery of high doses of active pharmaceutical ingredients (API) via the pulmonary route [12,13]. Lechanteur et al. developed an inhalation powder consisting of wrinkled particles to improve the aerodynamic performance of two active pharmaceutical ingredients, budesonide and formoterol fumarate [14,15]. The formulation, which combines these APIs with hydroxypropyl-β-cyclodextrin, raffinose, and L-leucine, along with specific spray drying parameters, resulted in particles diameter of approximately 2 μm and achieved a fine particle fraction (relative to the total dose) of about 60 %. While the powder exhibits excellent aerodynamic performance, flowability challenges persist due to the micrometric size of the particles.

In our earlier studies, we investigated the strategy of using a lactose carrier approach to enhance the flow properties of spray-dried (SD) powder [16]. Specifically, we mixed the SD powder with coarse lactose to form an adhesive blend. The resulting mixture contained 50 % lactose and 50 % SD powder, with a higher proportion of micron-sized particles compared to a conventional carrier-based mixture. This 50:50 blend demonstrated improved flow characteristics, thereby optimizing processability by facilitating capsule filling. Furthermore, the balance between cohesive and adhesive forces ensured both the stability of the blend by preventing segregation and the efficient dispersion of the SD particles, allowing the powder to maintain its high aerosolization performance.

An alternative approach to improve micrometric powders flowability involves the generation of softpellets through the controlled agglomeration. Softpellets are agglomerates of micrometric particles held together by relatively weak physical interactions, which facilitate their effective separation during inhalation. Softpellets are found in Pulmicort® Turbuhaler®, which contains only budesonide in its formulation. Despite its considerable potential, the phenomenon of controlled agglomeration remains relatively underexplored [17–19]. Moreover, the fragility of the agglomerates led to the withdrawal of this product from the market in Belgium, and elsewhere.

Various manufacturing processes, such as vibration, agitation, or powder rolling, have been studied to form agglomerates, either with or without the addition of a binder. In the context of inhalation, it is essential to avoid the use of a binder to facilitate deagglomeration. Indeed, interparticulate forces must not be excessively strong in order to allow the softpellets to break into individual particles during inhalation. AstraZeneca's patent describes a method for agglomerating the powder. The process involves passing it through a screw feeder, followed by spheronization in a tilted, rotating container [20]. Other manufacturing processes for softpellets have been investigated, such as the formation of agglomerates from a mixture of melatonin and lactose using air jet mixing, as described by Zhang et al. [21], and by resonant acoustic mixing [22]. Vibration-based processes have also been studied for agglomerate formation, as demonstrated by Hartmann et al. [23] and Etschmann et al. [24,25].

The mechanism underlying the auto-agglomeration of micrometric powders is not yet fully elucidated. Agglomerates are composed of particles bound together by relatively weak interactions, such as van der Waals forces, liquid bridges, or electrostatic interactions [21]. Regarding agglomerate formation, it can be hypothesized that vibration, agitation, or mixing processes may induce an exchange of electrical charges between particles through contact electrification. This phenomenon could lead to the spontaneous agglomeration of powders [26].

The classical approach of triboelectricity based on the triboelectric series, which ranks empirically materials based on their tendency to acquire electric charge upon contact, suggests that when two surfaces made of different materials come into contact, one surface becomes uniformly positively charged while the other acquires a uniform opposite charge [27]. Moreover, the greater the distance between materials in the triboelectric series, the more pronounced the contact electrification effect is expected to be. This implies that two particles made of the same material and therefore positioned at the same position in the triboelectric series should not charge during contact. However, charge transfer has been observed even when two identical materials come into contact [28]. Indeed, any form of asymmetry can promote this charge transfer. Therefore, if two particles of the same insulating material interact and exhibit differences in size, shape, or surface roughness, charge transfer is likely to occur [29,30]. Additionally, charge generation is influenced by environmental conditions such as relative humidity and pressure, as well as by the type and intensity of collisions between particles [31]. It has also been demonstrated recently that when two

materials are brought into contact, charge distribution occurs in a mosaic pattern, with some sites being positively charged and others negatively charged [28–30]. Thus, a particle is not uniformly positive or negative, which helps explain the phenomenon of charge transfer between two identical materials. Furthermore, Preud'Homme et al. [32] simulated granular flows with a customized DEM model implementing mosaic patterns formed of so-called patches. A predefined fraction of patches are charge acceptors while the other patches are charge donor. If we consider that the transferred charges are electrons, the donor patch charges positively while in contact with an acceptor patch. It has been observed that powder cohesiveness increases with the amount of charge transferred between the patches when the powder is in motion within a rotating drum. Thus, a flowing powder represents an ideal system for the generation of electrostatic charges between particles, as well as through contact with surfaces leading potentially to agglomeration.

Most pharmaceutical powders are insulating materials and are prone to electrostatic charging during handling. Triboelectric charging is nearly inevitable during powder processing operations, such as mixing, transport, and filling [26,31,33]. While the pharmaceutical industry often seeks to mitigate this charge transfer phenomenon, it could potentially be advantageous, particularly in facilitating the formation of agglomerates to enhance powder flow properties.

In this paper, an agglomeration method is investigated to enhance the flowing properties of fine powders by producing softpellets. The method based on a vibrating inclined plane has been tested. Two micrometric powders ($D_{50} < 5$ μm) were agglomerated: a fine model lactose (Inhalac® 500) and a homemade engineered spray-dried powder. The agglomerates were characterized in terms of size, morphology, flow properties, as well as mechanical strength and deagglomeration performance. Moreover, experimental evidences show that triboelectric charges play an important role in the agglomeration process. The goal of this study is to develop agglomerates that are robust enough to ensure stability during storage and transport, yet sufficiently friable to disintegrate into individual particles when needed. For example, to preserve the high aerosolization capacity of the powder in the framework of pharmaceutical powder inhaler application.

2. Materials and methods

2.1. Materials

Two powders have been used: Inhalac® 500 (Lac500), an inhalation-grade α-lactose monohydrate acquired from Meggle (Wasserburg, Germany), and a homemade engineered powder produced by spray drying (SD powder). The latter contained two APIs: budesonide (BUD) and formoterol fumarate (FOR). The composition and the spray drying method are described in Supplementary materials.

2.2. Methods

2.2.1. Vibrating inclined plane

The powders were sieved through a 1.25 mm mesh before being subjected to self-agglomeration while flowing down a 50 cm-long inclined U-shaped stainless steel plane set at an angle of 10° with the horizontal (Fig. 1). The apparatus design was inspired by the Vibro-Pelletiser developed by Etschmann [24] and featured two customized vibrators, built using Beyma MI100 audio speakers separated by a distance of 30 cm. The use of two vibrators offers several advantages. First, it ensures a more homogeneous distribution of vibrations across the plate, minimizing dead zones where vibrations might be less intense. Secondly, it enables the application of different vibration amplitudes and phase shifts along the plate, offering the flexibility to test and optimize various vibration settings for enhanced control over the agglomeration process. The relative humidity in the room is maintained between 42 % and 48 % with a temperature between 20 °C and 21 °C.

After a process optimization study detailed in Section 3.2, the following parameter were used. A sinusoidal signal at 40 Hz was generated using a Rigol DG1022Z function generator, controlled via a custom Python script. This signal was amplified by a QSC USA 900 amplifier before being transmitted to the speakers. The measured acceleration was 3.31 g for the speaker at the upper part of the plate and 3.78 g for the one positioned lower. These accelerations correspond to vibration amplitudes of 0.52 mm and 0.59 mm, respectively. The oscillatory motion of the vibrating plate was monitored using a Rigol DS1054Z oscilloscope, with two ADXL-356CZ accelerometers.

With each powder sample, the flowing process on the vibrating plane was repeated three times (called runs hereafter) to ensure that the

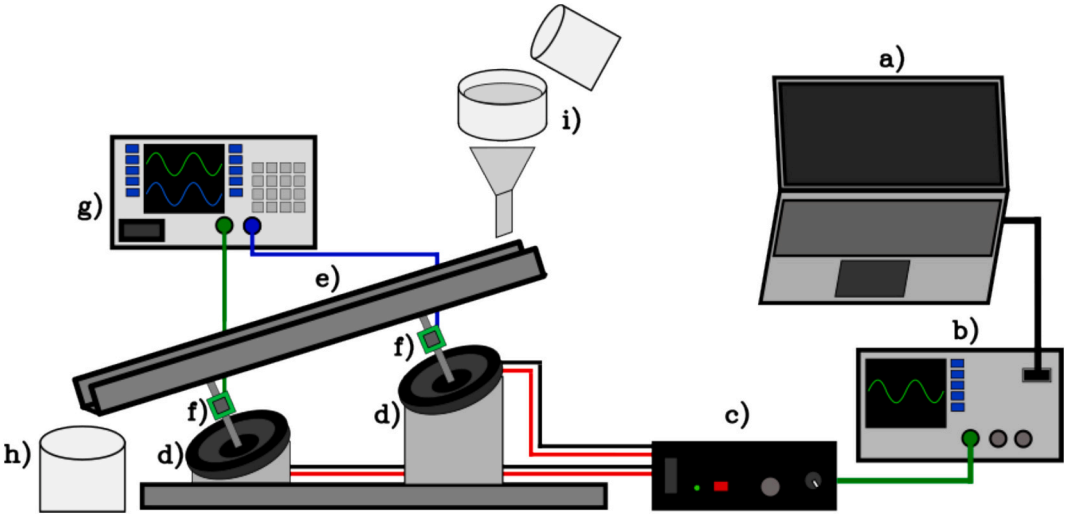

Fig. 1. Schematic representation of the vibrating inclined plate. The experimental setup consists of a signal generator (b) controlled by a computer (a). The generated signals are amplified (c) and applied to the vibrators (d), which support a 50 cm U-shaped plate (e) with a variable incline set at 10°. The vibrators are attached to the plate 10 cm from the ends. The oscillation of the vibrating plate is monitored using an oscilloscope (g) with the aid of two accelerometers (f). The experimental protocol is as follows: the powder passes through a mesh sieve of 1.25 mm (i) before being introduced onto the plate via a funnel. The powder then flows along the vibrating plate before being deposited into the receiving container (h).

softpellets traveled a total distance of 1.5 m. The softpellets were collected in a stainless-steel container, subsequently transferred to a sealed glass container, and stored in a stability chamber at 25 °C and 60 % relative humidity (RH) for a minimum of 7 days prior to analysis. For the electrostatic investigation, the number of runs is higher (5 runs) to investigate a possible saturation and the collecting container is replaced by a faraday cup, as explained in the next section.

2.2.2. Electrostatic charge measurement

To measure the electric charge Q of the powder after its flow on the vibrating inclined plane, the receiving container (see Fig. 1 (h)) was replaced by a Faraday cup connected to an electrometer. The Faraday cup used was the GranuCharge cup (GranuTools, Awans, Belgium) with an extension cable. This system was connected to a computer allowing to record the charge evolution over time. The charge density q (in nC/g) is the charge Q (in nC) divided by the mass of recovered powder (in g).

The charge measured with the Faraday cup method corresponds to the total net charge inside the powder. As discussed in the introduction, recent studies on triboelectric effect [1,2,4] have shown that negative and positive charges are distributed at the surface of the grains defining sites or patches. The resulting distribution of charges at the surface of the grains induces cohesive forces between positive and negative patches even if the total net charge of the powder is zero. The vibrated inclined plane is a system that promote the charge transfer due to the high rate of collisions and friction between the grains and between the grains and the plane. The inter-grain contacts induce a distribution of opposite charges keeping the total net charge constant, while the grain-plane contacts lead to a modification of the total net charge. Indeed, the inclined plane is grounded and remains at zero electrical potential while exchanging charges with the grains. This net charge modification due to grain-plane contacts can be measured by the Faraday cup. To summarize, after a flow on the vibrated inclined plane, we expect a distribution of charges at the surface of the grains inducing cohesive forces with a shift to one particular sign due to the stainless-steel plane.

2.2.3. Particle size and morphology

The particle size distributions (PSD) of the starting powders were analyzed using laser diffraction with the Malvern Mastersizer 3000® (Malvern Instruments, Worcestershire, UK) equipped with an AeroS unit (high-energy venture). Approximately 150 mg of each sample was dispersed in air at a pressure of 4 bars. A micro-tray was utilized due to the limited quantity of powder, with the feed rate adjusted to 30 % to maintain an obscuration range of 0.5–8 %. The particle size data were processed using Malvern Mastersizer software, and the average PSD (± standard deviation, SD) was derived from three replicates for each sample.

The particle size and shape profile of the produced softpellets were evaluated using the QicPic dynamic image analysis system (Sympatec GmbH, Clausthal-Zellerfeld, Germany) in combination with the GRADIS/L free-fall dry dispersion module and an M7 measurement range. For this purpose, samples were introduced into the entrance of the fall shaft of the GRADIS module using a VIBRI vibratory feeding module. The GRADIS was employed to ensure that the softpellets remained intact during measurement. Data analysis and sphericity calculations were performed using version 6.2 of the PAQXOS system software (Sympatec GmbH, Clausthal-Zellerfeld, Germany). Sphericity is the ratio of the perimeter of the equivalent circle to the perimeter of the actual particle. The aspect ratio is defined as the ratio of the minimal to the maximal Feret diameter. The results presented are the average (± SD) of three replicates.

Digital microscopy was conducted using a Bysameyee USB Microscope (Shenzhen, China) with a magnification of 40× to characterize the morphology and size of softpellets. Images were captured and analyzed with CoolingTech software, which includes measurement tools. Before acquisition, a micrometer calibration ruler was used to ensure measurement accuracy. Replicates were conducted with three different powder batches, analyzing 50 agglomerates per batch, with results reported as the mean (± SD).

Scanning Electron Microscopy (SEM) was performed using a TESCAN Clara SEM (Brno, Czech Republic) to evaluate the morphology of both agglomerates and primary particles. Prior to imaging, the samples were prepared with a sputter coater to apply a thin layer of gold. Carbon adhesive tape was used to attach the samples, and carbon lacquer was applied to stabilize the agglomerates during imaging. An acceleration voltage of 5 kV was employed to capture images of the agglomerates, while 10 kV was used for the primary particles. The imaging was conducted using secondary electron detection with the TESCAN Essence software.

2.2.4. Quantification of active pharmaceutical ingredients

The quantification of budesonide (BUD) and formoterol fumarate (FOR) was carried out using an Agilent 1100 Series HPLC system (Santa Clara, USA). A 3 × 50 mm column packed with 3.5 µm C18 (X Bridge BEH C18 Column) was utilized in conjunction with a UV detector set to 243 nm. The mobile phase comprised an ammonium acetate buffer at pH 10 mixed with methanol, following this gradient profile: 0 min – 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 maintained at 0.7 mL/min, with the column temperature set at 30 °C, the sampler temperature at 10 °C, and an injection volume of 10 µL for the sample.

Process validation was performed using total error as the decision criterion. Acceptance limits were established at 10 % within the concentration ranges of 100 µg/mL to 1 µg/mL for BUD and 10 µg/mL to 0.1 µg/mL for FOR. Accuracy profiles for both BUD and FOR were developed using their respective calibration models: weighted quadratic regression ($1/X^2$) for BUD and weighted linear regression ($1/X^2$) for FOR. The limit of detection (LOD) and the lower limit of quantification (LOQ) for BUD were determined to be 0.2899 µg/mL and 4.395 µg/mL, respectively. For FOR, the LOD was found to be 0.1161 µg/mL, while the LOQ was established at 0.9282 µg/mL. All validation results were calculated using Enoval software (Arlenda, Liège, Belgium).

For the quantification of the API content in both the starting powders and the agglomerates, three samples were collected from each of the three batches and analyzed to determine the API concentration.

2.2.5. De-agglomeration characterization

2.2.5.1. In vitro aerosol performance. Size 3 HPMC capsules were filled with 15 ± 1 mg of either SD powder or softpellets of SD powder. The powder was weighed directly into the capsules using an analytical balance (AT261 DeltaRange®, Mettler Toledo, Switzerland). The in vitro aerosol performance was assessed using a Next Generation Impactor (NGI; Apparatus E, Copley, Nottingham, UK). This impactor consists of 8 stages and is equipped with a pre-separator. The induction port was connected to the inhaler device via a suitable mouthpiece adapter. The airflow was set to 30 L/min using a flow controller (TPK; Copley, Nottingham, UK) for 2.4 s per test. A Plastiape RS01 high-resistance inhaler was employed in this study, with a batch of 12 capsules being tested during each run. All tests were performed in triplicate.

The powder deposited on each stage of the NGI was collected with a 65 % *v*/v methanol-in-water solution and analyzed by HPLC. The recovery dose (RD) was calculated as the total mass of the API retrieved from the capsules and the device down to the final stage of the NGI. The emitted dose (ED), representing the percentage of drug released from the inhaler, was determined from the cumulative powder mass from the induction port to the last NGI stage. The fine particle dose (FPD) was defined as the drug mass with an aerodynamic diameter below 5 µm, and the fine particle fraction (FPF) was calculated using the following equation.

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

2.2.5.2. Laser diffraction at different pressures. The de-agglomeration of softpellets was evaluated using laser diffraction analysis at various pressures with a Malvern Mastersizer 3000® (Malvern Instruments, Worcestershire, UK), equipped with an AeroS unit. The standard Venturi was chosen to minimize the energy applied to the agglomerates during dispersion. Samples of approximately 150 mg were dispersed in air, and analyses were conducted at pressures of 0.1, 0.5, 1, 2, 3, and 4 bar. A micro-tray was utilized with a feed rate set at 15 % to achieve an obscuration range of 0.5–8 %. The PSD of the powders was analyzed using Malvern Mastersizer software, and the average PSD was measured from three replicates of each sample.

2.2.6. Mechanical properties of softpellets

The mechanical resistance of the agglomerates was evaluated using a compression test with a TA-XT2 Texture Analyzer (Ametek, Berwyn, USA) equipped with a TA-5 N load cell. A compression test was performed using a 4 mm spherical probe. Prior to the test, the agglomerate size was analyzed using digital microscopy. The agglomerate was carefully centered under the probe during the test. Before starting, the probe was positioned less than 1 mm from the agglomerate, and compression was applied at a speed of 1 mm/min. Ten independent analyses were conducted following the production of three separate batches of soft pellets.

The rupture force, representing the mechanical strength of the softpellets, was recorded and analyzed using Nexigen® Plus 3 software (Ametek, Berwyn, USA). It corresponds to the first significant drop in the force-deformation curve, which shows a progressive increase as the probe contacts the agglomerate, followed by a peak and a sudden drop. This rupture force indicates the point at which the agglomerate loses its ability to withstand further compression and is considered the maximum strength or fracture force of the agglomerate.

2.2.7. Density measurement

The bulk and tapped densities were assessed using the Granupack (Granutools, Awans, Belgium), an automated system designed for measuring tapped density and characterizing the packing behavior of powders. Initially, the powder is placed in a metallic tube with a diameter of 26 mm and a length of 70 mm. A lightweight hollow cylinder is then gently positioned on top of the powder to maintain a flat surface during the compaction process. The cylindrical cell containing the powder undergoes a series of free falls, known as "taps." In this study, 35 mL of powder was subjected to 500 taps. After each tap, a distance sensor records the position of the hollow cylinder, from which the height and volume of the powder bed are calculated. Given that the mass of the powder is known, the bulk density—defined as the mass-to-volume ratio—is computed after each tap. The Hausner ratio, which is the ratio of tapped density to initial bulk density, is used to evaluate the flowability of the powder.

2.2.8. Cohesive index measurement

The cohesive index was determined using the Granudrum (Granutools, Awans, Belgium), an automated device designed to evaluate powder flowability and cohesion. A partially filled, hermetically sealed drum with transparent walls is positioned horizontally. During the measurement, the drum rotates at an angular velocity ranging from 2 RPM to 60 RPM. Images are captured throughout each rotation, and an edge detection algorithm is employed to identify the air/powder interface in the images. After image acquisition, the average position of the interface and its corresponding fluctuations are analyzed. The dynamic cohesive index is derived from these fluctuations. The values reported in this study correspond to a rotation speed of 6 RPM.

2.2.9. Water content measurement

The residual moisture content of all powders was determined using coulometric Karl Fischer titration with a Mettler Toledo V30 Volumetric Titrator. Approximately 40 to 80 mg of each powder sample was introduced into the titration cell containing Hydranal® Composite 5 K, and the moisture levels were assessed. Each powder was analyzed in triplicate.

2.2.10. Physical stability of softpellets

The stability of the softpellets formulated with Lac500 and SD powder was evaluated. Each formulation was replicated in triplicate and placed in sealed glass containers within a stability chamber (Pharma 600, Weiss Technik®, La Verrière, France) that maintained a temperature of 25 °C with a relative humidity (RH) of 60 %. The stability of the softpellets was assessed at three time points: one week after their production (W1), at two weeks (W2), and at four weeks (W4). Key stability parameters, including moisture content, mechanical strength, and digital microscope analysis, were measured.

2.2.11. 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. Initial fine powders characterization

Analysis of the SEM images shows that the Lac500 particles exhibit a rough, irregular surface texture and an angular morphology, while the spray-dried (SD) powder is characterized by a spherical shape with a wrinkled surface. As indicated in Table 1, the particle size distribution for both Lac500 and SD powders is predominantly below 5 μm, resulting in significant cohesive forces among the particles. Indeed, the measurement of the cohesion index of SD powder could not be performed due to the powder's cohesive nature, which caused it to adhere to the walls of the drum and obstruct image capture. This cohesive behavior is further evidenced by the tapped density measurement, which yielded a Hausner ratio of 1.58 ± 0.06 (Fig. 6A-B). This cohesive behavior has also been demonstrated for Lac500 showing very poor flow characteristics according to the European Pharmacopoeia 11.0. The moisture content of the powders was determined to be 4.98 ± 0.03 % for Lac500 and 5.23 ± 0.31 % for the SD powder.

3.2. Setting of vibrating plane parameters

Initial experiments were conducted on micronized lactose powder (Lac500) to identify parameters that facilitate powder agglomeration. These parameters were then applied to a SD inhalable powder engineered for high aerosolization efficiency but exhibiting poor flowability.

Two plate configurations were compared: one in a V shape and the other in a U shape. The V-shaped plate caused powder accumulation along its edges, resulting in material loss before reaching the collection container. This phenomenon was not observed with the U-shaped plate. The process is strongly influenced by the intensity of the applied vibrations. Experiments were conducted across a frequency range of 25 Hz to 100 Hz with varying amplitudes to evaluate the agglomeration potential under different vibration conditions. The experiments demonstrated that a high frequency of 100 Hz was inefficient to promote powder movement along the plate, while a frequency of 75 Hz led to slow powder flow. Additionally, regardless of frequency, a sufficiently high amplitude was found necessary to initiate agglomeration.

Table 1
Particle size of bulk powder measured by laser diffraction.

	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)	Span
Lac500	0.92 ± 0.01	3.12 ± 0.04	6.87 ± 0.03	1.91 ± 0.02
SD Powder	1.17 ± 0.02	2.56 ± 0.13	5.32 ± 0.41	1.62 ± 0.05

Specifically, amplitudes below 0.20 mm did not induce adequate particle collisions to support agglomeration. However, excessively high amplitudes may result in a powder flow along the plate that is too fast, preventing sufficient time for particle self-agglomeration. Thus, an optimal balance must be established: the flow should be slow enough to allow for powder self-agglomeration without diminishing process efficiency, while the amplitude must be sufficient to facilitate particle collisions.

Based on observations from the different experiments, parameters were selected for the self-agglomeration of micrometric powders, specifically a frequency of 40 Hz and amplitudes of 0.52 mm and 0.59 mm for the upper and lower speakers, respectively. The process is repeated three times, as the softpellets exhibit an increasing tendency to become rounded during their passage along the vibrating plate, likely due to the adhesion of additional particles to the primary agglomerates. Indeed, as shown in Fig. 2A, the Lac500 agglomerates formed after a single passage over the vibrating plate appear irregular, with smaller agglomerates attaching unevenly to the surface of the larger ones. This results in a rough and uneven surface texture, making the overall structure appear less spherical. By contrast, after three passages, the softpellets appear more rounded and have a smoother surface, as confirmed by the microscope images presented in Fig. 2B.

3.3. Electrostatic charges measurement

Fig. 3 shows the temporal evolution of the powder charge Q at the output of the inclined plane. Globally, the measured charges are negatives, which is common for lactose powders charging against stainless steel [2,4]. The charge Q decreases from zero to negative values to reach a minimum Q_{min} at the end of the process. The results are presented raw and unfiltered. It is well known that electrostatic charge measurements can be tricky, and the regularity and the clear trends showed by the curves already shows that the measurement has been carried out correctly.

The comparison of the normalized charge temporal evolution $Q/|Q_{min}|$ (Fig. 3) reveals the time required to empty the inclined plane for the different runs. This discharging time is longer for the first run and decreases in subsequent runs, indicating that the flowability increased due to the agglomeration process. Indeed, we start with the fine powder having a poor flowability and end-up with free-flowing agglomerates.

The final charge density $q_{min} = Q_{min}/m$ is presented in Fig. 4 for each successive run. The absolute value of this charge density decreases with the run number. Since the discharging time becomes shorter, the agglomerates remain in contact with the vibrating plane for a shorter duration. Additionally, as the agglomerates become more spherical and develop a smoother surface, the number of contact points with the vibrating plane decreases. Furthermore, as agglomerates form, the number of individual particles decreases for a given mass, resulting in fewer points of contact with the vibrating surface. These factors combined result in a reduction in the number of contacts, resulting in lower charges.

The typical value of this charge density (around -15nC/g) is high compared to what can be found in the literature, showing that the vibrating inclined plane and the parameters selected for this study are efficient to promote triboelectric charging of the powder. In comparison, the charge density measured with lactose (InhaLac 230) in [2] with GranuCharge is around -10nC/g. In this study, the powder was charged in a vibrating V-tube optimized to enhance triboelectric charging. The study presented in [3] shows that excipients having a charge higher than -5nC/g are prone to produce agglomerates inducing strong fluctuations in feeders used in the framework of continuous manufacturing. Therefore, the strong triboelectric chargeability obtained in the present study allows us to conclude that the charges and the associated cohesive forces play a dominant role in the agglomeration.

3.4. Characterization of lactose and spray-dried powder softpellets

The parameters optimized for the self-agglomeration of Lac500 were subsequently applied to the SD powder, leading to the effective formation of agglomerates. The resulting agglomerates were characterized in terms of size, morphology, mechanical properties, moisture content, and flow properties, along with their deagglomeration characteristics, which include both aerodynamic behavior and analysis via laser diffraction.

3.4.1. Agglomerate size and morphology

As shown in Table 2, the size distribution indicates an average size of 790.99 ± 7.52 μm for Lac500 samples and 807.48 ± 58.57 μm for SD powder samples, both of which are substantially larger than the initial particle sizes. The image analysis also indicated sphericity values of 0.83 and 0.82 for the Lac500 agglomerates, reflecting relatively comparable characteristics (Table 2). In contrast, the Pulmicort® softpellets demonstrated a higher sphericity of 0.91, which can be attributed to their smoother surface with fewer surface irregularities [23].

The SEM images (Fig. 5-B,C) reveal that lactose particles have agglomerated to form a softpellet characterized by a relatively spherical shape and a rough surface. The agglomerate appears as a solid mass, with closely associated particles forming a cohesive entity. The arrangement of these particles is likely to influence the robustness and stability of the agglomerate, contributing to its overall structural integrity. Additionally, it can be inferred that a denser and more compact agglomerate would exhibit greater resistance to disaggregation, thereby reducing its susceptibility to fragmentation under mechanical stress. The agglomerates of SD powder also exhibit a roughly spherical shape (Fig. 5-E, F). The wrinkled particles are distinctly visible on the surface, indicating that particles engineered through spray drying are preserved throughout the self-agglomeration process. Preserving the morphology of the wrinkled particles is essential for maintaining the functional properties of the powder.

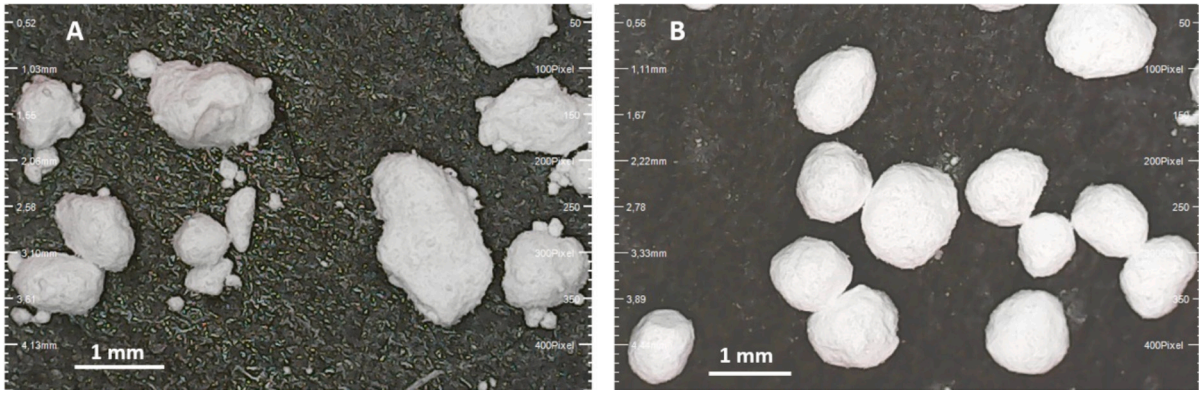

Fig. 2. Digital microscopy images of Lac500 agglomerates after one passage (A) and three passages (B) on the vibrating inclined plate.

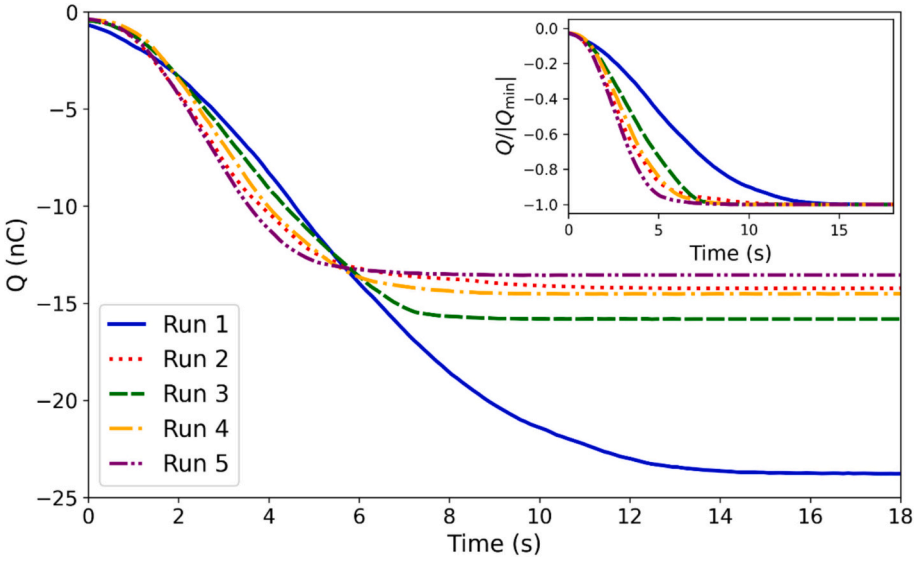

Fig. 3. Typical temporal evolution of the charge Q measured by the Faraday cup at the output of the inclined plane for the different runs of an experiment. The insert shows the normalized version of the curve to highlight the time needed to empty the inclined plane for each run.

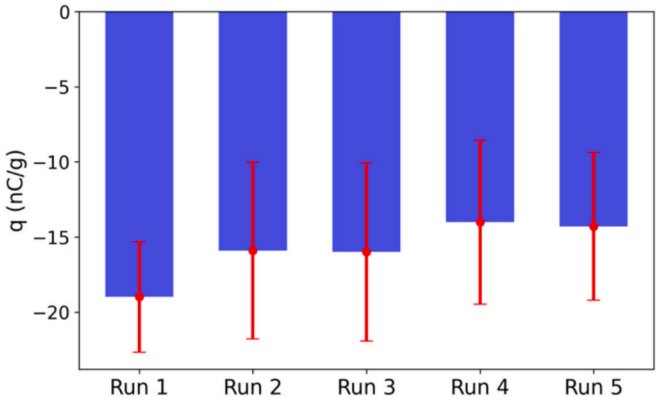

Fig. 4. Total charge density q for the different runs with the error bars corresponding to the standard deviation computed over three measurements.

Table 2
Agglomerate size measured by dynamic image analysis and compared to values from the Pulmicort Turbohaler reported by Hartmann et al. [23].

	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)	Sphericity
Lac500 Softpellet	315.8 ± 9.1	790.9 ± 7.5	1400.4 ± 8.9	0,83
SD Softpellet	464.9 ± 18.2	807.5 ± 58.6	1270.4 ± 121.1	0,82
Pulmicort® Turbubaler [23]		519.6		0,91

3.4.2. Flow properties of agglomerate

The generation of agglomerates from micron-sized powder particles significantly enhanced powder flowability, as evidenced by a reduction in the cohesive index (Fig. 6 A). For Lac500, the cohesive index decreased from 30.61 ± 3.02 to 17.92 ± 3.37. While the non-agglomerated SD powder could not be measured due to its high cohesiveness, the cohesive index for the SD powder softpellets was found to be 16.71 ± 1.16. For comparison, these cohesive index values are comparable to, or even superior in terms of flowability, to those of Inhalac 230, which has a measured value of 19.29. Inhalac 230 is widely used in inhalation powders due to its relatively large particle size (d50 = 101.54 μm ± 0.35), where it serves effectively as a carrier to improve flowability [26]. Additionally, agglomeration led to a decrease in the Hausner ratio, further reflecting improvements in flow properties (Fig. 6 B). Specifically, the Hausner ratio for Lac500 decreased from 1.44 ± 0.07 for the powder to 1.27 ± 0.05 for the softpellets, while for the SD powder, it dropped from 1.58 ± 0.06 to 1.34 ± 0.04.

3.4.3. Moisture content analysis

Regarding the residual moisture content measured in the Lac500 agglomerates, Fig. 6 C shows that no increase in moisture content was observed, even after 4 weeks of storage. The values ranged from 4.98 % ± 0.03 for the non-agglomerated powder, 5.01 % ± 0.01 for the softpellets after 1 week of storage, and 5.19 % ± 0.07 after 4 weeks of storage. In contrast, the softpellets formed from SD powder show a slight increase in residual moisture content over the course of their storage. The values range from 5.23 ± 0.31 % for the non-agglomerated powder, 5.45 ± 0.27 % after 1 week of storage for the softpellets, and 5.98 ± 0.02 % after 4 weeks of storage.

3.4.4. Mechanical strength of agglomerates

In the self-agglomeration process, the mechanical strength of the agglomerates is a critical factor. Indeed, in the context of inhalation, only particles smaller than 5 μm can reach the lower respiratory tract to exert their therapeutic effect. Therefore, the softpellets must disaggregate into individual particles upon inhalation, and for this to occur, they must not be overly robust. However, these agglomerates must also withstand certain mechanical stresses to remain stable during transport and storage. A balance must be achieved to ensure both effective aerosolization and physical stability of the formulation. Another challenge is measuring this mechanical strength, as, by definition, softpellets are characterized by a relatively loose agglomeration of particles held together by weak interparticle forces. Consequently, accurately measuring the force required to break apart these agglomerates is not straightforward due to their inherent fragility.

In this study, a compression test was performed using a load cell with a sensitivity of 0.0001 N, enabling the measurement of the force

1.1.1

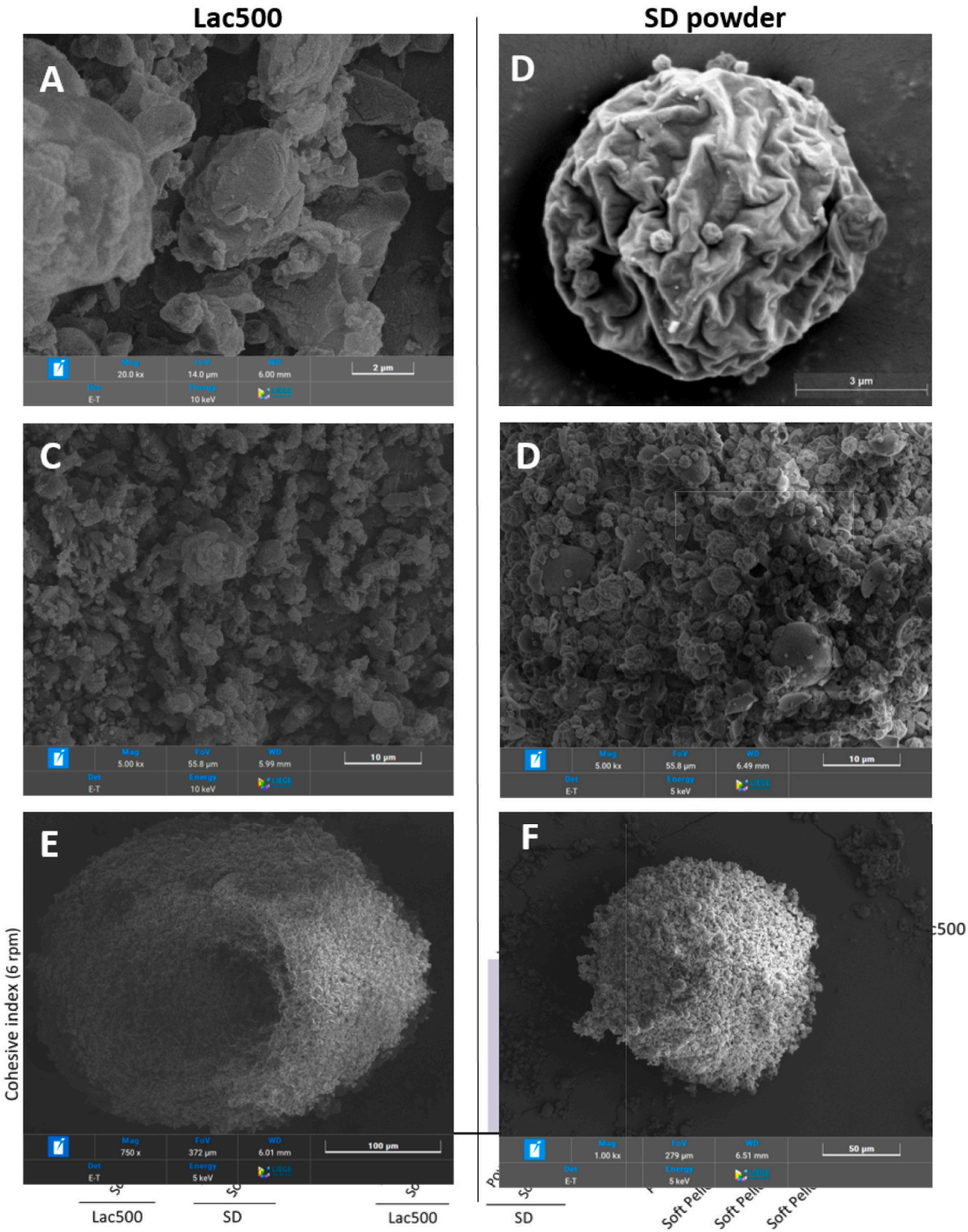

Fig. 5. SEM images of non-agglomerated powders and soft pellets: (A) non-agglomerated Lac500 (20,000×), (B) Lac500 softpellet (5000×), (C) Lac500 softpellet (500×), (D) non-agglomerated SD (9700×), (E) SD soft pellet (5000×), (F) SD soft pellet (1000×).

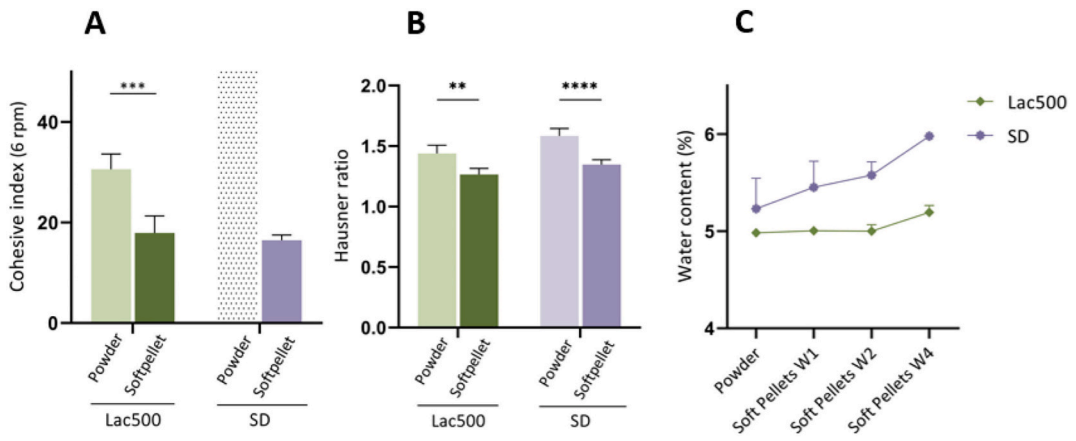

Fig. 6. Cohesive index (A), Hausner ratio (B) of either Lac500 or SD powder in their native (powder) or agglomerated forms (Softpellet).Water content (C) of Lac500 and SD powders and their agglomerates (Softpellets) analyzed after one week (W1), two weeks (W2) and four weeks (W4) after storage.

required to deform the softpellets. The recorded measurement corresponds to a drop in force, indicating the point of rupture, which occurs after a progressive increase in force, from the moment the probe makes contact with the agglomerate until rupture or deformation. The rupture force of Lac500 agglomerates after one week of storage (W1) is 3.77 mN ± 1.96, while the agglomerates made from SD powder exhibit a rupture force of 2.00 mN ± 1.82 (Table 3). Trofast et al. defined a lower threshold of 0.5 mN for the hardness of agglomerates, with optimal values typically ranging between 0.5 and 20 mN [20]. The results indicate that the softpellets produced using the process described in this study possess sufficient mechanical strength to ensure stability for pharmaceutical manufacturing processes. This is further corroborated by comparison with the softpellets used in the Pulmicort Turbuhaler®, where literature reports rupture forces ranging from 1.1 mN ± 0.23 [23] to 1.83 mN ± 0.83 [22].

The results demonstrate a difference in mechanical strength between Lac500 and SD softpellets, with Lac500 softpellets exhibiting higher resistance. While Boerefijn et al. compared the fragmentation of agglomerates of different sizes and observed that smaller agglomerates are more susceptible to breaking than their larger counterparts [34], this study demonstrates that agglomerates of similar size can also exhibit distinct mechanical strengths. This difference in strength may be attributed to the composition of the agglomerates, which influences their mechanical properties.

3.4.5. Deagglomeration behavior

3.4.5.1. Aerodynamic behavior. In a previous study, we demonstrated that using a high-resistance (HR) device significantly improved the in vitro pulmonary deposition of the SD inhalation powder at a low inspiratory flow rate of 30 L/min, compared to a low-resistance (LR) device. This improvement was attributed to the increased turbulence generated by the higher resistance, which facilitates more effective powder de-agglomeration. In the current study, an HR inhaler was used to promote the de-agglomeration of the softpellets, with the aim of optimizing their performance even under suboptimal inspiratory conditions (30 L/min). It is important to note that this test was carried out under the most stringent operating conditions in order to observe differences between the powders tested.

Tests were conducted on the non-agglomerated powder, as well as on the SD powder agglomerates after one week (W1) and two weeks of storage (W2). Table 4 presents the results of fine particle fraction (FPF), based on the total dose recovered, emitted dose (ED), and active pharmaceutical ingredient (API) content, both for budesonide (BUD) and formoterol (FOR). After one week of storage, the FPF for BUD was 55.40 % ± 2.00, indicating efficient de-agglomeration of the softpellets despite the low inspiratory flow rate (Fig. 7A, Table 4). The substantial deposition of BUD in the lower stages of the NGI further confirms the effective de-agglomeration of the powder during inhalation, supporting the sustained high aerosolization performance of the powder produced through particle engineering.

After two weeks of storage, the emitted dose decreases from 77.99 ± 0.99 to 73.20 ± 1.62, with a slight proportion of the API remaining in the device (Fig. 7). This resulted in a lower FPF of 47.61 % ± 1.58. This decrease in dispersion and de-agglomeration of the softpellets could be attributed to the increase in residual moisture content during storage. The development of liquid bridges may have contributed to greater difficulty in de-agglomeration. A similar trend is observed for FOR in both the SD powder and the agglomerates. Once again, these results should be treated with caution as the operating conditions were chosen to highlight the differences in behavior. In practice, if these powders were used in asthmatic patients with superior inspiratory capacities, these differences could be minimized.

3.4.5.2. Laser diffraction analysis. Fig. 8 illustrates the deagglomeration of lactose agglomerates and SD agglomerates under varying pressures. For the lactose softpellets, the measured d50 values at pressures of 0.1, 0.5, 1, 2, 3, and 4 bar are 194.59 µm ± 33.49, 32.95 µm ± 3.20, 6.68 µm

Table 4
Fine particle fraction (FPF), emitted dose (ED) and API content (NGI 30 L/min).

		FPF (%)	ED (%)	API content (%)
BUD	SD powder	62.46 ± 0.91	77.99 ± 0.99	0.66 ± 0.02
	SD softpellets W1	55.40 ± 2.00	77.28 ± 1.98	0.66 ± 0.01
	SD softpellets W2	47.61 ± 1.58	73.20 ± 1.62	0.66 ± 0.01
FOR	SD powder	69.79 ± 3.73	83.40 ± 1.36	0.027 ± 0.002
	SD softpellets W1	57.95 ± 8.66	82.13 ± 1.01	0.025 ± 0.002
	SD softpellets W2	51.11 ± 3.81	78.62 ± 2.11	0.025 ± 0.002

Table 3
Rupture force of Lac500 and SD softpellets.

	Lac500 Softpellet W1	Lac500 Softpellet W2	Lac500 Softpellet W4	SD Softpellet W1	SD Softpellet W2	SD Softpellet W4
Rupture force (mN)	3.77 ± 1.96	4 0.06 ± 1.75	3.42 ± 1.46	2.00 ± 1.82	2.54 ± 0.85	2.60 ± 1.18
Normalized force (mN/mm)	2.81 ± 1.36	2.88 ± 1.12	2.39 ± 1.87	1.19 ± 0.97	1.67 ± 0.64	1.63 ± 0.74

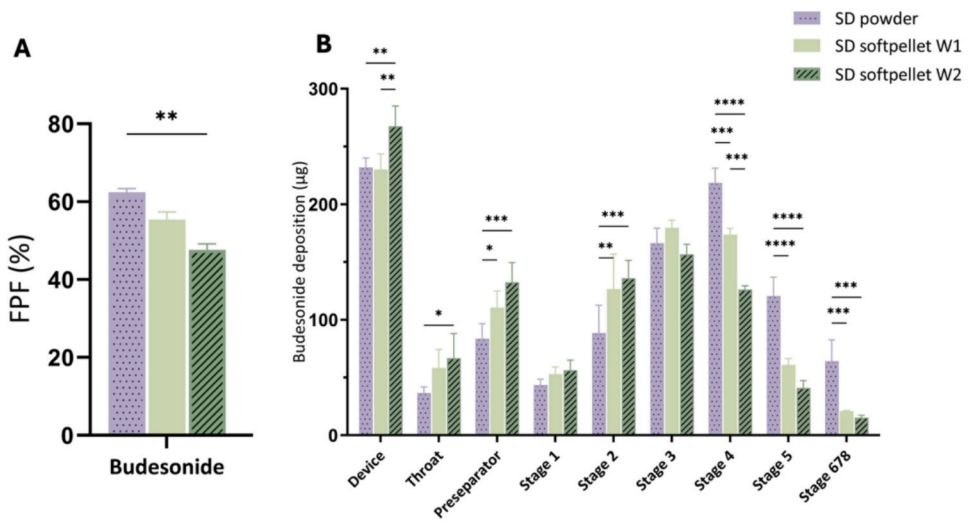

Fig. 7. Fine particle fraction (FPF) (A) and budesonide deposition (B) for spray-dried (SD) powder and SD agglomerates after one week (W1) and two weeks (W2).

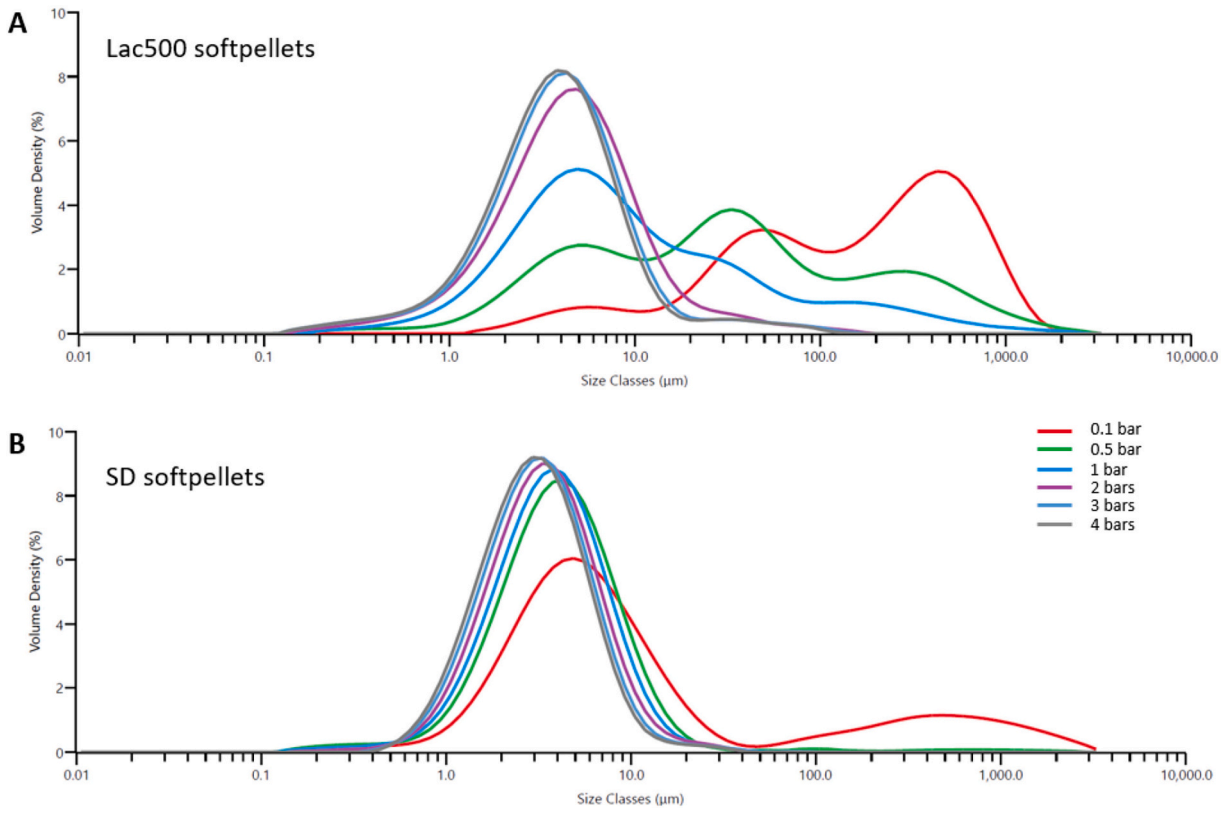

Fig. 8. Deagglomeration of Lac500 soft pellets (A) and spray-dried powder (B) at different pressures.

± 0.70, 4.14 µm ± 0.12, 3.69 µm ± 0.05, and 3.66 µm ± 0.15, respectively. Fig. A shows a shift towards smaller sizes as pressure increases, with a plateau observed starting at 2 bars. Regarding the SD softpellets, it is noted that these deagglomerate more easily, exhibiting a single size population starting at 0.5 bar. The d50 values obtained for pressures ranging from 0.1 bar to 4 bar are 6.48 µm ± 1.15, 4.05 µm ± 0.40, 3.66 µm ± 0.29, 3.35 µm ± 0.27, 3.10 µm ± 0.20, and 2.96 µm ± 0.21. These results align with the mechanical strength values measured, demonstrating greater robustness in the lactose agglomerates compared to the SD agglomerates.

4. Conclusion

This study presents the development of a device that can be used in the pharmaceutical industry to improve the flowability of cohesive powders, thereby facilitating processing. By optimizing a vibrating inclined plate, we successfully generated powder agglomerates called softpellets, whose formation is largely driven by electrostatic charging through friction with the plate. Notably, despite the different properties and compositions of the two tested powders (fine lactose and spray-dried powder), both were successfully agglomerated. The device parameters were adjusted to produce spherical agglomerates of several hundred microns in size, significantly enhancing powder flowability.

For inhalation powder applications, it was crucial to demonstrate that the agglomerates were robust enough to withstand transportation and filling processes (capsules, blisters, or reservoirs) while still breaking apart efficiently upon inhalation to ensure proper lung deposition. Mechanical strength analysis confirmed the stability of the soft-pellets, while aerosolization tests demonstrated effective deagglomeration even at low inspiratory flow rates, maintaining a fine particle fraction comparable to the initial powder (~60 %). However, further long-term studies are needed to assess the impact of ambient humidity on agglomerate stability and, if necessary, to optimize storage conditions.

A key finding of this study is the critical role of **electrostatic charges** in the agglomeration process. The triboelectric effect, induced by particle collisions and interactions with the vibrating plate, generates cohesive forces that promote spontaneous agglomeration. Charge measurements confirmed that the powder becomes increasingly charged with each passage on the plate, influencing both the cohesion and flowability of the resulting agglomerates. Understanding and controlling these electrostatic interactions could open new avenues for tailoring agglomerate properties and optimizing their performance in pharmaceutical applications.

Beyond inhalation powders, this study opens new perspectives for the pharmaceutical industry, particularly in the context of continuous manufacturing. Unlike conventional granulation methods that require binders and complex processing steps, our approach could enable direct integration of micronized powder agglomeration into a continuous production line, reducing the need for excipients and simplifying industrial implementation. By adjusting the vibration parameters of the inclined plate, the robustness of the agglomerates could be fine-tuned for specific applications: softer agglomerates for inhalation and stronger ones for applications such as tablet compression.

From a broader perspective, this process could also be applied to other industries handling fine powders, such as metallurgy or cosmetics. Future work will focus on extending this approach to other powder categories, exploring its potential for continuous manufacturing of solid pharmaceutical forms.

CRediT authorship contribution statement

Eva Gresse: Writing – original draft, Methodology, Data curation, Conceptualization. **Thomas Gemine:** Writing – review & editing, Methodology, Data curation. **Lena Renauld:** Data curation. **Brigitte Evrard:** Writing – review & editing, Funding acquisition. **Geoffroy Lumay:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Anna Lechanteur:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to improve the language and readibility. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.powtec.2025.121070.

Data availability

No data was used for the research described in the article.

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