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Research paper

Agglomerate behaviour of fluticasone propionate within dry powder inhaler formulations

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ABSTRACT

Due to their small size, the respirable drug particles tend to form agglomerates which prevent flowing and aerosolisation. A carrier is used to be mixed with drug in one hand to facilitate the powder flow during manufacturing, in other hand to help the fluidisation upon patient inhalation. Depending on drug concentration, drug agglomerates can be formed in the mixture. The aim of this work was to study the agglomeration behaviour of fluticasone propionate (FP) within interactive mixtures for inhalation. The agglomerate phenomenon of fluticasone propionate after mixing with different fractions of lactose without fine particles of lactose (smaller than 32 μm) was demonstrated by the optical microscopy observation. A technique measuring the FP size in the mixture was developed, based on laser diffraction method. The FP agglomerate sizes were found to be in a linear correlation with the pore size of the carrier powder bed (R^2 = 0.9382). The latter depends on the particle size distribution of carrier. This founding can explain the role of carrier size in de-agglomeration of drug particles in the mixture. Furthermore, it gives more structural information of interactive mixture for inhalation that can be used in the investigation of aerosolisation mechanism of powder. According to the manufacturing history, different batches of FP show different agglomeration intensities which can be detected by Spraytec®, a new laser diffraction method for measuring aerodynamic size. After mixing with a carrier, Lactohale LH200, the most cohesive batch of FP, generates a lower fine particle fraction. It can be explained by the fact that agglomerates of fluticasone propionate with very large size was detected in the mixtures. By using silica–gel beads as ball-milling agent during the mixing process, the FP agglomerate size decreases accordingly to the quantity of mixing aid. The homogeneity and the aerodynamic performance of the mixtures are improved. The mixing aid based on ball-milling effect could be used to ameliorate the quality of inhalation mixture of cohesive drug, such as fluticasone propionate. However, there is a threshold where an optimal amount of mixing aids should be used. Not only the drug des-aggregation reaches its peak but the increase in drug–carrier adhesion due to high energy input should balance the de-agglomeration capacity of mixing process. This approach provides a potential alternative in DPI formulation processing.

1. Introduction

In inhalation therapy, the typical size of respirable particles is generally below 5 μm. Within this range of size, they are able to penetrate into the lower lungs, i.e. the bronchiolar and alveolar sites. Although micronisation of the active drug is essential for deposition into the lower lungs during inhalation, due to their small size and high relative surface area, drug particles are very cohesive and naturally form agglomerates [1] that could prevent dispersion in the desired respirable size [2–4]. The agglomerated particles cannot reach the bronchiolar and alveolar sites of the lungs. Aggregate size and behaviour appeared to play an important role in powder aerosol dispersion [5,6]. Thus, de-agglomeration properties of drug-alone formulations had drawn a great attention of academic and industrial researchers.

Aerodynamic dispersion of cohesive powder is actually an active research field but more fundamental studies are needed to give better understanding on the de-agglomeration process upon interaction with air flow [7]. A new model describing the complete disintegration of dry powder agglomerates was recently proposed. In this model, the breakup of every single connection inside agglomerate is considered and the dispersion strength of model agglomerates is calculated and discussed. Depending on the intensity of applied dispersion stress, an instant de-agglomeration or a stepwise de-agglomeration of powder is possible. A linear relationship between the dispersion strength and χ_{Agg}/χ_p (diameter of

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agglomerate/diameter of primary particle) was demonstrated [1,8]. In reality, the cohesion between primary particles is not homogenously distributed in agglomerates. In that case, agglomerates are first divided along areas of less cohesion into parts, so that smaller and relatively stable agglomerates remain at the end [8]. The similar observations were experienced with micronised budesonide and salbutamol sulphate as models, using Aerosizer® with various shear force [9].

From a practical point of view, strong cohesion forces between particles hinder the handling of the powder during the manufacturing process, especially in metering and filling steps [10,11]. Thus, formulations with fine drug particles and coarse carrier particles, usually α-lactose monohydrate, have been commonly used to facilitate aerodynamic dispersion and flow [11,12]. In this type of mixture, so-called ordered mixture or interactive mixture, the fine particles of drug adhere to the larger carrier particles in such a way that it results in good blend uniformity and flowability [11]. However, the adhesion should be adequate to effectively release the drug particles in respirable size range during inhalation, thus allowing them to reach the target sites into the lungs. Many commercial products have relatively poor efficiencies, with often less than 30% of drug being delivered to the lungs [13].

Interactions between particles are mainly dependent on the physicochemical characteristics of the interacting particles that will influence the drug/carrier blend process and also drug delivery from the carrier and its dispersion. The research on drug–carrier interaction and its relationship with aerodynamic performance of carrier-based formulation was extensively investigated. Different important factors were identified, such as particle size, shape [14], particle size distribution [15,16], roughness [2,17,18], surface energy [19], fine lactose content [16,19,20]. In these studies, the phenomenon drug–carrier adhesion was mainly examined.

In the interactive mixtures, if sufficiently high amount of drug is added, all drug particles cannot adhere to carrier and will form agglomerates [21]. The agglomeration phenomenon was also observed in the mixture of micronised drug and coarser particle. The kinetic of de-agglomeration was described, in function of carrier size and mixing conditions [22,23]. The excellent agreement between dissolution profiles and drug agglomerate size was reported. [22,24].

The role of carrier is to facilitate the de-agglomeration of cohesive drug particles that aids the powder flow, entrainment and aerosolisation. However, there is little research on the drug agglomeration phenomenon in carrier-based DPI formulations, linking with their aerodynamic performance. The aim of this work was to study the agglomeration behaviour of micronised fluticasone propionate within interactive mixture with alpha-lactose monohydrate for inhalation, especially the influence of carrier particle size and the mixing conditions.

2. Material and methods

2.1. Materials

Intrinsic fine particles of lactose were removed from Lactohale LH200 (Frieslands Foods Domo, The Netherlands) by air-jet sieving through a 32 μm sieve for 30 min with an airflow that produces a pressure drop of 4 kPa. This lactose without small particles was further sieved through 40, 63, 90 and 125 μm sieves to obtain three fractions: 40–63 μm; 63–90 μm and 90–125 μm. The obtained fractions were stored at 40% RH, 20 °C at least 24 h before further operations. Two batches of micronised fluticasone propionate (FP) (batch number 0712/019/410 and 92275, respectively) were used as supplied from two manufacturers.

For the Karl-Fischer titration, Hydranal®-Composite 5 (Sigma–Aldrich Laborchemikalien GmbH, Germany), containing imidazoles, sulphur dioxide and iodine in diethylene glycol monoethyl ether, was used. It has a titre of 5 mg water/mL. Chemicals and solvents used were ammonium acetate (AnalaR Normapur, VWR International, Belgium) and methanol (HPLC Grade, Fischer Scientific UK Ltd, United Kingdom). For HPLC analysis, water was purified by reverse osmosis (MiliQ; Milipore, Molsheim, France).

2.2. Powder characterisation

Particle size was measured by laser diffraction (Malvern Mastersizer 2000®, Malvern Instrument Ltd., Orsay, France) in liquid dispersion using the 300 RF lens and the small volume sample presentation unit.

For lactose, the dispersing medium was 0.5% Polysorbate 80 (Tween 80) in absolute ethanol saturated by lactose over 24 h and filtered through 0.25 μm prior to analysis. Lactose was dispersed in the dispersing medium for 3 min by magnetic agitation. The sample was further treated with sonication in a water bath for 1 min. Sample was added into sample cell containing the dispersing medium in order to obtain an obscuration between 10–30%. In case of fluticasone propionate, the dispersing medium was ethanol/water 10/90 (%.v/v) with 0.1% Polysorbate 80, saturated by fluticasone propionate. Size measurement of each sample was performed using 2000 sweeps. Size distribution and summary statistics are the average of at least three determinations. For each measurement, the mean diameter (VMD = Volume Mean Diameter), the median diameter (dv, 0.5), the diameter under which 10% particles (dv, 0.1) and 90% particles (dv, 0.1) were in consideration.

The true density of powder was assessed by helium pycnometer (AccuPyc 1330, Micromeritics, USA) using a 3 cm^3 sample cell. The results are expressed as the average of ten determinations.

Water content of lactose was analysed by Karl-Fischer technique, using Mettler DL18 Karl-Fischer titrator, a coulometric titration machine. Prior to analysis, the titrant concentration of Hydranal®-Composite 5 was determined using purified water as calibration sample. The background titrant consumption, usually caused by moisture absorption in the titration system, was also evaluated. The background titrant consumption value must be lower than 50 μg/min and was taken into account in the result calculation. 1 gram of lactose was weighed and dispersed in dry methanol (previously titrated out water). The results are calculated as the average of three determinations.

Apparent bulk volume (V_0) and volumes after 10 taps (V_{10}) and 500 taps (V_{500}) for 50 g powder were determined using the method described in European Pharmacopoeia 7. The bulk volume was measured after manually tapping the cylinder ten times on a flat table top surface (V_0). The graduated cylinder is placed on a tap density tester and the final volume is recorded after 500 taps. The packing ability V_{10}–V_{500} was also calculated.

The angle of repose is the angle formed by the horizontal base of the bench surface and the edge of a cone-like pile of granules. Funnel used was a glass funnel and the size of the orifice was 8 mm and the height from the beginning of funnel to end of orifice was 11 mm. The funnel was fixed in place, 6 cm above the bench surface. After the cone from 25 g of sample was built, height of the granules forming the cone (h) and the diameter (d) of the base were measured. The angle of repose (θ) was calculated as follows:

$$\theta = \tan^{-1}\left(\frac{2h}{d}\right)$$

The air permeability of powder was measured by means of a Blaine apparatus. A modified procedure for investigating the structure of powder was developed. A critical point of this procedure is

that no force is exerted on the powder bed in order to maintain the unmodified powder structure. The operational procedure was described in previous study [25]. Three samples are analysed. The results are calculated as the mean of the 24 measurements.

2.3. Powder characterisation by mercury porosimetry

Powder permeability was assessed by mercury intrusion porosimetry (Micromeritics® Autopore IV 9500). 1 (±0.02) g of powder sample was used. Mercury pressure working range was from 0.0034 MPa to 15 MPa in order to avoid particle compression or collapse due to high pressure. With range of working mercury intrusion pressure, this technique was utilised to investigate the structure of pore of powder bed, as mentioned in our previous work [25].

2.4. Mixing conditions and Homogeneity Evaluation

Fluticasone propionate (FP) at a concentration of 2.5% w/w and lactose were mixed in a Turbula mixer (Bachofen Maschinenfabrik, Basel, Switzerland) for 2 h at 90 rpm. Each blend was prepared in 50 g quantities in glass vessels adapted for Turbula mixer. The mixing was performed at controlled ambient conditions (40 ± 5% relative humidity and 20 ± 2 °C).

The quality of the blends was expressed by the coefficient of variation (cv) of sample drug content. Fifteen randomly selected samples (20.0 ± 0.2 mg) were dissolved in methanol/water 70/30 (% v/v) using 25 mL volumetric flasks. Sonication in a water bath ensured the total dissolution of drug. All fluticasone propionate samples were analysed by a validated HPLC method using an ODS chromatographic column, 50mm × 4.6 mm × 5 μm (Phenomenex). Mobile phase is composed of methanol/0.1% ammonium acetate buffer in 80/20 (% v/v) ratio and was passed through a filter of 0.22 μm prior to use. The flow rate was 1 mL/min and fluticasone propionate was detected at 236 nm. A linear range was obtained from 0.01 to 23.0 μg/ml (r^2 = 0.996).

2.5. Evaluation of adhesion

Adhesion characteristics were evaluated by submitting the blend to a sieving action by air depression with the Alpine air-jet sieve. 30 g of blend was placed on the 32 μm sieve section of the Alpine air-jet apparatus, in a sealed enclosure. Three samples of 20 mg were removed from the powder bed after sieving for different lengths of time: 5, 30, 60, 150 and 300 s. The quantity of drug remaining in on the sieve was determined by HPLC method.

2.6. Mixture investigation by optical microscopy

Powder mixtures were gently scattered onto the glass slides and one drop of light paraffin oil was applied without disturbing the powder structure. Samples were observed using a Nikon optical microscope equipped with digital image capture system.

2.7. Determination of particle size distribution of fluticasone propionate in mixture with lactose

The particle size of fluticasone propionate in mixture was assessed by laser size analyser. About 30 mg of mixture was suspended in ethanol/water (10:90; v/v). The lactose particles dissolved while the fluticasone propionate particles were suspended in the solution. The particle size distributions of suspensions were measured. The results are the mean of at least three determinations.

2.8. Aerodynamic evaluation

Each formulation was manually loaded into size 3 gelatine capsules (donated by Capsulgel, France). Fill weight was 20.0 ± 0.2 mg for fluticasone propionate mixtures giving the nominal dose of 500 ± 5 μg of drug per capsule. Following filling, capsules were stored at 40 ± 5% relative humidity and 20 ± 2 °C for at least 24 h prior to analysis.

Aerodynamic evaluation of fine particle fraction and emitted dose were obtained using a Twin Stage Impinger (TSI, Apparatus A, European Pharmacopoeia 7). Each deposition experiment involved the aerosolisation at 60 l/min via an Inhalator Ingelheim of 5 capsules. All stages of the Twin Stage Impinger were filled with Water/Methanol 30/70% v/v. The quantity of drug was determined by the methods previously described in mixture quality evaluation. For each blend, assays were performed in triplicate. All experiments were performed in controlled temperature and relative humidity (40 ± 5% relative humidity and 20 ± 2 °C).

- Emitted dose (ED) was the sum of drug collected from the upper and lower stages.
- Fine particle dose (FPD) is defined as the amount of drug deposited in the lower stages of the TSI, since their aerodynamic diameter was less than the cut-off diameter of the TSI (6.4 μm at an airflow rate of 60 l/min).
- The percentage emission was calculated as the ratio of ED to the average capsule content.
- The fine particle fraction was calculated as the ratio of FPD to the emitted dose.

3. Results and discussion

3.1. Powder characterisation

In the laser diffraction method for particle size distribution determination, the saturation of the dispersing medium with sample prevents the possible dissolution during the measurements. Sonication is believed to help the complete agglomerate separation into primary particles. Sample observation by optical microscope (40 and 100 times magnification) demonstrated the complete dispersion of fine particles and no particle fragmentation was detected. Investigation by optical microscope also revealed that air depression sieving removed successfully the fine lactose particles (Fig. 1A, C and E).

For all tested lactoses, the water content is about 5% which is in agreement with the lactose alpha-monohydrate specifications of the European Pharmacopoeia 7. True density determined by helium pycnometer is from 1.5410 to 1.5495 g/cm^3, comparable with other published values. The mass median diameter of fluticasone propionate is about 3.23 μm and 2.80 μm. It is adequate for deep penetration into the lungs. Table 1 gives an overview of particle characterisation of drugs and carriers.

All lactose fractions that are exempted from fine particles (<32 μm) have a good flowability. Bulk volumes, volumes after 10 taps and packing ability are comparable for the two fractions 125–90 μm and 90–63 μm, but are higher for the 63–40 μm fraction (Table 2). Although the void fraction in small size particle is more important, the arrangement between particles for small size powders is more difficult than bigger sized powders. This behaviour can explain a bad flowability of small size powder. The presence of particle smaller than 32 μm hinders the powder flow, in case of Lactohale LH200. A good agreement between the values of angle of repose, powder packing and flow time was demonstrated.

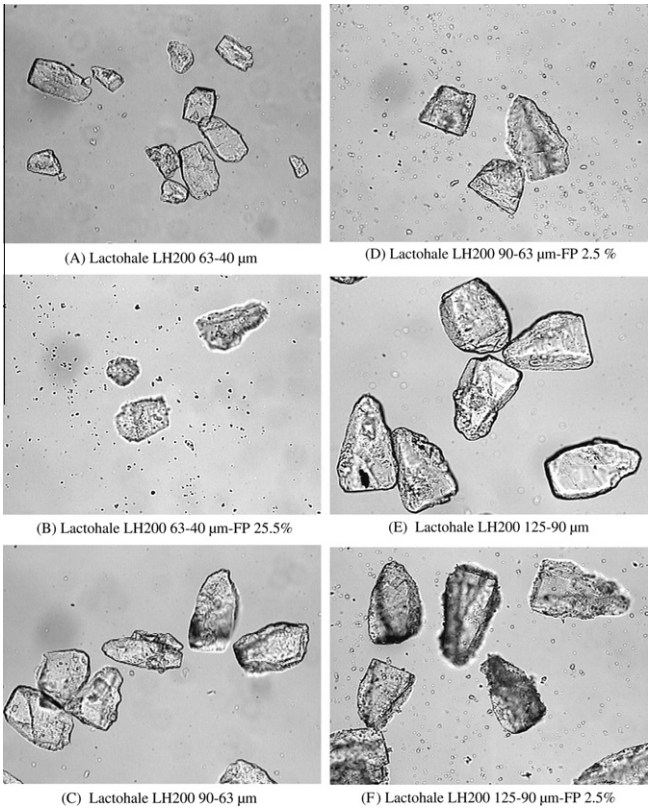

Fig. 1. Image of fraction of lactose (magnification × 20).

3.2. Powder structure determined by mercury porosimetry and Blaine apparatus

The pore structure is an important property of porous materials, especially in granular material like powder bed. It can be assessed by investigation of powder bed permeability and by non-wetting liquid intrusion like mercury porosimetry. In case of permeability, the air flow time reveals the air pathway system through a powder bed. It is more difficult for air to travel through a smaller and longer pathway. In the other hand, the mercury porosimetry gives more details of the pore structure thanks to its gradual intrusion. When the intrusion pressure increases, the mercury liquid fill sequentially the largest to smallest pores, from voids formed by inter-particulate spaces to surface pores depending on the intrusion pressure. At the critical pore size, defined as characteristic length, a continuous pathway through the material and a point of inflection in the rapidly increasing range of the cumulative intrusion curve can be observed. This inflection point corresponds closely to the pressure at which percolation begins (P_t). The value of characteristic length is then calculated from the Washburn equation for P_t.

The results of air permeability and powder pore structure by mercury porosimetry were shown in the Table 3. There is a good linear correlation between the permeability (Darcy) measured by mercury porosimeter and the reciprocal of air flow time through a powder bed, determined by Blaine apparatus (R^2 = 0.9629). Thus, the air permeability can be also useful for powder pore structure assessment. The pore size of powder bed depends on the particulate size. As comparing the characteristic length, that is to say the pore diameter of the carrier bed (Table 3) with particle size (Table 1), a smaller particle size contributes to a powder bed with smaller pore structure.

3.3. Mixture characteristics

All blends are acceptably homogenous with coefficient of variation less than 5%. The recovered drug contents are close to the theoretical values 2.5% nominal dose. Homogeneous blends were obtained for blends (Table 4).

When blends are submitted to the Alpine air-jet siever with a 32 µm sieve, drug is rapidly carried away by the airflow. The quantity of drug remaining after 30 s is an indicator of the quantity that could adhere to the carrier [17] or the quantity of drug agglomerates whose size is bigger than 32 µm. It was observed that the bigger the carrier particle size is, the greater the fraction of drug that remains attached to the carrier (Fig. 2). This is confirmed by the assays carried out using the TSI (Table 5). The fine particle fraction (FPF) of fluticasone increased when the particle size of the different sieved fractions of lactose decreases. A further decrease of the lactose fraction (40–63 µm) improves the FPF but it remains much lower than the one obtained with the Lactohale LH200 used as received. In case of initial lactose, the fine particles of lactose (smaller than 32 µm) in one hand could adhere to so-called "high energy sites" of coarse particles as "active sites theory" [26] or, on the other hand could form loose agglomerates with drug particles that could be easily aerosolised in respirable size range [20].

The particle size is one of critical characteristic of carrier in dry powder inhaler formulation. This factor could affect the fluidisation process and the adhesion of drug particles on carrier surface. Bell et al., 1971 found that particle diameter of lactose capable of

Table 1
Powder characteristics: VMD = Volume Mean Diameter.

	Batch	VMD (µm)*	dv, 0.1 (µm)*	dv, 0.5 (µm)*	dv, 0.9 (µm)*	Water content (%)**	True density (g/cm^3)***
Lactohale LH200	629707	61.14 (±2.17)	4.74 (±0.15)	54.33 (±2.57)	127.82 (±3.29)	5.14 (±0.03)	1.5400 (±0.0016)
Lactohale LH200 > 32 µm	629707	91.14 (±1.09)	41.07 (±1.22)	89.39 (±0.91)	147.19 (±1.60)	5.10 (±0.04)	1.5370 (±0.0013)
Fraction 125–90 µm	629707	109.60 (±2.89)	52.17 (±7.86)	112.56 (±3.18)	163.31 (±3.22)	5.13 (±0.03)	1.5495 (±0.0039)
Fraction 90–63 µm	629707	90.17 (±2.49)	39.47 (±5.05)	90.83 (±1.52)	140.33 (±4.01)	5.20 (±0.02)	1.5439 (±0.0018)
Fraction 63–40 µm	629707	67.19 (±0.14)	33.82 (±1.82)	65.98 (±0.31)	105.34 (±2.11)	5.12 (±0.09)	1.5410 (±0.0078)
Fluticasone propionate	0712/019/410	3.23 (±0.04)	0.51 (±0.01)	2.69 (±0.03)	6.69 (±0.10)	ND	1.3803 (±0.0038)
Fluticasone propionate	92275	2.80 (±0.08)	0.46 (±0.00)	2.07 (±0.01)	5.79 (±0.12)	ND	1.3997 (±0.0086)

* Value ± Standard deviation, n = 6.
** Value ± Standard deviation, n = 3.
*** Value ± Standard deviation, *n* = 10.

Table 2
Powder flow characterisation (value ± standard deviation, $n = 3$).

Lactose	Flow time (s)	V0 (mL)	V10 (mL)	V500 (mL)	V10-V500 (mL)	Angle of repose (°)
Lactohale LH 200	No flow	75.7 (±1.5)	71.0 (±1.0)	55.7 (±0.6)	15.30	52.1 (±2.4)
Lactohale LH 200 > 32 μm	2.5 (±0.12)	69.0 (±1.0)	64.0 (±0.0)	58.0 (±0.0)	6.00	31.3 (±1.2)
Fraction 125–90 of lactohale LH200	1.83 (±0.06)	69.7 (±0.6)	65.7 (±0.6)	61.3 (±0.6)	4.40	28.9 (±1.0)
Fraction 90–63 of lactohale LH200	2.00 (±0.36)	70.0 (±0.0)	64.7 (±0.6)	59.3 (±0.6)	5.40	32.8 (±1.3)
Fraction 63–40 of lactohale LH200	5.17 (±1.04)	75.0 (±1.0)	70.7 (±0.6)	63.3 (±0.6)	7.40	36.1 (±0.7)

Table 3
Powder pore structure characterisation.

	Pore diameter of the carrier bed (μm)	Permeability (Darcy)	Permeability by Blaine apparatus (s)*	$1/t$ (1/s)
Lactohale LH 200	17.58	440.0218	4.73 (±)	0.21
Lactohale 200 > 32 μm	24.55	1096.576	2.12 (±)	0.47
Fraction 125–90 μm of lactohale LH200	33.62	2290.4396	1.25 (±0.07)	0.80
Fraction 90–63 μm of lactohale LH200	26.07	1415.9135	1.74 (±0.08)	0.57
Fraction 63–40 μm of lactohale LH200	21.36	864.7171	2.23 (±0.09)	0.45

Table 4
Fluticasone propionate (FP) (batch number 0712/019/410) mixture characteristics ($n = 15$) (CV: coefficient of variation).

Blend	FP content (%)	CV (%)
Lactohale LH 200 + FP	2.47	2.17
Lactohale 200 > 32 μm + FP	2.42	2.06
Fraction 125–90 μm + FP	2.28	4.41
Fraction 90–63 μm + FP	2.31	3.31
Fraction 63–40 μm + FP	2.46	4.44

affecting maximum powder removal from a Spinhaler capsule is approximately 100 μm [12]. The dispersion of drug particles appeared to increase as the particle size of the lactose carrier decreased for the mixtures prepared from different particle size commercial samples of lactose and from different sieve fractions of the same lactose, due to the decrease of interaction force of type Van der Walls [21,27].

After mixing the lactose with the drug, a reduction in air permeability of each mixture was observed (permeability of carriers in Table 3 and permeability of mixture in Table 5). It can be explained by the fact that beside the adhesion on carrier particles, drug particles could distribute in the interstitial space between carrier particles and therefore it is more difficult for the air to move through the powder bed. Non-adhering drug particles can be seen on the microscopic image taken from mixture with lactose fraction exempted the particle smaller than 32 μm (Fig. 1B, D and F).

For further investigation of FP agglomerate in mixture, the FP size was then measured. By dissolving lactose in the measurement liquid, the size of agglomerates of fluticasone can be assessed by laser size analyser. It can be noted that even after mixing with lactose for 120 min, drug particles still remain in agglomerate form (Table 6). In our case, agglomerate sizes were found in good correlation with the pore size between carrier particles ($R^2 = 0.9382$) (Fig. 3). It can be speculated that during mixing, the natural agglomerates of drug should be dispersed and divided to small agglomerates according to the interstitial space size between the bigger particles of carrier. This finding is supported by percolation theory in binary mixture [28,29].

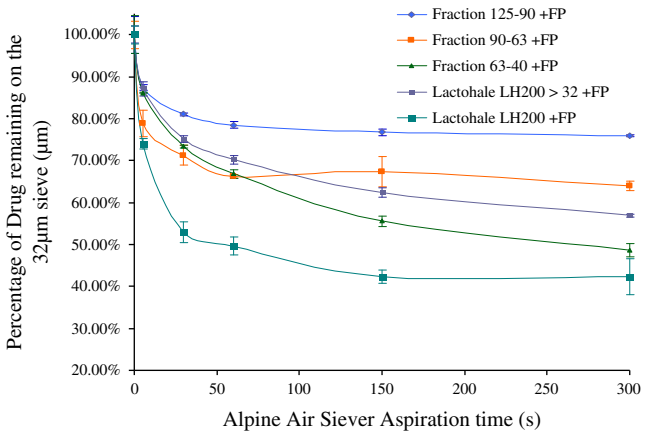

Fig. 2. Percentage of fluticasone propionate (FP) remaining in the blend in relation to the functioning time of the air-jet sieve. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4. Investigation of mixing conditions on agglomeration behaviour of fluticasone propionate in the mixture

To reach the inhalable size range (inferior than 10 μm), drugs are normally submitted to micronisation [30]. The thermodynamically activated particle surfaces due to high energetic process can cause high agglomeration behaviour [31]. Furthermore, it is difficult to control this process and the batch-to-batch difference is a common phenomenon [32–34]. In this study, two different batches (0712/019/410 and 92275) of fluticasone propionate were disposed. The Spraytec® technique was chosen to differentiate the agglomerate intensity of the two batches. The principle of this technique was described in previous studies [35,36]. Experiments were conducted using capsule size 3 containing about 10 mg of fluticasone propionate via Handihaler® of Boeringher Ingelheim. The flow rate through the Spraytec® was maintained at 90 L/min. All measurements were made on three replicates. Measurement was performed over 2.4 s with an arbitrary triggering level of 50, noise level 0 and background level of 100. The particle size distribution of fluticasone propionate obtained by Spraytec® was represented in the Table 7. The agglomerate behaviour of two batches of FP is quietly distinguished. Although their primary particle sizes are similar (VMD = 3.23 μm for Batch No. 0712/019/410 vs VMD = 2.80 μm for Batch No. 92275), their agglomerate sizes are

Table 5
Aerodynamic performance of fluticasone propionate (FP) (batch number 0712/019/410) mixture by twin stage impinger.

Blend	Air flow time (s)*	Emitted dose (%)*	Fine particle fraction (%)**
Lactohale LH 200 + FP	9.37 (±0.48)	79.17 (±1.61)	25.25 (±3.70)
Lactohale 200 > 32 μm + FP	3.28 (±0.10)	79.36 (±2.01)	9.41 (±2.78)
Fraction 125–90 μm + FP	1.99 (±0.19)	79.17 (±1.61)	4.29 (±0.28)
Fraction 90–63 μm + FP	2.67 (±0.21)	72.17 (±1.33)	7.67 (±0.70)
Fraction 63–40 μm + FP	3.56 (±0.09)	75.54 (±1.93)	9.46 (±1.07)

* $n = 3$.
** $n = 8$.

Table 6
Fluticasone propionate size in the mixtures with lactose (± standard deviation, $n = 6$) (FP batch 92275) (VMD: Volume Mean Diameter).

Blend	VMD (μm)	dv, 0.1 (μm)	dv, 0.5 (μm)	dv, 0.9 (μm)
Lactohale LH 200 + FP	5.59 (±0.30)	0.36 (±0.02)	5.65 (±0.10)	10.69 (±0.75)
Lactohale 200 > 32 μm + FP	9.47 (±0.35)	0.62 (±0.03)	7.26 (±0.09)	21.03 (±0.89)
Fraction 125–90 μm + FP	19.58 (±0.50)	3.29 (±0.09)	16.99 (±0.35)	39.43 (±1.26)
Fraction 90–63 μm + FP	11.30 (±0.28)	1.12 (±0.05)	8.95 (±0.17)	24.42 (±0.65)
Fraction 63–40 μm + FP	5.43 (±0.36)	0.59 (±0.03)	4.88 (±0.05)	10.39 (±0.65)

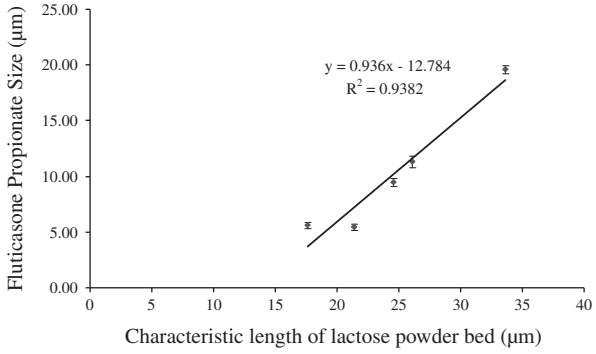

Fig. 3. Relationship between characteristic length of carrier powder bed and fluticasone propionate (FP) size in the mixture.

very different in aerolised state. Fluticasone propionate batch No. 92275 shows a most cohesive property and forms biggest aggregates (55.37 μm, approximately 20 times of primary particles).

In order to investigate the influence of mixing conditions on agglomeration of fluticasone propionate in mixture, especially for a very cohesive powder, fluticasone propionate (FP) (batch 92275, Volume Mean Diameter = 2.80 μm) at a concentration of 2.5% w/w was mixed with Lactohale LH200. The mixing process was carried out in a Turbula mixer for 2 h at 90 rpm under controlled relative humidity and temperature. Each blend was prepared in 5 grams quantity. The characteristics of 5 g mixture are similar with 50 g mixture ones (Data are not shown). Silica–gel beads (granular form of silica made from sodium silicate; despite its name it is a solid: diameter approx. 3–5 mm, 25 beads for 1 g readily equilibrated with experimented ambiance) were used as mixing aids based on ball-milling effect for de-agglomeration purpose. Five blends were prepared with 0%, 10%, 20%, 30% and 40% of these beads. The quality of the blends was expressed by the uniformity of drug content ($n = 20$). Quantitative analysis was carried out by validated HPLC method, as mentioned above.

The recovered drug content of all mixtures is close to the theoretical values (Table 8). FP content uniformity is lower than 5% that indicates a good homogeneity of all blends. 0% Silica–gel mixture has a higher content coefficient variation than other mixtures ($p < 0.001$). Thus, using silica–gel beads as mixing aid improves the homogeneity of FP mixture. At 40% silica–gel, the mixture shows the best uniformity.

In terms of aerodynamic performance of powder mixture, the fine particle fraction (FPF) of mixtures with mixing aids is significantly greater than simple Turbula-processed mixture (e.g. 7.29%) as it can be seen in Fig. 4. FPF improvement depends on the amount of added silica–gel beads. FPF reaches a peak when 30% of silica–gel beads was added and shows no significant improvement with increasing the amount of mixing aid.

The effect of amount of silica–gel beads on the size of drug and lactose particles was investigated and is presented in Fig. 6. Without mixing aids (0% silica–gel mixture), the FP size is much higher (about 40 μm) than the initial size of the FP materials (about 3 μm) because of the cohesive nature of the drug that tends to agglomerate. Biggest size FP agglomerates are found in this mixture, the

Table 8
Fluticasone propionate (batch 92275) mixture characteristics, $n = 20$.

Mixtures	Content (%)	RSD (%)
0% Silica–gel mixture	2.44	4.96*
10% Silica–gel mixture	2.42	1.45
20% Silica–gel mixture	2.46	1.73
30% Silica–gel mixture	2.45	1.22
40% Silica–gel mixture	2.40	0.77*

* Statistically different (Fischer test, $\alpha = 0.05$).

Table 7
Aerodynamic size of 2 batches of fluticasone propionate determined by Spraytec® (± standard deviation, $n = 3$) (VMD: Volume Mean Diameter).

Batch	VMD (μm)	dv, 0.1 (μm)	dv, 0.5 (μm)	dv, 0.9 (μm)	$V < 5.0$ μm (%)
0712/019/410	24.22 (±2.66)	2.29 (±0.19)	9.88 (±1.11)	73.99 (±11.59)	28.80 (±3.49)
92275	55.37 (±2.40)	3.08 (±0.19)	40.15 (±6.02)	130.70 (±1.22)	20.01 (±1.43)

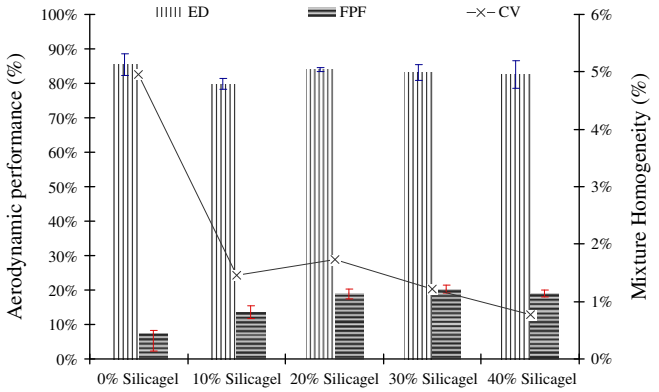

Fig. 4. Aerodynamic performance and homogeneity of fluticasone propionate mixtures. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

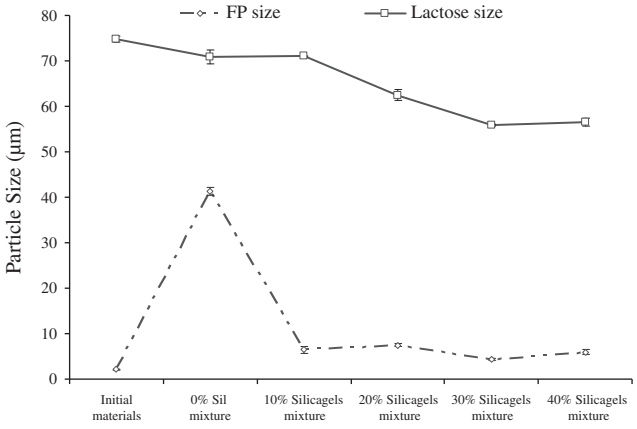

Fig. 6. Volume Mean Diameter of fluticasone propionate (FP) and lactose in the mixtures.

drug is not sufficiently dispersed. The FP agglomerate size decreases gradually when increasing the quantity of mixing aid. In one hand, the fine particle fraction of FP is consequently ameliorated. On the other hand, decreasing fluticasone propionate agglomerates improves the uniformity of drug in mixture.

There is a milling effect of the lactose when using silica–gel beads. Practically unchanged when 10% of silica–gel beads are added, the lactose particle size decreases gradually to a minimum when 30% of mixing aids are added. The improvement in the aerodynamic performance of FP formulations is possibly caused by both reduction of FP agglomerates and lactose particle size in the mixture. This is confirmed by air permeability of powder. Investigation of bulk quality of formulations and air permeability through powder bed of mixture reveals the same tendency (Fig. 5). Adding silica–gel beads in mixing process increased the air resistance of mixture but the optimum is obtained when 30% of mixing aids is used. The smaller agglomerates can contribute to the narrowing the air pathway of the powder bed. Therefore, an increasing air flow time through mixture was reported. However, the high energy input caused by high quantity of silica–gel beads can lead to higher adhesion of drug particles onto the coarser carrier particles. The air permeability was thus increased.

4. Conclusion

Carrier particle size plays an important role in the inhalation performance of interactive powder mixtures. Decreasing carrier particle size leads to a decrease of particulate interaction between drug and carrier. The reduced adhesion between drug and carrier particles increased drug detachment. In this study, drug agglomeration in mixture was investigated. Beside adhesion on the carrier particles, drug particles could distribute in the interstitial spaces of carrier in agglomerate form. The agglomerate size is a function of pore size formed between the carrier particles. Mixing process is a critical operation in the manufacturing of DPI formulations. Whereas simple low-shear tumbling mixer (Turbula) allows achieving acceptable homogeneity, agglomerates of very cohesive drug, such as fluticasone propionate, remain in the final mixture. Mixing aid using ball-milling effect improves the mixture homogeneity and the aerodynamic performance thanks to its de-agglomeration efficiency. Furthermore, the quantity of fine lactose particles is also increased due to the milling effect. However, there is a threshold where an optimal amount of mixing aids should be used. Not only the drug des-aggregation reaches its peak but the increase in drug–carrier adhesion due to high energy input should balance the de-agglomeration capacity of mixing process. This approach provides a potential alternative in DPI formulation processing.

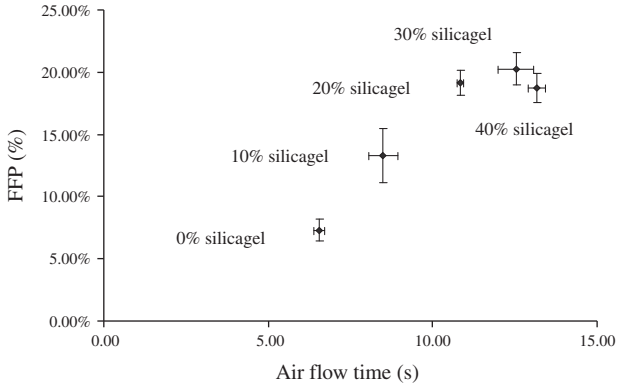

Fig. 5. Relationship between air permeability of powder and fine particle fraction of fluticasone propionate (FP).

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