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Fluidization of fine lactose for dry powder inhalation: A comparison of assisting methods

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Abstract

Fluidization of cohesive pharmaceutical powders is difficult to achieve and typically requires the introduction of external forces. This study investigates the fluidization of the fine inhalation grade of lactose powders (size range from 0.1-20 μm) that are specifically developed for dry powder inhalation (DPI) applications. The fluidization behaviour of fine lactose powders was evaluated under six conditions: without fluidization aids, with only vertical vibration (VFA), with only a downward-pointing micro-jet (MFA), with both vibration and pre-mixing with coarse particles (VCFA), with both vibration and micro-jet (VMFA), and with the combined assistance of vibration, micro-jet, and addition of coarse particles (VMCFA). The enhancement of fluidization due to the use of different assistance methods is reflected by the increase of bed expansion and the decrease in both the minimum fluidization velocity and agglomerate formation. However, applying micro-jet results in considerable powder losses due to the high fraction of fine particles stuck to the wall. Combining any two assisting methods leads to better fluidization than using a single approach. In particular, the combination of vibration and micro-jet shows the best performance in improving fluidization. Further addition of coarse particles does not play a significant influence on promoting fluidization. Finally, the analysis of the forces acting on the lactose agglomerates shows the enhancement of separation forces by introducing the fluidization assistance, which leads to a decrease in agglomerate size.

KEYWORDS

fine lactose powder, fluidization, micro-jet, premixing, vibration

1 | INTRODUCTION

Both active pharmaceutical ingredients (API) and excipients such as lactose, commonly used in dry powder inhaler (DPI) formulations, are micron-sized and form cohesive matrices due to strong inter-particle interactions.[1] Fine lactose powders in the size range from 0.1-20 μm have been specifically combined with coarse

lactose particles, known as the carrier, to improve the performance of DPIs. In particular, the objective is to enhance the flow properties of the formulation, and thus maximize the resulting drug deposition in the lungs. Several powder mechanics such as fluidization, flowability, and agglomeration/de-agglomeration can be used to characterize the DPI formulation and assess its aerosolization behaviour. Typically, it is expected that powders with good fluidization behaviour (ie, with limited cohesion) will show better performance in the DPI, since similar forces play a role in the emptying and dispersion process.[2]

Fine inhalation grade lactose powders, having a mass median diameter <10 μm, belong to group C particles according to Geldart's classification.[3] They are characterized as highly cohesive powders with a non-free flow due to the high surface-area-to-volume ratio and strong cohesive interaction, such as Van der Waals forces[4] and the electrostatic force.[5] Many methods have been proposed to enhance the fluidization of both cohesive nano-sized and micron-sized powders,[6,7] including mechanical vibration,[8,9] acoustic fields,[10] mechanical stirring,[11] centrifugal fields,[12] electrical fields,[13] pre-mixing with coarse particles,[14] secondary gas flow from a microjet,[15,16] and adding nano-additions.[17,18]

Mechanical vibration seems to be the simplest approach, as it does not require additional internals, and can directly act on aggregates and channels, thus increasing the uniformity of gas flow and improving the quality of fluidization.[19] In particular, the vibration allows large aggregates to break into smaller structures, thus providing good fluidization.[20] Pre-mixing with coarse particles can be also adopted to enhance fluidization.[21] Fluidization of cohesive Geldart's C particles can be improved by either adding a sufficiently large proportion of Geldart's A particles[22,23] or blending with different kinds of Geldart's C particles.[24] Secondary flows in the form of micro-jets at high gas velocities can enhance the fluidization of cohesive particles by promoting turbulent mixing. Pfeffer et al[15,16] have described such a method for enhancing the fluidization of agglomerates of nanoparticles based on the use of micro-jets produced by micro-nozzles (diameter of a few hundred microns) pointing downwards at a close distance to the gas distributor. Micro-nozzles pointing upwards also proved to be effective,[25] but some remaining powder between the distributor and the nozzles may not participate in the fluidization. Wang et al[26] explored the flow behaviour of cohesive particles in a cylindrical fluidized bed for different jet velocities based on a two-fluid model simulation. It showed a good agreement between the numerical simulations and experimental results of the micro-jet penetration length. Although each assisting method mentioned above can play a role in improving the fluidization of Geldart's C particles, very little research has been devoted to comparing the effect of different assistance methods on the fluidization behaviour of low-micron-sized powders. Moreover, investigating which conditions ensure a good fluidization quality for low-micron-sized pharmaceutical powders is relevant for their handling in coating processes such as atomic layer deposition.[27,28]

In this study we investigate the enhancement in fluidization of inhalation-grade lactose powders (LH300, d_{50} = 3.5 μm) by employing mechanical vibration and other flow-assisted methods, such as pre-mixing with larger particles or using micro-jets produced by micro-nozzles facing downwards at a close distance to the gas distributor. The fluidization behaviour of LH300 lactose powder is evaluated without fluidization aids, only with vertical vibration (VFA) or micro-jet assistance (MFA), with both vibration and pre-mixing of coarse particles assistance (VCFA), with both vibration and micro-jet assistance (VMFA), and with the combined assisted approaches of vibration, micro-jet, and adding coarse particles (VMCFA). The effect of different assistance methods on the fluidization quality, that is, fluidization index, bed expansion, agglomerate formation, and powder loss due to fine particles deposited on the bed wall, of the fine lactose powder, is systematically examined.

2 | MATERIALS AND METHODS

2.1 | Materials

The inhalation grade lactose powder, Lactohale LH300, was received from DFE Pharma. Prior to any fluidization

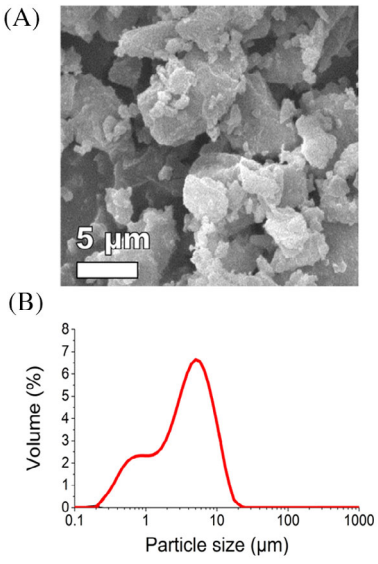

FIGURE 1 A, scanning electron microscopy (SEM) image of LH 300 lactose powders; and B, particle size distribution measured by dry powder laser diffraction

experiment, the powder was dried in a desiccator in N_2 atmosphere to limit the amount of moisture adsorbed. Figure 1 shows the SEM image and particle size distribution (PSD) of LH300 lactose powder. The PSD spans from 0.1-20 μm with a median diameter d_{50} = 3.5 μm. Moreover, the fine lactose particles exhibit complex and irregular shapes.

2.2 | Methods

The experimental set-up consisted of a cylindrical glass column that is 50 cm high and has a 2.5 cm inner diameter. The column was mounted on a vibrating table, which can generate vertical sinusoidal vibration with a range of frequency (f) and strength. The overall schematic of the experimental setup is shown in Figure 2. Powder samples were fluidized with high purity nitrogen at a gas flow rate ranging from 0-5 L/min, supplied to the fluidized bed through a gas distributor at the bottom, consisting of a sintered metal plate. A pressure sensor (FSM Elektronik, type DPS) was used to measure the bed pressure drop. One of the pressure-measuring points was connected to the column above the distributor plate, the other one was connected just below the freeboard. A second distributor plate was placed at the top of the column to act as a filter. The exhaust gas from the bed was led through two washing bottles filled with water and an additional HEPA filter to trap any elutriated ultrafine particles. The downward-pointing micro-jet was placed with its tip at a height of 3 cm above the distributor. The microjet was connected to a pressure regulator used to generate the secondary flow. A nozzle with a diameter of 500 μm was used, which is identical to the nozzle size used by Pfeffer et al.[15] A medium pressure line (ranging from 0 bar (0 kPa)-6 bar (600 kPa), corresponding to the gas flow rate of 0-3.9 L/min.) supplies compressed nitrogen to the micro-nozzles as the secondary flow. The secondary flow generated from the micro-jet ranged from 0%-44% of the total gas flow rate, which is in the same ranges used in the study of Quevedo et al.[16]

Before each experiment the fine lactose powder was sieved to remove clusters of agglomerates larger than 500 μm that were formed during transportation and storage. For each experiment without coarse particles, 15 g of lactose powder samples were filled into the glass column, resulting in an initial bed height of 6.8 cm. When adding coarse particles, 12 g of lactose powders were mixed with 3 g of coarse aluminium particles with an average diameter of 2 mm. The mass ratio of coarse to fine particles was thus 20:80. As has been shown in a previous study,[10] it was found that fluidization can be improved by increasing frequency from 30-50 Hz while using a fixed vibration amplitude. In this study, the vibration frequency was fixed at 37.5 Hz for each fluidization experiment with mechanical vibration. The experimental variables are summarized in Table 1.

The fluidized bed height expansion was determined from visual measurements of bed height, and the bed pressure drop was measured using the pressure meter for all fluidization experiments under different operating

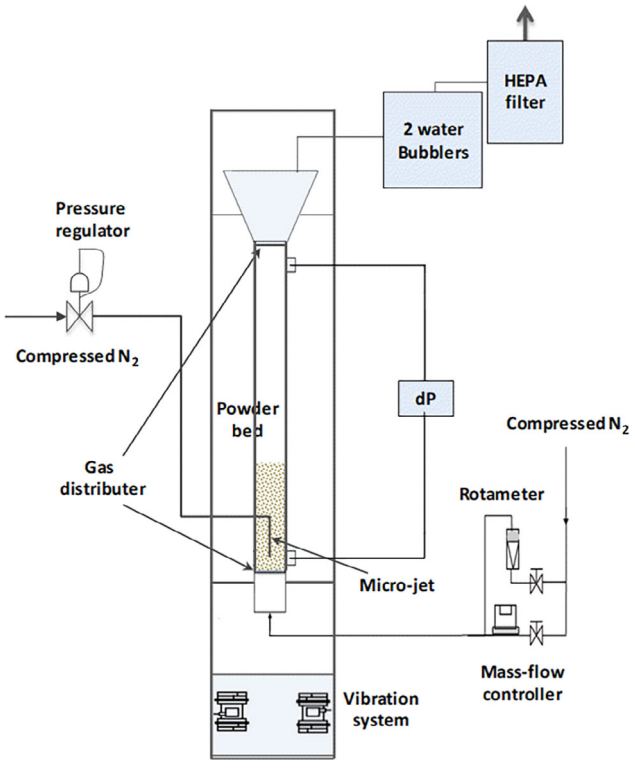

FIGURE 2 Schematic diagram of the experimental setup

TABLE 1 Experimental conditions

Particle type	LH300 Lactose
Median particle size d_p (μm)	3.5
Particle density ρ_p (kg/m^3)	1558
Bulk density ρ_b (kg/m^3)	260
Vibration frequency f (Hz)	37.5
Coarse particle mean size d (mm)	2
Coarse particle proportion (%)	20
Gas flow rate S_g (L/min)	0-5
Superficial gas velocity (cm/s)	0-6
Gas temperature T (°C)	20
Column diameter D (cm)	2.5
Initial bed height H_0 (cm)	6.8
Micro-jet flow S_m (L/min)	0-3.9

conditions. Before measuring the pressure drop at each change in gas velocity, the bed was kept at that specific velocity for 3 minutes to let it stabilize. The minimum fluidization velocity (U_{mf}) was determined by following the pressure drop across the fluidized bed vs the superficial gas velocity.[29] In particular, U_{mf} corresponds to the superficial gas velocity at which the pressure drop flattens out, that is, when it equals the powder weight. The fluidization index, which is the ratio of measured pressure drop over the weight of the bed, is used to characterize the fluidization quality.

The particle size distribution of the powder samples after fluidization tests undergoing different assistance methods is measured by a mechanical tapping sieve with six particle-size meshes (38-1500 μm). The fluidized samples were weighed using the weighing balance and poured into the top sieve. After being vibrated with the same strength and time, agglomerates at each mesh size were collected and weighed. Particle size distributions were calculated based on the results from this sieve analysis.

3 | RESULTS AND DISCUSSIONS

3.1 | Fluidization index and U_{mf}

The normalized pressure drop (the ratio of the actual pressure drop to the weight of powders per surface area) as a function of superficial velocity is shown in Figure 3. In general, all the curves show the same trend with increasing gas velocity. The pressure drop increased initially and then levelled off at high gas velocities. The pressure drop that equals the weight of the bed is an indication of good fluidization, that is, the fluidization index number is equal to 1. Without assistance methods, the incomplete fluidization of fine lactose powders is reflected by the low fluidization index number, around 0.85. This result is in agreement with the observation of fluidization behaviour by increasing the gas flow rate. Channels formed at low gas velocities and the powder bed partially fluidized with only particles in the higher part of the bed being fluidized. Contrary to the unassisted fluidization case, the lactose powders showed greatly improved fluidization with the assistance of the various fluidization aids. With each assisted-fluidization technique, the measured pressure drop across the bed at high gas velocities approximately equalled or was slightly lower than the weight of the bed per unit cross-sectional area. The pressure drop that was measured as slightly lower than the weight of the bed may have resulted from either a loss of powder sticking to the wall, or powder elutriation, or possibly from some non-uniformities in the gas flow resulting from the relatively porous distributor used.[10] The slope of the pressure drop curves further increased with use of the combined assistances methods (VMFA and VMCFA system) compared to the single assisting method (VFA or MFA system), which indicates that lactose powders are fluidized more easily.

The minimum fluidization velocity can be determined based on the pressure drop curves demonstrated in Figure 3. Accordingly, the results of the minimum fluidization velocity (U_{mf}) are shown in Figure 4. U_{mf} obtained without fluidization assistance was 7.2 cm/s, which is far larger than the calculated value of 0.06 cm/s by using the widely known Wen and Yu correlation[30] for the primary

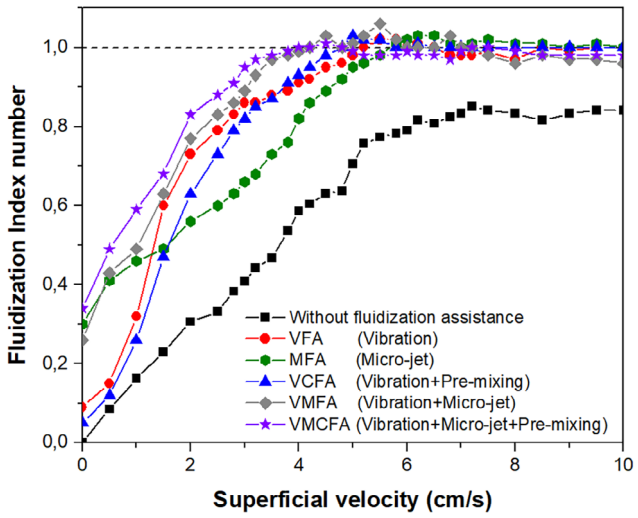

FIGURE 3 Fluidization index of lactose powders under different fluidization assistances. When using vibration, frequency f is 37.5 Hz, and when using micro-jet gas flow corresponding to the superficial gas velocity in the column of 12.2 cm/s

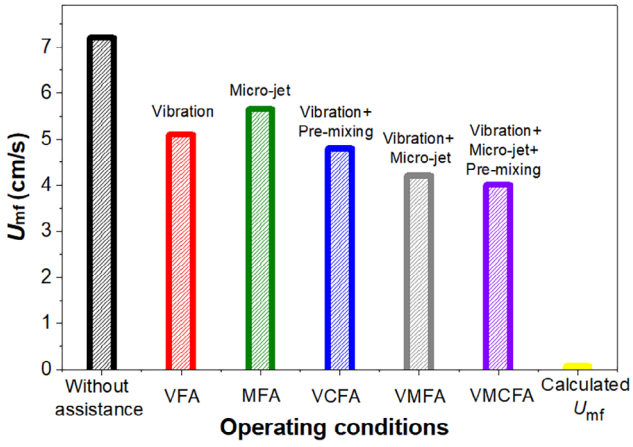

FIGURE 4 Effect of different fluidization assisting methods on minimum fluidization velocity (U_{mf}) of LH300 lactose powder with vibration frequency f = 37.5 Hz, and micro-jet gas flow corresponding to the superficial gas velocity in the column of 12.2 cm/s. The calculated U_{mf} is based on individual particles, while in reality the particles form agglomerates

particle diameter of 3.5 μm. This large difference indicates that the fine lactose particles were fluidized in the form of agglomerates rather than the individual particles. Figure 4 also shows that using fluidization assistance leads to lowering U_{mf}, and that combining methods decreases U_{mf} even further.

3.2 | Bed expansion

The enhancement of fluidization due to the use of different assistance methods was also reflected by the increase of powder bed height, as shown in Figure 5. The fine lactose powders in the unassisted fluidized bed showed typical agglomerate bubbling fluidization (ABF) behaviour, which refers to bubbling fluidization with a relatively low bed expansion ratio. Size segregation phenomena occurred along with the bed height with a fixed bed or slow-moving large agglomerates at the bottom; a fluidized region of smaller agglomerates in the middle; and a dilute-phase region of very fine agglomerates, including individual particles, which formed on the top region of the fluidized bed, as previously observed by other researchers.[31,32]

Each assistance method was found to increase the bed expansion. In particular, the bed expansion when using both vibration and microjet with a gas pressure of 6 bar (600 kPa, corresponding to the superficial gas velocity in the column of 12.2 cm/s) increased by 2.6 times at around 10 cm/s, as seen in Figure 5. Instead, the bed expansion without micro-jet is significantly reduced, with an increase smaller than 2 times for the cases assisted by single vibration (VFA) or combined vibration and coarse particles (VCFA). The use of coarse particles in addition to vibration and micro-jet was not able to significantly change the bed expansion. The secondary flow in the form of micro-jet seems to play a major role in the expansion of the powder bed compared to other assisting methods. This is attributed to the increase in superficial gas velocity through the downward-pointing micro-jet. It is however worth stressing that, despite the use of high flowrate with the micro-jet, that is, 3.9 L/min (corresponding to the superficial gas velocity in the column of 12.2 cm/s), when supplying no gas flow from the bottom distributor, the powder cannot remain fluidized, resulting in a fluidization index <1 (Figure 3) and a negligible bed expansion (Figure 5). It can also be noted that the bed expansion ratio in both VFA and VCFA systems is less than 1 at low gas velocities, as depicted in Figure 5. This is attributed to the initial bed compaction induced by vibration, as the particles tend to change their orientation and stay closer together when low superficial gas flow is applied.

Figure 6 compares the bed expansion by applying vibration and micro-jet, but under different gas pressures (gas flow rates). Micro-jet pressure plays an important role in powder bed expansion during fluidization. The bed expansion was significantly decreased by reducing the micro-jet pressure from 6 bar (600 kPa)-2 bar (200 kPa).

3.3 | Agglomerates formation

The size distributions of agglomerated particles were determined using sieve sizing following each experiment. The measured size distribution curves are presented in

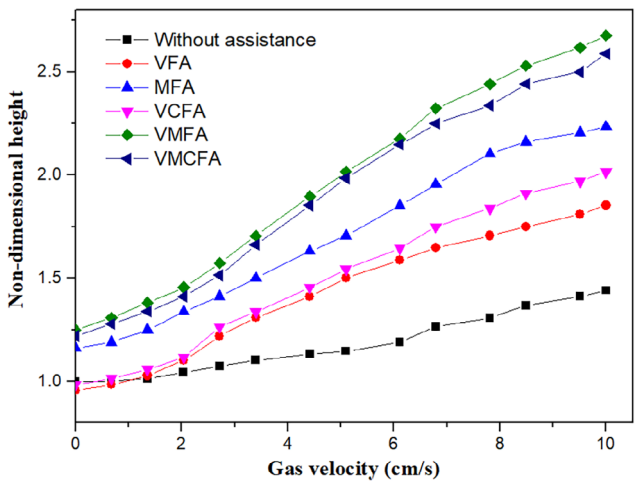

FIGURE 5 Non-dimensional height of LH300 lactose powders as a function of gas velocity with different fluidization assisted methods where vibration frequency $f = 37.5$ Hz when using micro-jet gas flow corresponding to the superficial gas velocity in the column of 12.2 cm/s

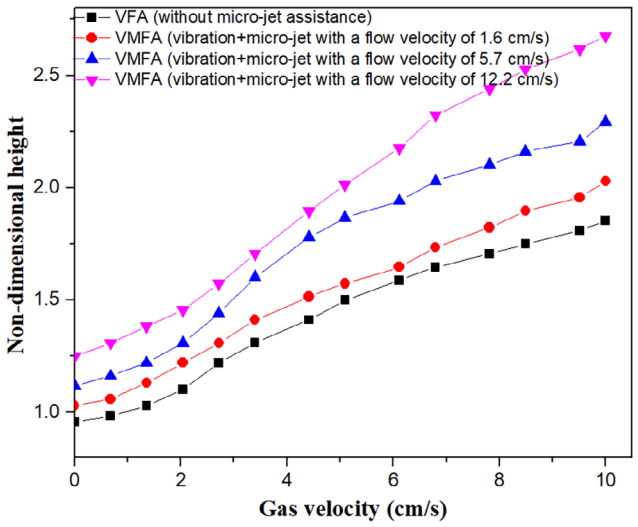

FIGURE 6 Effect of secondary gas pressure on non-dimensional bed expansion of LH300 lactose powders using the combined fluidization assistance of vibration (frequency $f = 37.5$ Hz) and micro-jet

Figure 7 using a frequency histogram, and in Figure 8 using a cumulative size distribution curve. The median diameter (d_{50}) of the aggregate particles is used to compare the effect of different flow-aids on the size of agglomerates formed after the fluidization process. Considerable amounts of agglomerates formed without fluidization assistance, with a median diameter (d_{50}) of 472 μm and 18% of large clusters of aggregates larger than 500 μm. However, the use of fluidization assisting methods can effectively reduce the agglomerate size. The median size of agglomerates (d_{50}) for each method of fluidization assistance is shown in Table 2. As already evidenced by the U_{mf} results, the combined assisting methods performed better in limiting the agglomerate formation than the single assistance. In particular, the presence of mechanical vibration played a strong role in reducing the median size of the agglomerates.

It should be noted that due to the fragile nature of the agglomerates, the size distribution results obtained by sieve analysis may not be able to represent the actual median agglomerate size in the bed. The relatively strong mechanical shaking needed to sieve the fluidized samples possibly causes unavoidable breakages of agglomerates, which of course influences the final results. Therefore, some in-situ measurement techniques, which are capable of sampling the agglomerates, without disrupting their sizes or structures from any parts of the bed, can be further adapted to measure the size distribution more

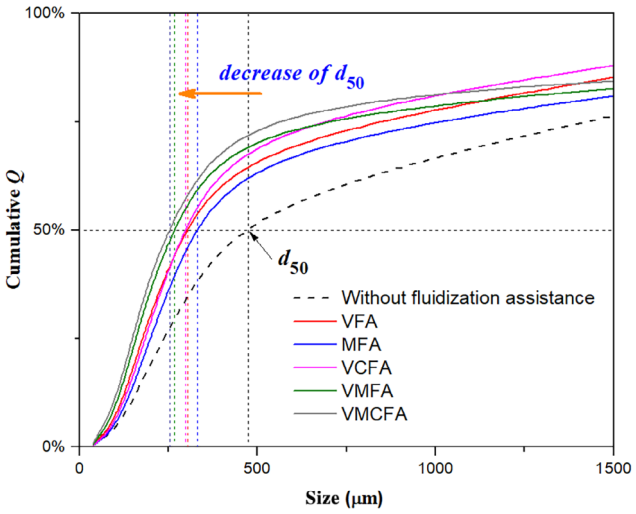

FIGURE 8 Cumulative (Q) size distribution of LH300 lactose powders after fluidization by using various fluidization-assisted techniques

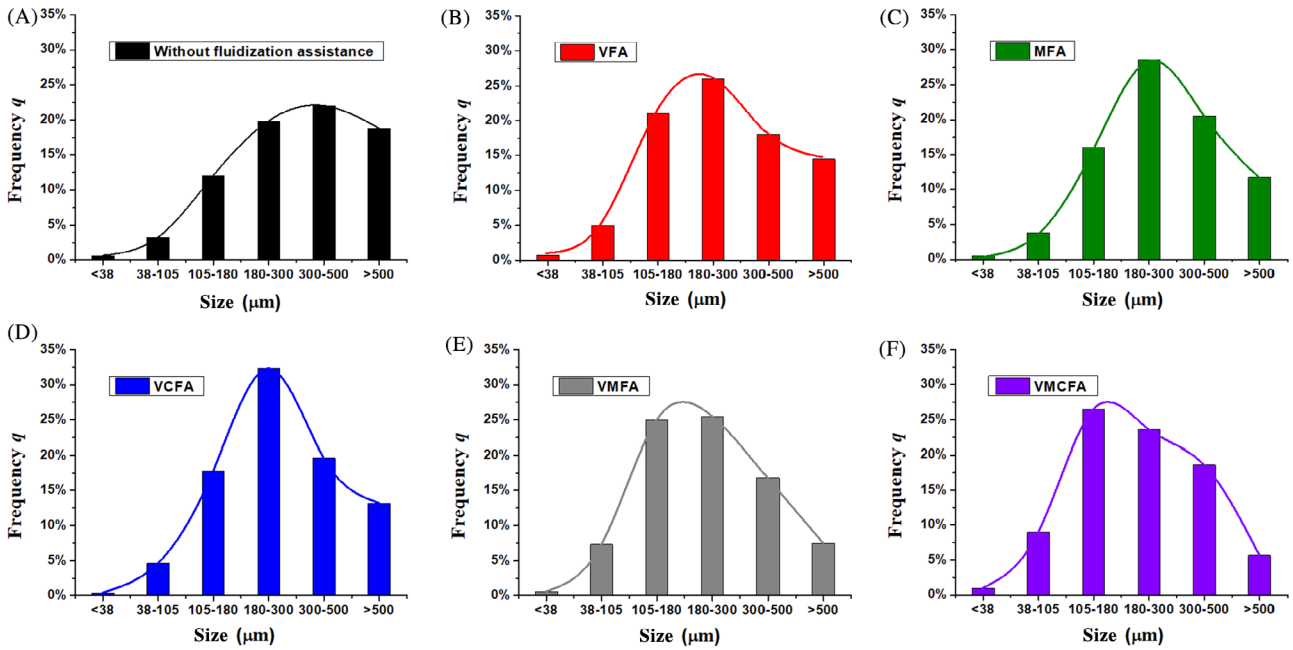

FIGURE 7 Volume-weighted frequency (q) size distribution of LH300 lactose powders after fluidization by using various fluidization-assisting techniques

TABLE 2 The median size of agglomerates

Fluidization conditions	Without assistance	Vibration	Micro-jet	Vibration + pre-mixing	Vibration + micro-jet	Vibration + micro-jet + pre-mixing
d_{50} (μm)	472	308	330	301	270	259

precisely. Examples include the online sampling technique developed by Xu and Zhu,[33] laser-based planar imaging,[34] and the settling tube with in-situ borescope imaging.[35–37] Nevertheless, our analysis enables a relative comparison of the different assistance methods and combinations thereof.

3.4 | Loss of powders sticking to the wall

In addition to the agglomerate formation after fluidization, a considerable number of fine particles were found to be stuck on the internal wall surface, probably due to the electrostatic forces and hydrogen bonds. The fraction of the amount of agglomerate clusters (size larger than 500 μm) in the powder bed with respect to the total loaded amount of fine lactose powders and the proportion of fine particles stuck to the wall to the total loaded amount of lactose powders are shown in Figure 9. Assistance by mechanical vibration seems to be the most effective in reducing the number of particles sticking to the wall, especially obvious in the decrease from 23%-11% achieved by applying vibration and adding coarse particles. Vibration can also reduce the formation of large agglomerates (>500 μm), but the positive effect is not as large as when using the micro-jet, which can reduce the agglomerate fraction from 14%-7% compared to the single vibration case. The high-speed injection of gas from micro-jet can induce a strong shear force to break-up large agglomerates. However, micro-jet is not able to properly control the fraction of particles sticking to the wall. There is less than a 4% decrease of powder particles sticking to the wall in the micro-jet assisted bed compared to the unassisted case. The highly turbulent flow

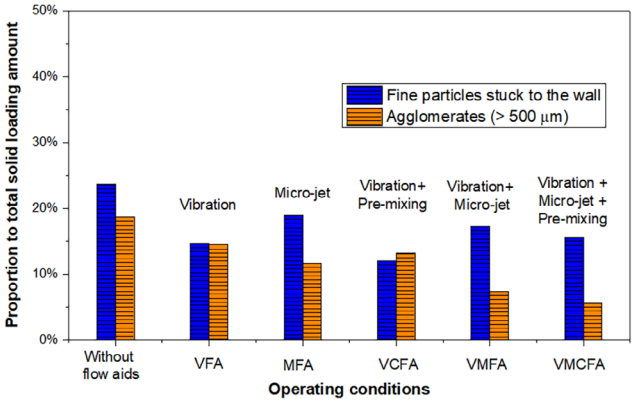

FIGURE 9 The volume percentage of cluster agglomerates (>500 μm) and particles sticking to the wall under different fluidization-assisted conditions. When using vibration, frequency *f* is 37.5 Hz, and when using microjet gas flow corresponding to the superficial gas velocity in the column of 12.2 cm/s

generated from the micro-jet makes the fine particles much more likely to float higher with considerable speed and gradually deposit on the higher position of the bed wall, resulting in considerable powder losses. Some methods have been proposed to minimize the electrostatic effects which lead to the sticking of powder to the column wall. Pfeffer and Quevedo[38] suggested removing electrostatic effects by adding alcohol or another solvent (water) to the fluidization gas. However, as the lactose powders are moisture-sensitive materials, bubbling the fluidization gas through a volume of water/alcohol gives rise to a stickier powder bed. When processing particles at an industrial scale, equipment of a much larger size will be used, which will also lead to reduced particle-wall interactions. A reasonable estimate is that an industrial fluidized bed for pharma applications will have a 30 times larger diameter, which would mean a reduction of the surface to volume ratio by a factor of 30. As a first estimate, it is reasonable to assume that the deposition at the wall will reduce by a similar factor, so below 1%.

4 | THEORETICAL ANALYSIS

To better understand the impact of different fluidization assistance methods on the fluidization behaviour of cohesive lactose powders, a force analysis and calculations were conducted. The lactose particles are fluidized in the form of agglomerates that are continuously colliding. The fluidization behaviour of lactose particles can be illustrated with steadiness or disruption of agglomerates after two agglomerates come into collision.[39] The steadiness or disruption of an agglomerate depends on the balance of the forces acting on a fluidized agglomerate, which are divided into two main categories: cohesive and separation forces.[40] The Van der Waals and electrostatic forces are cohesive, while gravity, collisional, and drag forces are separation forces.

4.1 | Force analysis without fluidization assistance

Van der Waals force F_{vdw} is considered to be the dominant inter-particle force when no liquid is present in the system. For simplification purposes, we calculated the Van der Waals force for two spherical ultrafine particles interacting in the fluidized bed. With these assumptions, and using the Lifshitz theory, the expression of Van der Waals interaction force is expressed as follows[41,42]:

$$F_{vdW} = -\frac{A_H}{6\delta^2}\left(\frac{R_1 R_2}{R_1 + R_2}\right) \quad (1)$$

where the Hamaker constant A_H defines the strength of the interactions. The value of Hamaker constants for most of the pharmaceutical particles is on the order of 10^{-20}-10^{-19} J.[43] The two particles have radii R_1 and R_2, respectively, and the particles are separated by a distance δ. We also assume that their radii are much larger than the surface-to-surface separation δ.

The gravitational and buoyancy force F_g can be expressed as follows:

$$F_g = \frac{\pi}{6} d_a^3 \left(\rho_a - \rho_f\right) g \tag{2}$$

where d_a is the diameter of the agglomerate, ρ_a is the density of the agglomerate, ρ_f is the density of the induced fluid, and g is the gravitational constant.

The drag force is formulated as Equation (3)[44]:

$$F_d = 0.055\pi\rho_f d_a^2 u^2 \varepsilon^{-4.8} \tag{3}$$

where u is the superficial gas velocity, and ε is the bed voidage.

The collision force between particle 1 and particle 2 can be expressed as follows[45]:

$$F_{col} = 0.2516\left(\frac{\pi V_r^6 \rho_a^3}{k^2}\left(\frac{d_{a1}^3 d_{a2}^3}{d_{a1}^3 + d_{a2}^3}\right)^3 \left(\frac{2d_{a1}d_{a2}}{d_{a1}+d_{a2}}\right)\right)^{0.2} \tag{4}$$

where k is a function parameter of Poisson's ratio and Young's modulus, and d_{a1} and d_{a2} are the diameter of particle 1 and 2, respectively. If $d_{a1} = d_{a2}$, then the collision can be rewritten:

$$F_{col} = 0.166\left(\frac{\pi V_r^6 \rho_a^3}{k^2}\right)^{0.2} d_a^2 \tag{5}$$

where V_r is the relative collision velocity defined as follows:

$$V_r = \left(1.5\bar{P}_{sn} D_b g \varepsilon\right)^{0.5} \tag{6}$$

where $\bar{P}_{sn}$ is the dimensionless average particle pressure of the non-sticky system, $\bar{P}_{sn} \approx 0.077$[46]; and D_b is the bubble diameter in the fluidized bed and is given by the following[47]:

$$D_b = 0.625 A_t \left(U - U_{mf}\right)^{0.4} \tag{7}$$

where A_t is the cross-section area of the bed.

4.2 | Modifications of forces with fluidization assistances

Based on the method of Mawatari et al,[48] the impact of vibration on the gravitational and buoyancy force F_g was mainly considered by replacing the gravitational constant (g) in Equation (1) with the effective gravitational constant g_{eff}:

$$g_{eff} = (1 + \Lambda) g \tag{8}$$

where Λ is the vibration strength, determined by the following:

$$\Lambda = A\frac{(2\pi f)^2}{g} \tag{9}$$

where A is the vibration amplitude and f is the vibration frequency.

The introduction of gas-jet provides quite considerable gas flow into the fluidized bed. It accordingly changes the superficial gas velocity (U) and relative collision velocity (V_r). Therefore, using gas-jet influences both the drag force and collision force that act on the fluidized lactose agglomerate.

According to Equation (4), adding the coarse particles mainly influences the collision force. Besides the collision between ultrafine particles with the same size (d_a), the collision between ultrafine particle (d_{a1}) and coarse particle (d_{a2}) should be also considered. Given that the mass ratio of coarse to fine particles is 20:80, the collision force can be modified as follows:

$$\begin{aligned} F_{col-premixing} &= 0.2 \times 0.2516\left(\frac{\pi V^6 \rho_a^3}{k^2}\left(\frac{d_{a1}^3 d_{a2}^3}{d_{a1}^3 + d_{a2}^3}\right)^3 \left(\frac{2d_{a1}d_{a2}}{d_{a1}+d_{a2}}\right)\right)^{0.2} \\ &+ 0.8\left(\frac{\pi V^6 \rho_a^3}{k^2}\left(\frac{d_{a1}^3 d_{a1}^3}{d_{a1}^3 + d_{a1}^3}\right)^3 \left(\frac{2d_{a1}d_{a1}}{d_{a1}+d_{a1}}\right)\right)^{0.2} \end{aligned} \tag{10}$$

4.3 | Calculation results

The calculations of cohesive and separation forces for the lactose agglomerate with or without fluidization assistances are presented in Figure S1. The parameters used for the calculations are listed in Table S1. The size of the lactose agglomerates can be predicted by the force balance between cohesive and separation forces.

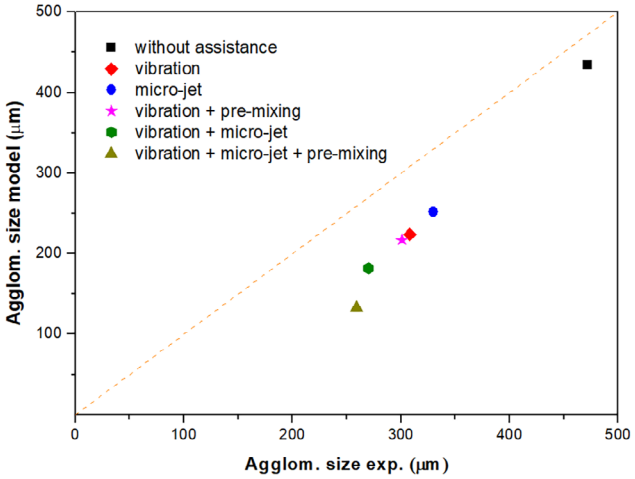

FIGURE 10 The comparison between the agglomerate size obtained by experimental and predicted by the force balance model

Therefore, the estimated agglomerate size was determined by the crossing point between the Van der Waals force F_{vdw} and the total separation force (the sum of gravitational and buoyancy force F_g, drag force F_d, and collision force F_c), as shown in Figure S2. The calculated and experimental agglomerate sizes are shown in Figure 10. Without fluidization assistance, the dominant separation force acting on lactose agglomerates is the collision force rather than the drag or gravitational force. The estimated agglomerate size is around 434 μm, which is reasonably close to the experimental result of 472 μm.

By adding coarse particles, the collision forces are slightly enhanced, resulting in a decrease of agglomerate size. The high-speed secondary gas flow from micro-jet can strongly promote both the collision force and drag force, giving rise to a considerable decrease in calculated agglomerate size (ie, 252 μm), as shown in Figure 10. The use of mechanical vibration significantly increases the gravitational and buoyancy force, and therefore a decrease of predicted agglomerate size (224 μm) is achieved. It seems that all the calculated agglomerate sizes are smaller than the experimental ones, and the differences between the calculated and experimental results get larger if combined assistance is adopted. This may be due to the complex mechanical response (force acting) of the fluidized agglomerates upon the assisting methods, which is hard to theoretically describe when considering the action and interaction of multiple forces. Simply reflecting these comprehensive effects by adding up all the separation forces amplifies the actual separation forces acting on the lactose agglomerate, leading to the smaller estimated agglomerate size. While the calculated values for agglomerate size do not exactly match the experimental ones, an accurate prediction of the trends for agglomerate size reduction by the different assistance methods can be observed (see Figure 10).

5 | CONCLUSIONS

A variety of fluidization assistance methods have been employed to fluidize inhalation grade lactose powder (median diameter of 3.5 μm), which is a highly cohesive material. The fine lactose powder shows typical ABF behaviour in the unassisted fluidized bed with channelling occurring at low gas velocity and strong bubbling at high velocity, resulting in a very limited bed expansion. In contrast to the unassisted case, using vibration, micro-jet, or pre-mixing with coarse particles can enhance the fluidization in the form of higher powder bed expansion, and reduced minimum fluidization velocity and agglomerate formation. In general, the combination of any two fluidization assisted approaches showed better results compared to applying a single approach. In particular, the combination of vibration and micro-jet performed best in improving fluidization. The additional use of coarse particles seemed to have no significant effect on promoting fluidization quality. Mechanical vibration worked well in reducing agglomerate size, whereas it had a relatively small influence on improving bed expansion. A micro-jet can both significantly inhibit the agglomerate formation and strongly improve bed expansion, but the powder losses due to the fine particle stuck to the wall after the fluidization process can be considerable.

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NOMENCLATURE

d_{50}	median particle size (μm)
ρ_p	particle density (kg/m^3)
ρ_b	bulk density (kg/m^3)
f	vibration frequency (Hz)
d	coarse particle mean size (mm)
S_g	gas flow rate (L/min)
S_v	superficial gas velocity (cm/s)
T	gas temperature (°C)
D	column diameter (cm)
H_0	initial bed height (cm)
S_m	micro-jet flow (L/min)

PEER REVIEW

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