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Use of an impinging jet for dispersion of dry powder inhalation aerosols

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Abstract

The dispersion of Ventodisk® (salbutamol sulphate with lactose) from different drug reservoirs by an air jet at normal impingement is examined experimentally. The effect on dispersion efficiency of jet velocity, nozzle location, reservoir size and shape, and the loaded dose is investigated for possible design of new dosing methods or inhalers. Results show that higher jet velocity (as high as feasible), lower drug loading (2 mg or smaller), a cylindrical hole reservoir (6 mm in diameter and 3 mm in depth) and a medium distance (approximately 5 jet diameters) from the nozzle to the reservoir yield optimum dispersion. The dispersed fine particle dose improves by a factor of 2–3 times between optimized conditions and poor conditions.

Keywords: Aerosol; Dry powder inhaler; Impinging jet; Powder dispersion; Powder deagglomeration; Cascade impactor

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1. Introduction

An effective dry powder inhaler should be portable, easy to use and efficient in delivering a certain amount of drug powder to the deep lung. For such inhalers, the dispersion of the drug powder or its separation from carrier particles remains one of the biggest challenges (Dunbar et al., 1998).

The successful dispersion of dry powders as aerosols during inhalation depends upon a number of closely related factors (Finlay, 2001; Hickey et al., 1994), which are mainly divided into intrinsic properties and dynamic flow effects. Interparticle forces are one of the important intrinsic properties (Rietema, 1991). It has been shown that the adhesion between drug and carrier particles, as well as the fine particle fraction generated from these mixtures, can be influenced by a variety of factors, including the surface properties of drug and carrier particles, drug to carrier ratio, carrier particle size, mixing time and method, humidity and electrostatic behavior. The intrinsic physico-chemical properties of the drug particles have been shown to be very important in the optimization of their delivery as aerosols (Ganderton and Jones, 1987). However, flow dynamics driving dispersion also plays a crucial role in deagglomeration and delivery of powder aerosols (Dunbar et al., 1998). Indeed, the dynamics of flow and dispersion, which are related to ease of particle separation, can be evaluated as the basis for modification of powder performance (Finlay, 2001). The principal forces leading to deagglomeration within reservoirs remain unclear, but are often divided into the following closely coupled categories: (i) shear force fluidization; (ii) turbulence and

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(iii) particle collision. The majority of the literature points to turbulence as the principal factor without considering the detailed nature of turbulent fluid flow and its interaction with dispersed particles (Ganderton and Kassem, 1992; Ganderton, 1992; Lee et al., 1996; Timsina et al., 1994; Vidgren et al., 1988; Ward et al., 1992). However, recent results (Voss and Finlay, 2002) indicate that turbulence alone is not responsible for deagglomeration in the Ventodisk inhaler.

In general, jets have been considered a very effective method in particle removal and lift from a surface (Smedly et al., 1999; Zhang et al., 2002), and are often used in powder deagglomeration (e.g. the Ventodisk® Inhaler (GlaxoSmithKline) and powder dispenser described in US Patent 4895034 (Poole, 1990). While deagglomeration in actual inhalers is usually due to several of the mechanisms mentioned above, the purpose of the present work is to continue the approach used by Voss and Finlay (2002) where individual deagglomeration mechanisms are isolated and explored. While Voss and Finlay (2002) examined the effect of turbulence, as well as collision on meshes, we have investigated the dispersion and deagglomeration caused by a single pressurized air jet directed at a reservoir of powder.

As shown in Fig. 1, a jet impinging on a wall normally produces a complex flow, exhibiting non-isotropic turbulent fluctuations, strong deceleration of the jet toward the impingement wall, radial acceleration of the wall jet after impingement, steep streamline curvature in the stagnation region and considerable variation of the static pressure in that region (Jambunathan et al., 1992). In the developing region, the shear or mixing region produced by an impinging jet surrounds a core region, where the fluid velocity is nearly equal to the nozzle velocity. The end of the core region is defined as the point where the axial velocity is 0.95 times the nozzle exit velocity. A development (effective) length of six diameters has been suggested by Gauntner et al. (1970).

In this experiment, it must be noticed that, different from the plain wall impinging jet, the flow structure produced by the jet used here will be significantly affected by the curvature of the reservoir. In addition, for partially filled deep reservoirs, the flow turns into a reversed jet and lifts the dispersed powder, resulting in a number of interesting and hard-to-predict features. The particles in the dispersal drug reservoir undergo impaction, rotation, collision then fluidization, and are finally dispensed. In addition to jet parameters, we also examine the effect of different shapes of reservoirs and loading doses on dispersion.

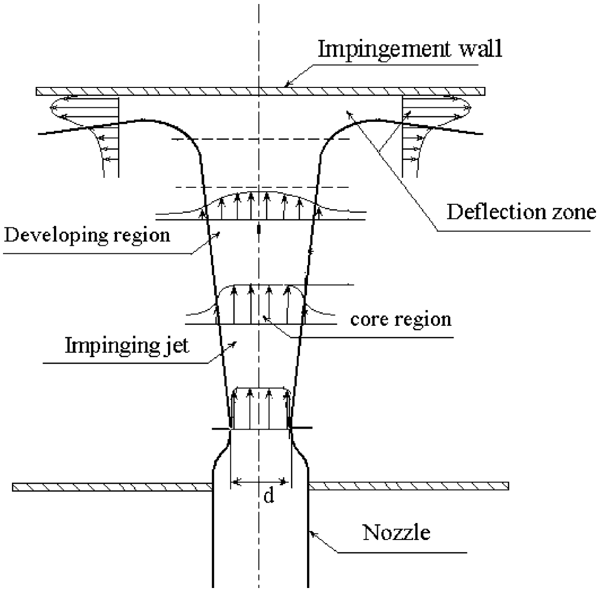

Fig. 1. Flow zones of impinging jet on a wall.

To the authors' knowledge, there is currently no systematic study of the influence of the above parameters on powder dispersion in the literature. It is expected that the experimental data and conclusions presented provide further understanding of the dispersion mechanisms and valuable information for quantitative research.

2. Experimental method

The apparatus developed to test the deagglomeration of dry powder aerosols by an impinging jet was designed with several criteria in mind: the operating conditions should be easy to control; the device should be easy to load with powder; no powder should exit the system upstream during the short period when the jet with high velocity is being fired; the parameters that influence the deagglomeration should be isolated as much as possible.

To satisfy these constraints, the apparatus illustrated in Figs. 2 and 3 was developed. The system consists of

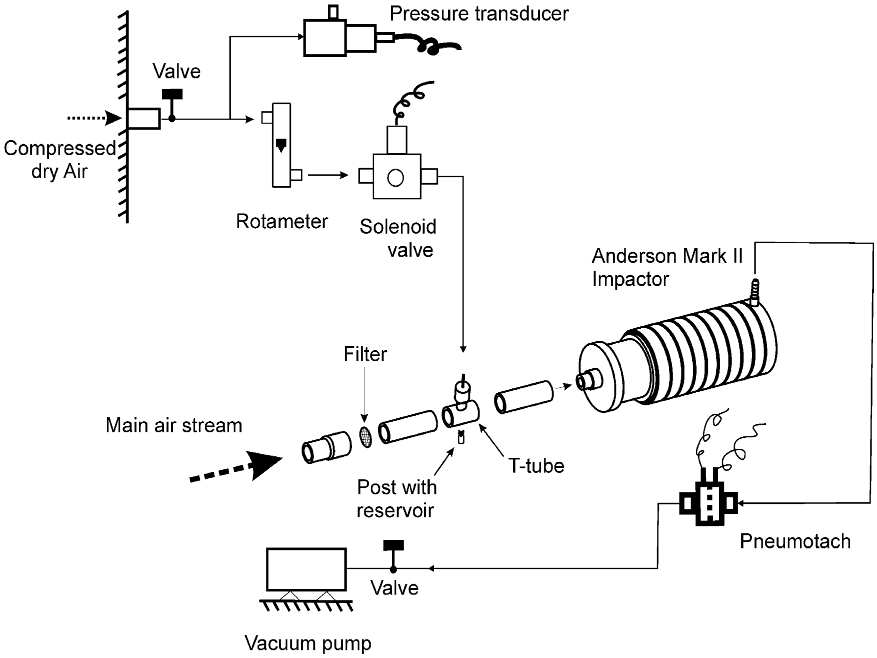

Fig. 2. Schematic drawing of experimental set-up.

a T-shape tube (19.04 mm i.d., 25.53 mm o.d.), a circular jet nozzle (1.05 mm i.d.) and a reservoir built inside a screwed-in post. The T-shape tube and screw-in reservoir orthogonal to the main flow direction are specially designed for keeping powder in the reservoir from being carried away by the main air stream before the jet is fired. A solenoid valve is connected to the jet line and controlled by an electrical switch. The nozzle is aligned vertically inside the top tube (see Fig. 3). The height of the nozzle can be changed and set with help of a removable rod that is used as a distance gauge. The jet pressure and velocity can also be adjusted using the valve and continuously measured with a calibrated rotameter and a Validyne DP15 pressure transducer (Validyne Engineering Corporation Northridge, CA, USA). Opposite to the nozzle, the post with drug reservoir is screwed into the horizontal tube and leveled with the internal bottom surface of the tube. In order to keep powder lifted by the jet from exiting upstream, a filter pad with very

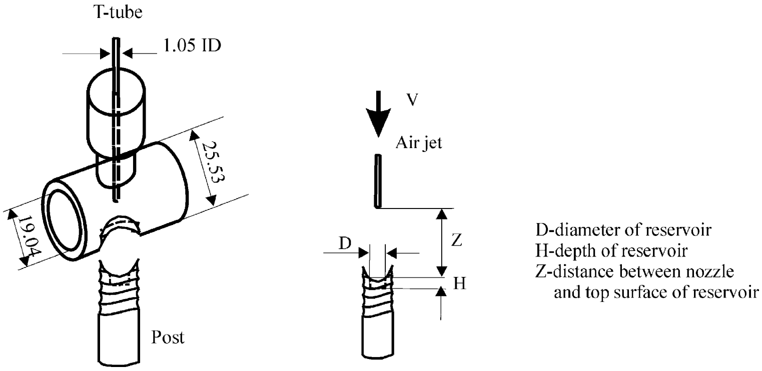

Fig. 3. Structure of T-tube and reservoir.

Table 1
Volume flow rates, mass flow rates and pressures in dispersion apparatus

Number (i)	Jet velocity (m/s)	Volume flow rate at rotameter location (l/min)	Absolute pressure at rotameter location (kPa)	Mass flow rate (kg/s)	Velocity ratio v_i/v_1
1	15	2.66	104.14	0.0544	1.0
2	65	4.761	140.71	0.1315	4.33
3	95	7.184	195.91	0.2763	6.33
4	120	9.659	273.20	0.5181	8.0

Atmospheric pressure = 704 mmHg, $T = 298$ K, nozzle size $d_{\text{nozzle}} = 1.05$ mm i.d., $M_{\text{air}} = 28.966$ g/mol.

low pressure resistance (41.0522P30, Pari, Starnberg, Germany) is used on the upstream end of the tube.

The selection of nozzle locations, $Z = 0$, 5 and 10 mm (Z is the nozzle height above the reservoir), was based on data from Gauntner et al. (1970) and the dimension of the T-tube. Three reservoir shapes, cylindrical hole, half sphere and square, were chosen based on the same opening area. Experiments with 1/3, 1/6 and 1/12 of a unit dose used as reservoir loadings were chosen to examine whether the concentration of gas–solid two-phase flow created by the jet influences the dispersion and delivery.

The four jet velocities shown in Table 1 are used in this study, which are measured by Laser Doppler Anemometry (LDA) similar to Voss and Finlay (2002). Four jet velocities were selected corresponding to equal intervals on the rotameter scale used in the experiment. The real velocity, however, does not increase in equal intervals due to compressibility effects. For the assessment of parameters other than jet velocity, the velocity was set at 95 m/s in order to avoid working near the set-up limits. For reference, volume flow rate at the rotameter location and the mass flow rate associated with the measured pressure at the rotameter connection are also listed in Table 1.

2.1. Measurement of fine particle fraction (FPF)

A standard Mark II Anderson impactor (Graseby Andersen, Smyrna, GA, USA) was used to measure the fine powder fraction. The impactor flow rate was set at 60 l/min, maintained by a vacuum pump (Emerson Electric Co., USA), and monitored by a Pneumotachometer (PT) (4719, Hans Rudolph Inc., 0–100 l/min). This flow rate is different from the flow rate of 28.3 l/min (1 SCFM) recommended by the manufacturer for the Anderson impactor, so the cut points have been recalibrated at 60 l/min (Nichols et al., 1998).

In our experiments, essentially all drug powder was carried away by the air after the jet was fired and a negligible amount (<5%) was left in the T-tube and adaptor. Therefore the emitted dose can be considered essentially equivalent to nominal (loaded) dose. After powder dispersion was completed, the powder deposited on each impactor plate, the pre-separator and the test apparatus was washed off with 10 ml distilled water and collected separately into two groups. The fine particle fraction (FPF) was defined as the fraction of the loaded powder that was collected on plates 1–6 (i.e. aerodynamic diameter $\leq 5.6\,\mu$m). The powder collected on plate 0, pre-separator, adaptor and T-tube was considered as the coarse particle fraction (1-FPF). The solutions containing drug powder were analyzed with UV spectroscopy (using a Diode Array Spectrophotometer, model 8452A, Hewlett-Packard, Tulsa, OK, USA) at 224 nm absorbed wavelength. Then the amount of drug as well as FPF of dispersion was calculated by comparing with the standard solution of 10 μg/ml salbutamol sulphate.

2.2. Drug powder

Drug powder from the GlaxoSmithKline Ventodisk® (the disk-shaped blister packs used in the Diskhaler®) was used as our test powder. The powder contains about 25 mg carrier lactose (approximate mean diameter 60 μm) and 200 μg of the albuterol drug Ventolin® (existing as 240 μg albuterol or salbutamol sulphate, approximate mean diameter 2.5 μm). This powder drug was chosen for several reasons: it is a well-known pharmaceutical powder; it is easy to remove from the Ventodisk®; it is completely soluble in water, which facilitates the assay; albuterol sulphate has strong, linear UV absorbance over a sizable range; and it is inexpensive (Voss and Finlay, 2002). To load the powder into the reservoir, a blister from the Ventodisk is cut open and the powder is emptied into a paper tray. Then a specially designed spoon is used to transfer a fraction of the blister dose into the reservoir. The transfer and use of any one peeled blister is done within 5 min to minimize humidity absorption. In our experiments, the ranges of temperature and relative humidity are 20–24 °C and 11–21%, respectively.

2.3. *Operating procedures*

During operation, the jet velocity was first set at one of the four values in Table 1. The Ventolin® blister was then peeled and emptied into a paper tray. A special spoon was used to load a certain fraction of one dose into the reservoir on top of the post, and then the post was screwed into the T-shape tube. The vacuum pump was then switched on and the jet was fired for at least 5 s after the main air flow rate had reached 60 l/min. The jet duration was more than what was required for entrainment of the powders, ensuring the powder reservoir was completely emptied. After one run, the procedures above were repeated with a second run. In total two doses of drug powder were dispersed in one test to reach the concentration for UV measurement. The vacuum pump and jet were stopped during the feeding process.

For each measurement, at least three tests were performed and the values were averaged. Statistical tests were performed using single factor analysis of variance (ANOVA) and Tukey HSD means comparisons.

3. Results and discussion

In order to discern the influence of each parameter on the dispersion, jet velocity, jet location, reservoir shape and the amount of loaded dose were investigated in this experiment.

3.1. *Influence of jet velocity*

In this experiment, four jet velocities, 15, 65, 95 and 120 m/s, were used (see Table 1). As shown in Fig. 4, the fine particle fraction (FPF) of drug powder increases with impinging jet velocity after

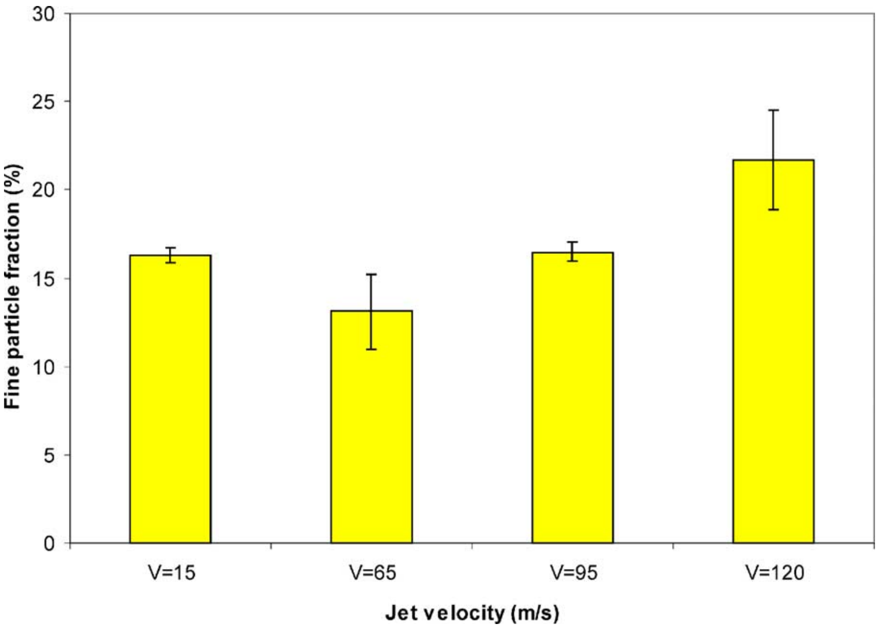

Fig. 4. FPF of loaded dose changes with jet velocity (m/s), Nozzle height $Z = 5$ mm above the cylindrical hole reservoir ($D = 6$ mm, $H = 3$ mm), drug filled with 1/3 dose each time). Error bars indicate standard deviation ($n = 3$).

decreasing somewhat at low jet velocities. This result indicates that higher jet velocities can produce higher flow turbulence and cause higher powder dispersion/deagglomeration. However, only the FPF with the fourth jet significantly differs ($P \leq 0.05$) from the FPFs produced by the other three jets.

3.2. *Influence of nozzle height*

The effect of varying nozzle height, Z, is seen in Fig. 5 for a jet velocity of 95 m/s. Compared with the results on particle removal by impinging jets on a plane wall (Zhang et al., 2002), in which the removal efficiency has generally been found to increase with increasing jet pressure and decreasing nozzle height, we only find this to be true for longer nozzle height ($Z = 10$ mm versus $Z = 5$ mm). Reducing the nozzle height from $Z = 5$ to 0 mm actually decreased fine particle dispersion in our experiments. This is probably because the powder was lifted out of the reservoir too quickly and there was less interaction between the output two-phase flow and the ongoing impinging jet. A maximum fine particle fraction was obtained at the 5 mm jet location (approximately 5 jet diameters), which is similar to the most effective height described by Gauntner et al. (1970) for particle removal using an impinging jet on a plane wall. It also indicates that the interaction between the particles/agglomerates in the lifting two phase flow and ongoing impinging jet flow reached a maximum, resulting in maximum powder deagglomeration.

3.3. *Influence of drug reservoir shape*

Drug reservoir holes with different diameters and depths were tested in our experiments. The fine particle fractions obtained depend on both the hole diameter and depth. Fine particle fractions achieved by using a variety of reservoirs are compared in Fig. 6. The three cases shown differ significantly in FPF ($P < 0.05$). For the same cross-sectional area as the 6 mm cylindrical hole, the square reservoir is better than the half sphere but worse than the cylindrical hole. Among the three shapes of reservoirs (i.e. cylindrical hole, half sphere and square shapes) the highest fine powder fraction is achieved by using a cylindrical hole reservoir. Higher fine powder fraction was found for a 6 mm diameter cylinder hole reservoir than for a 3 mm diameter at the same 3 mm depth (see Fig. 7). This result demonstrates that a good drug reservoir should be designed as hole-shaped with circular cross-section

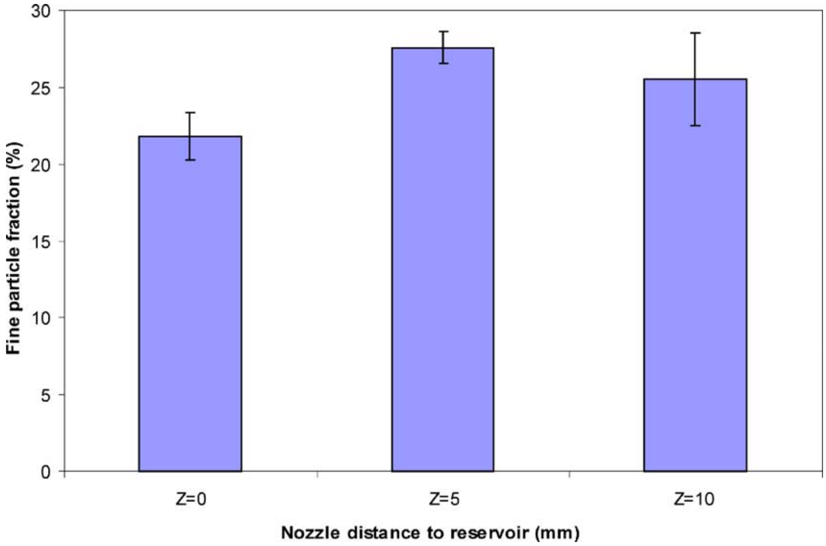

Fig. 5. FPF of loaded dose changes with nozzle distance to cylindrical hole reservoir ($D = 6$ mm, $H = 3$ mm) (jet velocity $V = 95$ m/s, drug filled with 1/6 dose each time). Error bars indicate standard deviation ($n = 3$).

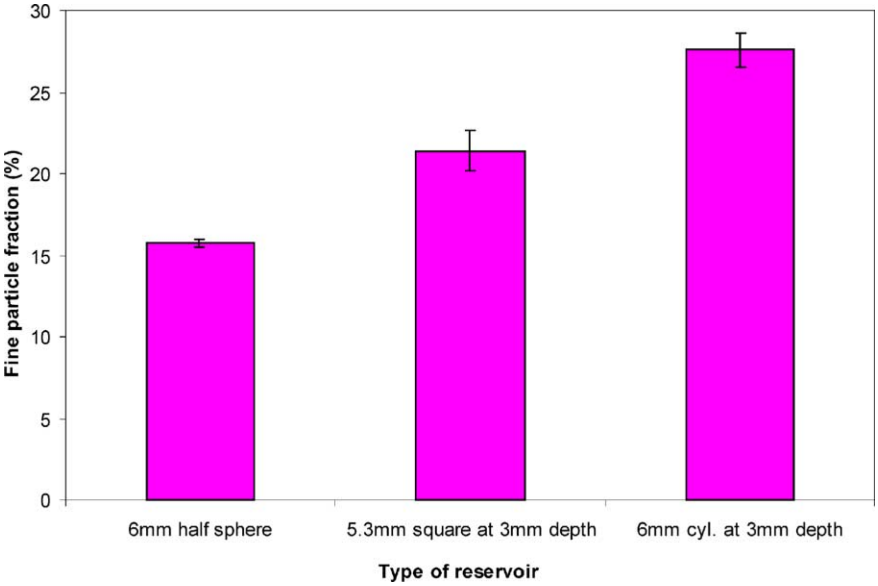

Fig. 6. FPF of loaded dose emitted by using three different reservoirs (jet velocity $V = 95\,\text{m/s}$, drug filled with 1/6 dose each time. Nozzle distance $Z = 5\,\text{mm}$). Error bars indicate standard deviation ($n = 3$).

and a certain depth if a jet-like flow is used to lift and dispense the drug powder.

From a theoretical perspective, shear fluidization and particle collision are the dominant mechanisms in this deagglomeration process. The drug particle agglomerates are firstly lifted and pushed by the impinging jet towards the reservoir wall, then collided with the wall to become dispersed. Agglomerates that

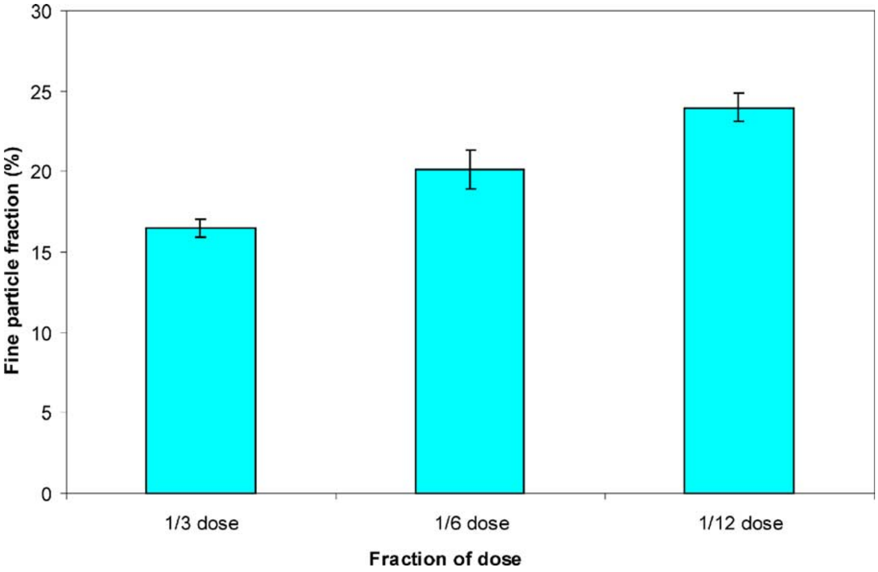

Fig. 7. FPF of loaded dose changes with drug powder loaded each time (jet velocity $V = 95\,\text{m/s}$, nozzle distance $Z = 5\,\text{mm}$ from the 3 mm cylindrical hole reservoir). Error bars indicate standard deviation ($n = 3$).

remain in the output two-phase flow would continue to interact with the developing region of the impinging jet, resulting in particle–particle collisions and in further dispersion. Compared with square or cylindrical shape reservoirs, using a reservoir with sloped or smooth-angle internal surfaces, e.g. a half sphere, will induce less deagglomeration due to weaker particle–wall collisions.

3.4. Influence of the amount of loading powder

The influence of loading quantity on FPF has been assessed in this experiment. The results demonstrate that the amount of loaded dose is also an important parameter for powder dispersion. For this purpose, as shown in Fig. 7, drug powder of 1/3, 1/6 and 1/12 of the unit dose in one blister is loaded each time into a 3 mm cylindrical hole reservoir with 3 mm depth. The three cases shown differ significantly in FPF ($P < 0.05$). The results indicate that for dispersion of powder using an impinging jet, the less the powder loaded into the reservoir at one time, the higher is the FPF obtained. This result can be explained from energy considerations. The smaller the dosage, the more the energy that is exerted by the jet flow on each particle/agglomerate. This increased energy from the jet is directly correlated with larger deagglomeration forces and thus with increased powder dispersion. This result suggests that new loading designs with small dose may yield increased powder dispersion or deagglomeration, for example, gradual dose feeding or multi-channel feeding.

4. Conclusions

We have examined the effect of several parameters on the fine particle dispersion caused by an impinging jet on Ventodisk® powder (salbutamol sulphate with lactose carrier). Jet velocity, nozzle location above the reservoir, the shape of drug powder reservoir and amount of drug powder loaded each time are found to be important to dispersion, and can result in 2–3 times higher fine particle dose delivery when optimized. Higher jet velocity, lower drug loading, a cylindrical hole reservoir and a medium distance (approximately 5 jet diameters) from the nozzle to the reservoir yield better dispersion. Flow turbulence, shear fluidization, jet energy, and particle collision have been used to partially explain the phenomenon and results. These results are expected to be helpful to further research and development of more efficient powder deagglomerators.

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