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Impact angles as an alternative way to improve aerosolisation of powders for inhalation?

Santoso Adi [a], Zhenbo Tong [b], Hak-Kim Chan [a,*], Runyu Yang [b], Aibing Yu [b]

[a] Advance Drug Delivery Group, University of Sydney, Sydney, NSW 2006, Australia
[b] School of Materials Science and Engineering, University of New South Wales, Sydney, NSW 2052, Australia

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ABSTRACT

This study aims to investigate the role of impact angles on the de-agglomeration performance of powders for inhalation. Agglomerates of a model drug mannitol were impacted at customized impaction throats containing two angles (15–75° and 45–45°) or a single angle (15°, 45° and 90°) using various air flow rates. The mass fraction of fine particles <5 μm in the aerosol (FPF_{Loaded}) was measured by a liquid impinger coupled to a laser diffractometer. Results showed that for the two-angle throats, there existed an optimal angle (45°) and air flow (120 l min^{-1}) for the FPF_{Loaded}, resulting from a balance between improved de-agglomeration and enhanced throat deposition with increasing air flow. When the throat contained two equal angles of 45°, most powder deposition occurred at the first angle, indicating that the first angle was likely to cause major de-agglomeration, while the second angle might act as a facilitator for further break-up, but the deposition was minimum as the fragment sizes and velocity at the second impaction were smaller. This hypothesis was supported by further studies using single-angle throats and numerical simulation (DEM–CFD). These findings imply the potential importance of using angular design features for multiple impactions to improve DPI performance.

1. Introduction

Agglomeration commonly occurs in dry powder inhalation (DPI) formulation (Adi et al., 2008; de Boer et al., 2004; Paajanen et al., 2009). Due to the fine particle size of the active pharmaceutical ingredient (API) used (<5 μm) (Pritchard, 2001), drug tends to form agglomerates since the interparticulate forces are large compared with aerodynamic and gravitational forces (Calvert et al., 2009; Dunbar et al., 1998). Such agglomeration may lead to formulation variations and a decrease in the inhaler efficacy (Hickey et al., 1994). This may increase the amount of energy required to separate and stably entrain drug particles into the air stream upon inhalation, leading to reduced aerosolisation performance (Hodson and Greenleaf, 1995). Optimum control on de-agglomeration is crucial to achieve maximum aerosolisation efficiency and therefore a better understanding of the de-agglomeration process is required.

Powder de-agglomeration in DPI is a complex process involving interaction of fluid mechanics, adhesion forces in irregular shaped particles, transient dynamics of the powder delivery, and turbulent conditions (Daniher and Zhu, 2008). Principal forces that cause the agglomerate break-up are not completely known. Turbulence was proposed as a major cause for the break-up due to the aerodynamic lift, drag and shear force generated by the eddies (Brown et al., 2003; Coates et al., 2005a,b; French et al., 1996; Li et al., 1996; Timsina et al., 1994). In addition, mechanical impaction may be equally or even more important (Dunbar et al., 1998; Finlay, 2001; Voss and Finlay, 2002; Xu and Zhu, 2006), and mechanical features such as jets, grids, baffles and orifices can contribute to further de-agglomeration. Among these factors, mechanical impaction due to impact angle was mostly reported to contribute to agglomerate breakage (Moreno and Ghadiri, 2006; Moreno et al., 2003; Tong et al., 2009a,b), although experimental data are largely missing.

Our recent attempts to understand agglomerate break-up using numerical simulation showed that increasing impact velocity improves agglomerate breakage and a 45-degree impact angle provides the maximum breakage for a given velocity (Tong et al., 2009a; Yang et al., 2008). A drawback from these studies however was that air flow was not considered and only mono-sized particles were used. To overcome these limitations would necessitate simulation using the discrete element method (DEM) coupled with computational fluid dynamics (CFD).

In the present study, customised impaction throat models were developed to investigate the correlation between impact angles and de-agglomeration performance. The breakage pattern of agglomerate was investigated using single agglomerate impact test method and explained further using DEM–CFD simulation.

* Corresponding author. Tel.: +61 2 9351 3054; fax: +61 2 9351 4391.
E-mail address: kim.chan@sydney.edu.au (H.-K. Chan).

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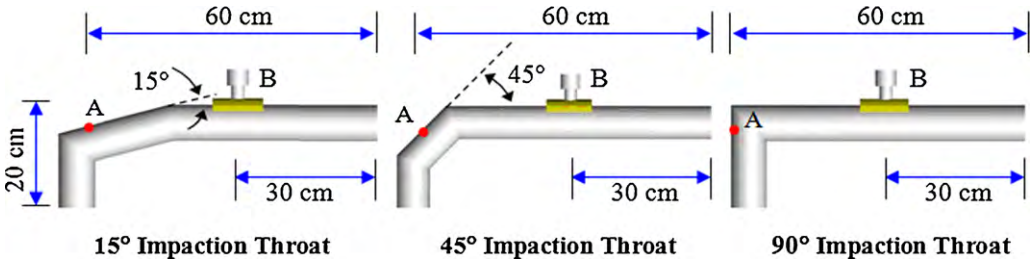

Fig. 1. Throat models (11 mm internal diameter) with 15°, 45° and 90° impact angles. (A) is the impact point, which is located 60 cm from the inlet of the main section. (B) is a customized sliding device made of clear plastic material used to feed single agglomerate into the throat via a 4 mm opening. In the figure, 30 cm is the entrance length (L_e) required to establish a steady state flow profile.

2. Materials and methods

2.1. Materials

Spray-dried mannitol (volume median diameter $d_{0.50} = 3.0 \pm 0.1\,\mu m$) was supplied by Pharmaxis (Frenchs Forest, NSW, Australia). Water was purified by reverse osmosis (MilliQ, Millipore Australia Pty Ltd., Sydney, Australia).

2.2. Preparation of mannitol agglomerates

Mannitol agglomerates were prepared by rolling 500 mg of mannitol powder in a stainless steel container (25 mm in diameter and 40 mm in length) using an electric tube roller (RATEK Instruments, Australia) at 60 rpm for 10 min at 22 ± 0.6 °C and 55 ± 2% RH. All samples were kept in a desiccator (22 ± 0.6 °C and 15 ± 0.5% RH) for storage.

2.3. Light microscopy

A stereo microscope (Model MZ6, Leica Microsystems, North Ryde, Australia) at 4.0× magnification was used for agglomerate size selection and observation of the agglomerate fragments after impaction. To maintain size and shape consistency for the study, spherical agglomerates with a diameter of 2.8 ± 0.2 mm were selected for study. Smaller agglomerates below the limit of chemical quantification were not included.

2.4. Impaction throat models

Throat models containing a mitered joint assembled with a specific angle were used to study the agglomerate breakage behavior. Three angles (15°, 45° or 90°) were selected representing small, medium and large angles. The throat is made of acrylic for clarity and visualization purposes. Schematic details are shown in Fig. 1. The selected diameter is similar to the mouthpiece diameter of a commonly used powder inhaler (Aerolizer®). The selected length of the throat is designed to achieve fully developed flow region from the feed point (point B) towards the base of the throat. The design is also to make sure that the moving agglomerate has achieved its terminal velocity prior to impaction (point A) and hence the impaction should occur at its full momentum at a selected operating flow rate. Developed flow region is defined as a region where the velocity profile no longer changes along the throat and expressed as the entrance length, L_e. Considering that steady state turbulent flow has been achieved at a selected operating flow rate (Q), L_e for a selected throat diameter (D) is calculated as follow (Munson et al., 2001):

$$\frac{L_e}{D} = 4.4R_e^{1/6} \quad (1)$$

where R_e is Reynolds number and dimensionless, calculated using the following relationship:

$$R_e = \frac{QD}{\nu A} \quad (2)$$

where A is the cross-sectional area of the throat and ν is the air kinematic viscosity at the operating temperature (22 ± 0.6 °C). The R_e values were 7660, 15320 and 19151 at 60, 120 and 150 l min^{-1}, respectively, confirming that turbulence (i.e. $R_e > 4000$) (Coulson et al., 1999) was achieved in all operating flow rates used in the study.

2.5. Dispersion methodology

Single mannitol agglomerate (3 mm, with an approximate average weight of 6.5 mg) was fragmented using the throat models described above at various flow rates (60, 120 and 150 l min^{-1}). The impaction setup is shown in Fig. 2. The throat outlet was connected to a laser diffraction system (Spraytec, Malvern Instruments Ltd., Worcestershire, United Kingdom) for particle size distribution measurement. The particles were subsequently collected downstream using a multiple stage (four stages plus filter) liquid impinger (MSLI, Copley, Nottinghamshire, UK), setup as described elsewhere (British Pharmacopoeia, 2009). The runs were performed in triplicate to obtain mean values. Mannitol was assayed by high-performance liquid chromatography (Shimadzu, Kyoto, Japan) using refractive index detection (RID 10-A model, Shimadzu, Kyoto, Japan). Samples (100 μl) were injected into a C18 radial-pak column (Resolve C18 5 μm model, Waters Corporation, Milford, United States) with deionized water as the mobile phase running at a flow rate of 1 ml min^{-1} for 4 min. A calibration curve was constructed using four standard mannitol solutions (0.01, 0.1, 1 and 5 mg/ml), which allowed the mass of powder deposited on each stage of the impinger and the fine particle fraction to be determined. Fine particle fraction (FPF_{Loaded}) was defined as the mass fraction of particles smaller than 5 μm in the aerosol, referenced against the total mass of powder loaded into the impaction throat. Numerically, FPF_{Loaded} was calculated

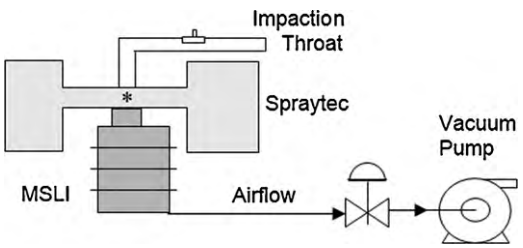

Fig. 2. Setup of the impaction test coupled to directly sizing devices using MSLI and Spraytec Laser Diffraction. * indicates the laser diffraction measurement zone, where the fragments size were determined after exiting the throat.