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# Effect of turbulent kinetic energy on dry powder inhaler performance

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ABSTRACT

Dry powder inhalers (DPIs) have been extensively used for delivering medication to the lungs. Different designs of DPI devices affect the aerosolization processes of the drug particles. The processes cannot be easily visualized in experiments, thus computational fluid dynamics were used to investigate the turbulence kinetic energy and particle impaction. In this research, 3 size ranges of lactose carrier and the Cyclohaler® and Inhalator® devices were used as models for the computational simulations. The velocity vector, the turbulence kinetic energy (TKE) and particle trajectory were obtained. An aerosol dispersion experiment was performed using the Andersen Cascade Impactor. The TKE was directly related to the flow-rate. The TKE in the Cyclohaler® was lower than that in the Inhalator® due to its narrow geometry and this resulted in a high velocity air-flow. In the Cyclohaler® the probability of deagglomeration by impaction was high because of the cyclone-like design while the cross grid of the Inhalator® was an important factor for deagglomeration of the particles. The FPF varied from 7 to 30% and the FPF increased as the flow-rate increased. The MMAD was in the range of 4–6 μm. The carrier size also affected the probability of deagglomeration at 60 and 90 L/min, but not at 30 L/min. In summary, maximizing the TKE and the particle impaction rate by adding a grid and providing a cyclone-like design was key factor to achieve a high deagglomeration of the particles.



## 1. Introduction

Dry powder inhalers (DPIs) have been extensively used for delivering medication to the lungs. This is a good choice, especially for delivering bronchodilator and corticosteroids to asthmatic patients [1]. Many research works have extended DPI applications for systemic drug delivery such as for insulin. Currently available DPI devices have various designs such as for their mouthpieces, air inlet channels and the aerosolization chambers each leading to differences in the aerodynamic characteristics [2–4] of the air flows. The different designs of the device greatly affect the DPI performance such as the Fine Particle Fraction (FPF) and the Mass Median Aerodynamic Diameter (MMAD) [5].

### 1.1. DPI formulations

The formulation of DPIs usually employs lactose as a bulk carrier with only a few milligrams of the drug. The drug to carrier ratios can be varied such as 1:67.5 (Diskhaler®, Rotahaler® and Cyclohaler®), 1:4.6 (Pulmicort Flexhaler 180 μg®) and 1:24 (Inhalator®) [6,7]. The mixing of lactose and drug particles also improves the efficiency of drug delivery by reducing drug particle aggregations [1]. After aerosolization process in a DPI device, the large carrier particles deposit on the upper airways, whereas the smaller drug particles reach the lower parts of the lungs [8].

### 1.2. Interparticulate force and aerodynamic force

Drug particles loosely attach to the surface of the lactose carrier with inter-particle force such as Van der Waals force, capillary force and electrostatic force. The Van der Waals force is a molecular attraction and repulsive interaction on the surface of particles. For ideal system with smooth spherical particles, Van der Waals force is a function of particle radius and separation distance. The Van der Waals separation radius of particles is affected by the surface roughness and shape of particles that controlled the contact areas between particles. High surface roughness reduces the contact area (increases separation distance) while a flat surface of particles increases the contact area (decreases separation distance). The surface asperities having effective separation distances above 1 μm remove the Van der Waals force [9]. The Van der Waals force becomes more significant as the particle size decreases [10]. The Van der Waals attraction dominates in particles of less than 20 μm as the pick-up of velocity from the powder bed was significantly increased, while the 40–100 μm particle pick up of velocity was not much different [11]. In this manner, micrometer domain particles were not significantly affected by the Van der Waals forces [12]. The capillary force and electrostatic force are briefly two times weaker than the Van der Waals in a moderate humidity [10]. However, if the humidity increases the

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capillary force will become dominant and as electrostatic forces weaken the Van der Waals force becomes insignificant [13]. The carrier particle in the DPI formulation is usually in the range of 50–100 μm so that the fluid force in the DPI device is strong enough to overcome the adhesion force [1,14].

During the aerosolization process, the drug particles are detached from the carrier surface if the energy from either the fluid shear or mechanical impaction overcomes the adhesion forces between the drug-carrier particles [15,16]. The viscous force acting on particles is a drag force ($F_{drag}$) that is related to particle cross-sectional area ($d^2$) (Eq. (1)). For particle collision the inertial force is the kinetic energy function ($E_k$) that is proportional to the particle volume ($d^3$) (Eq. (2)).

$$F_{drag} = C_d \frac{\pi}{8} \rho_a d^2 V^2 \quad (1)$$

$$E_k = \frac{\pi}{12} \rho_p d^3 V^2 \quad (2)$$

| | |
|---|---|
| $C_d$ | drag coefficient |
| d | diameter of the particles (m) |
| V | fluid velocity (m/s) |
| $\rho_p$, $\rho_a$ | Particle density, fluid density (kg/m3), respectively. |

### 1.3. The computational assisted DPI research

Computational fluid dynamics (CFD) is used in engineering fields and is now also gaining in popularity in some areas of pharmaceutical research [3,17–19]. It is useful for investigating aerodynamic parameters such as the turbulence kinetic energy (TKE), pressure and aerodynamic shear force and the trajectory of particles. These parameters allow us to better understand the aerosolization processes in the DPI devices than any in vitro experiments. There was an attempt to use the non-dimensional specific dissipation (NDSD) parameter to predict dispersion performance in carrier-free DPI devices. The NDSD was classified into 3 categories, flow-based factor, turbulence based factor and particle based factor. The flow-based factor such as pressure drop and flow-rate had a weak correlation to dispersion performance. The turbulence-based factors such as TKE and turbulence intensity (TI) and particle-based factors such as wall impaction count and average trajectory integral were fairly to weakly predict MMAD [20]. However, some research indicated that particle–wall impaction dominated in powder dispersion mechanism [21]. The level of turbulence and particle collisions is influenced by the air inlet channel while the design of the mouthpiece controls the outlet air velocity and flow pattern [22]. The flow pattern in the device and the outlet air velocity may cause drug loss in the oropharyngeal region by inertial impactions [23]. In addition to the experimental approach of Voss and Finley, they found that turbulence was also an important mechanism by adjusting the magnitude of the turbulence thus maximizing the particle impaction velocity. Whereas, the effect of the mechanical impaction on the dispersion of the particles was still unclear in the salbutamol sulfate–lactose carrier DPI dispersion [24]. Recently, discrete element modeling (DEM) was used to dynamically simulate particle de-agglomeration. It provided acceptable prediction of particle aerosolization when coupled with CFD [25]. The CFD–DEM coupling could analyze the interaction collision between particles–particles and particle–wall. The investigation in the Aerolizer® device indicated that the particle–wall impaction had a major role in deagglomeration especially in the dispersion chamber of the inhaler [26]. Although the DEM method offers a sophisticated computational analysis, this method needs high computational power and the coupling scheme is still limited to small numbers of large particles [27].

In this research, the carrier particle–wall impaction using only the CFD discrete particle model without DEM would be simpler and less computational intensive than that of the CFD–DEM. The aims of this research were to investigate the TKE, particle impaction and device performances for delivery of the drug during the aerosolization processes in the DPI devices using simple CFD particle tracking.

## 2. Materials and methods

### 2.1. Preparation of the lactose carrier

The particle size of the lactose carrier in the range of 10–100 μm was prepared by the use of a Ball mill (Planetary MonoMill pulverisette 6, Fritsch GmbH, Idar-Oberstein, Germany) operating at 350 rpm for 1 h. Milled carrier particles were separated by size with a sieve series having open diameters of 90, 71, 30 and 20 μm. The separated size ranges of the carrier in this study were from 71–90, 30–71 and 20–30 μm. These three size fractions of lactose carrier were used to prepare formulations #1, #2 and #3 respectively to investigate their different drug delivery efficiencies.

### 2.2. Particle size distribution measurement and fitting

Carrier sizes were determined using a laser diffraction technique (Beckman Coulter LS 230, CA, USA). In this study, the dispersion medium was prepared by suspending lactose in methanol overnight and the lactose saturated methanol was filtered through a 0.22 μm membrane. Lactose particles were suspended in a dispersion medium. Ultrasonication was used for 15 s to reduce lactose particle aggregation (Ultrasonicator, Elma, Germany). A background measurement was taken first and then the sample was added and mixed homogeneously with the medium until the percentage obscuration was about 10. The particle size distribution was calculated as the volume median diameter and its associated geometric standard deviation. Five measurements were carried out for each sample. The particle size distribution was fitted to the Rosin–Rammler equation to obtain the distribution parameter for the computational simulation (Eq. (3)). The fitting was solved using the Microsoft Excel® GRG nonlinear solver optimizing k and λ for minimal root mean square error between fitted and raw data.

$$F(x,k,\lambda) = \begin{cases} 1 - e^{-(x-\lambda)^k} & , x \geq 0 \\ 0 & , x < 0 \end{cases} \quad (3)$$

F(x; k; λ) is the fraction of particles with diameter <x.
λ is the mean particle size.
k is a particle size spread.

### 2.3. Formulation of the salbutamol dry powder inhaler

The formulations were prepared by mixing micronized salbutamol sulfate (DDSA Pharmaceutical, London, UK) with lactose carrier at a ratio of 1:67.5 w/w. Each formulation contained 40 mg of drug and 2.7 g of each carrier in a vial. Hand mixing was carried out for 10 min, and then mixed using a Turbula® mixer for 30 min (Willy A. Bachofen AG Maschinenfabrik, Switzerland). The uniformity of powder blends in each formulation was determined by five random samplings from different positions of the formulation powder for an assay of salbutamol sulfate content. The sampled powder was dissolved with water, diluted to an appropriate concentration and analyzed using a spectrofluoroscopic technique with an excitation wavelength of 218 nm and an emission wavelength of 309 nm [28]. The powder mix was filled into no. 3 capsules (1 dose = 27.4 mg, consisting of 400 μg drug), for use with two commercial inhaler devices (Cyclohaler® Pharbita, Netherlands and Inhalator® Boerhinger Ingelheim, Germany).

### 2.4. Drug deposition studies

The drug deposition was evaluated using the 8-stage Andersen Cascade Impactor (ACI; Copley Scientific Limited, Nottingham, UK),