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In vitro study on the aerosol emitted from the DPI inhaler under two unsteady inhalation profiles

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ABSTRACT

The aim of the current work was to investigate the assumption that: dynamics of inspiration affects the aerosol characteristics emitted from the passive dry powder inhaler and, subsequently, influences the total quantity of drug penetrating lower respiratory tract.

Real-time aerosol behavior of the spray-dried powder was studied experimentally utilizing New Generation Cyclohaler for two breathing curves, at the outlet of the inhaler. Aerosol characterization was done by laser diffraction, reliably capturing the aspects of time dependency. It resulted in time evolution of volumetric particle size distribution and was extended with the analysis of local particle dynamics over the studied cross-section.

Results presented in the paper confirm its assumption to be true. Different inhalation curves were associated with substantially different inhaler performances. The quicker and more forceful curve II produced better dispersion. Aerosol dynamics is particularly susceptible to the strong aerodynamic effects of unsteadiness acquired from relatively small values of flow rates. The initial part of inspiration may contribute to achieving higher respirable dose content before the peak inspiratory flow is attained. Deaggregation upon impactions with chamber wall and subsequent collisions with grid are assumed to produce desired fine particle fraction. The paper elucidates the relevance of considering time-varying character of inspiration.

Contents

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1. Introduction

The fundamental goal of drug delivery via the pulmonary route is to achieve the desired clinical outcome, which is determined by the total quantity of particles deposited on the respiratory epithelium (Gehr & Heyder, 2000). A prerequisite to a successful DPI (Dry Powder Inhaler) drug administration is the need for a good-quality aerosol cloud to inhale, resulting from a satisfactory fluidization and deaggregation of a powder dose. The part and parcel of effective aerosol release is to meet the demand of the maximized respirable dose content (fine particles smaller than 5 μm in diameter), as it ensures achieving craved penetration and deposition in the addressed area within lungs (Atkins, 2005). However, this task is not fulfilled straightforwardly, owing to the complexity of the process analysis dealing with the interplay between the powder formulation, DPI inhaler design and patient-related factors including inhalation technique. The last aspect is profound for the most marketed DPI inhalers, whose principle of operation is to breath-activate the drug dose. This so called “passive” system relies solely on the energy derived from human inspiratory air flow to re-entrain powder clusters into respirable aerosol. Therefore, numerous avenues are being pursued in further advances in widespread, aerosol-minded research.

Regarding the powder-handling strategy, particle engineering technology is used to construct suitable particles for the required respiratory formulation (Nandiyanto & Okuyama, 2011; Gradoń & Sosnowski, 2014). Obtaining drug powder with expected bulk properties, such as particle size, density, morphology and surface composition is vital for the enhancement of dispersibility with reduced interparticle forces to overcome during powder uptake.

Another extensively explored research direction is redesigning existing DPI devices and development of totally novel systems for dry powder inhalation (Atkins, 2005; Islam & Gladki, 2008; Islam & Cleary, 2012; Hoppentocht, Hagedoorn, Frijlink & de Boer, 2014). The predominant aim is to construct an ideal inhaler, which would exhibit flow independent delivery, superior reproducibility of drug dose and quality in conjunction with the best clinical efficacy possible. Dynamics of inspiration is therefore expected to affect the aerosol characteristics emitted from the passive DPI inhaler, which influences the dose entering lower respiratory tract.

Regarding the relevance of considering patient-related factors, it has been recognized by pulmonary specialists that drug administration during dry powder inhalation is strongly dependent on the applied inhalation technique with its varying inspiratory flow (Lavorini et al., 2008; Melani et al., 2011; Laube et al., 2011). It should be kept in mind that different types of DPIs require different manners of inhaling. Dynamics of the inspiration is therefore expected to affect the aerosol characteristics emitted from the passive DPI inhaler, which influences the dose entering lower respiratory tract.

Essentially, many studies have handled a great challenge to investigate the collective effect of drug formulation (Tong et al., 2010), device design modifications (Coates, Fletcher, Chan & Raper, 2004, Coates, Fletcher, Chan & Raper,; 2005a, Coates, Chan, Fletcher & Raper,; 2006; Coates, Chan, Fletcher & Chiou, 2007; Moskal & Sosnowski, 2012) and air flow of patient usage (De Boer, Bolhuis, Gjaltema & Hagedoorn, 1997; Chew & Chan, 1999; Chew, Bagster & Chan, 2000; Chavan & Dalby, 2000, 2002; Coates, Chan, Fletcher & Raper, 2005b; Martin, Marriott & Zeng, 2007) on DPI inhaler performance. Due to the complex nature of these factors affecting one another, the overall outcome of powder aerosolization is likely to change and the vast majority of papers attempted to capture the aforementioned variables in different combinations. Moreover, a number of approaches have been developed in order to examine the exact mechanisms of aerosolization phenomenon and their contribution to the process (Grzybowski & Gradoń, 2005, 2007; Gac, Sosnowski & Gradoń, 2008; Gradoń, 2009; Wong, Fletcher, Traini, Chan & Young, 2012; Longest, Son, Holbrook & Hindle, 2013; Tong, Zheng, Yang, Yu & Chan, 2013; Tong, Kamiya, Yu, Chan & Yang, 2015). However, the real issue is evaluating the dispersion process in terms of realistic air flow profile, as it has been shown recently by aerosol researchers. Inertial impaction sizing techniques utilizing impingers and impactors are routinely employed for *in vitro* aerosol characterization. In accordance with US FDA (Food and Drug Administration) and EMA (European Medicines Agency) guidelines, these methods are suggested as a standard for DPI

Table 1
Spraying conditions for sodium benzoate powder used in the study.

Feed concentration [% by mass]	5
Inlet temperature [°C]	150
Outlet temperature [°C]	60
Feed flow rate [ml/min]	2.5
Nozzle gas flow rate [m^3/h]	0.473
Aspirator capacity [m^3/h]	38