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Research paper

A personalized medicine approach to the design of dry powder inhalers: Selecting the optimal amount of bypass

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ABSTRACT

In dry powder inhalers (DPIs) the patient's inhalation manoeuvre strongly influences the release of drug. Drug release from a DPI may also be influenced by the size of any air bypass incorporated in the device. If the amount of bypass is high less air flows through the entrainment geometry and the release rate is lower. In this study we propose to reduce the intra- and inter-patient variations of drug release by controlling the amount of air bypass in a DPI. A fast computational method is proposed that can predict how much bypass is needed for a specified drug delivery rate for a particular patient. This method uses a meta-model which was constructed using multiphase computational fluid dynamic (CFD) simulations. The meta-model is applied in an optimization framework to predict the required amount of bypass needed for drug delivery that is similar to a desired target release behaviour. The meta-model was successfully validated by comparing its predictions to results from additional CFD simulations. The optimization framework has been applied to identify the optimal amount of bypass needed for fictitious sample inhalation manoeuvres in order to deliver a target powder release profile for two patients.

1. Introduction

Dry powder inhalers (DPI) are devices used to deliver drug powder to the pulmonary airways of a patient. In DPIs drug powder is initially stored in an entrainment compartment. Typically, this is a pre-filled and foil sealed 'blister' that is pierced or opened to allow air to flow through. When a patient inhales through the device, the flow of air entrains the powder and delivers it to the lung. Since the patient generates the inhalation airflow him/herself, drug delivery by means of a DPI is inherently variable and highly patient dependent: when a patient generates a strong inhalation flow rate drug is entrained comparably faster. However, for optimal delivery it is desired to design DPIs that can deliver drug to similar pulmonary airways, independent of a patient's ability to use a device. There have been various attempts to improve DPI drug delivery by studying and optimizing different parts of a DPI. For example, these attempts include: (i) numerical optimization of the entrainment compartment of a DPI (Kopsch et al., 2016a; Zimarev et al., 2013), (ii) experimental investigation of the effect of add-on spacers on de-agglomeration (Ehtezazi et al., 2008) and (iii) numerical investigations into the effect of DPI geometry on powder de-agglomeration (Chen et al., 2013; Coates et al., 2006; Wong et al., 2011a,b, 2010).

Controlling de-agglomeration of drug particles during the entrainment process is necessary to deliver the formulation to the correct pulmonary regions: small particles ($d < 5\,\mu m$) are typically cohesive and thus form large agglomerates ($d > 10\,\mu m$). Such agglomerates are not easily inhalable due to their aerodynamic properties. Good lung deposition requires particle sizes between 0.1 μm and 10 μm (Heyder, 2004). It is therefore a key requirement for effective drug delivery that agglomerates of particles are broken up in the device during inhalation. Wong et al. evaluated the influence of turbulence (Wong et al., 2010) and impaction (Wong et al., 2011a,b) on de-agglomeration; impaction was found to be most effective.

There is an opportunity to apply numerical techniques, such as computational fluid dynamics (CFD), to the development of DPIs. Multiphase CFD techniques have been successfully applied to predict the entrainment of drug in a DPI (Milenkovic et al., 2014; Tong et al., 2013; Wong et al., 2011b). Consequently, in our previous work, we applied a CFD technique to optimize the entrainment geometry of a DPI (Kopsch et al., 2016a; 2015; Zimarev et al., 2013).

Abbreviations: CFD, computational fluid dynamics; DPI, dry powder inhaler; EE, Eulerian-Eulerian; MDI, metered dose inhaler.

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The optimization objective was to achieve drug dose emission that (A) is independent of the inhalation manoeuvre and (B) targets the dose to a specific pulmonary region in the lung. This optimization objective was achieved by using a multiphase CFD technique to predict the rate of drug release from an entrainment geometry for two different sample inhalation profiles. The predicted rate of drug entrainment was used to calculate the value of a cost function that quantified the optimization objectives (A) and (B). Finally, the entrainment geometry was systematically varied to achieve lower values of the cost function. The result was an optimized DPI entrainment geometry that achieved better performance in terms of the objectives (A) and (B).

Even though some theoretical progress has been made to reduce patient dependence of DPI drug dose delivery, no practical solution is currently on the market. Drug delivery by means of a DPI is still considered less reliable than delivery by other types of inhalers, i.e. nebulizers or metered dose inhalers (MDIs). One reason is that devices are often made to be used by a wide range of patients (a 'one size fits all' approach). In this study, we investigate, by computational method, if a DPI design can be personalized for the patients it is intended to treat. We propose the amount of air bypass as a DPI design factor to control powder entrainment rate when the entrainment geometry design has been 'locked down' and present a fast computational method that can determine the optimal amount of bypass needed to minimize the variability in drug delivery rate between different inhalation manoeuvres of a given patient. The computational method uses measurements of several inhalation profiles of a particular patient to predict the effect of varying the amount of air bypass in a DPI for that patient. We validate the computational method and demonstrate by means of numerical simulations how such a method may be used to achieve the optimization objective, i.e. to target the dose to a specific pulmonary region in the lung. The focus of this work is to develop the computational method, not the design of a new DPI *per se*, since inhaled products are often retro-engineered into existing commercial platform devices. Therefore, the current approach adopts an existing DPI design where other design elements have been locked down (for example, in the generic design shown in Fig. 1), to study the effect of varying of the magnitude of airflow through the bypass channel.

2. Methods

2.1. Concept development

A simple DPI layout may be thought of as an entrainment compartment and a bypass element in parallel, see Fig. 2. When patients inhale through the device, they generate a total flow rate $Q(t)$. The incoming air divides so that a portion of the air flows through the entrainment compartment, where it may entrain drug powder, and the remainder flows through the bypass element. The flow rates through the entrainment compartment and the bypass element are $Q_{ent}(t)$ and $Q_{bypass}(t)$ respectively.

Note that the inhaled volume of air $V(t)$ is the integral of the total flow rate $Q(t)$ over time.

$$V(t) = \int_0^t Q(t\prime)dt\prime \tag{1}$$

However, $M(t)$, the mass of drug powder released as a function of time t, only depends on the flow rate through the entrainment compartment $Q_{ent}(t)$. In pharmaceutical applications it is important when the drug is released with respect to the total volume of inhaled air V_{tot}, because this determines which pulmonary locations the drug may be able to reach. Drug released early in the tidal inhalation flow can penetrate deeply into the expanding lungs, whereas later released drug will only reach the upper airways. As explained in Kopsch et al. (2016a, 2015), it is convenient to express the mass of released drug M as a fraction x of the scaled volume, where

$$x = \frac{V(t)}{V_{tot}} \tag{2}$$

The relative flow resistances of the entrainment compartment and the bypass element control the amount of air that flows through each part. For example, if the flow resistance of the bypass element is increased then more air will flow through the entrainment compartment. DPIs may be characterized by the bypass ratio

$$r = \frac{Q_{bypass}}{Q_{ent}} \tag{3}$$

If effects due to the presence of the drug powder are neglected this ratio is approximately constant during an inhalation manoeuvre. For most commercially available DPIs the bypass ratio is fixed at manufacture. However, it may be beneficial to adapt this ratio to the patient. A patient who generates a lower total inhalation flow rate may choose a lower ratio r in order to still achieve a good flow rate Q_{ent} through the entrainment compartment.

As an illustration, Fig. 3 shows the influence of r on the timing of drug release: Fig. 3a shows three possible measurements of inhalation flow rate $Q(t)$ through a DPI. Correspondingly, Fig. 3b–d shows the released drug as a function of scaled volume x for low, medium and high amounts of bypass respectively. As indicated a low bypass can achieve an early delivery of drug, while a high bypass achieves a more continuous delivery. The amount of bypass may be 'tuned' to achieve a better match with a desired release profile.

2.2. Development of a meta-model

The goal is to predict $M(x)$, the mass of drug that has left the entrainment part as a function of scaled volume x, for any given

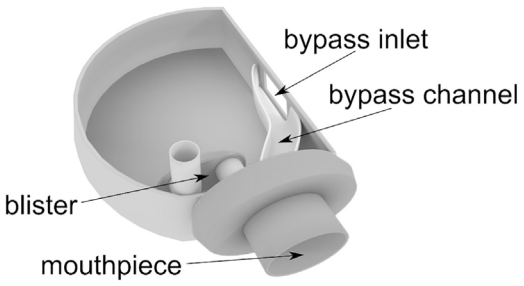

Fig. 1. Simplified drawing of a DPI (top removed) with a blister (powder entrainment compartment) and a fixed bypass. The dimensions of the bypass channel influence the amount of air that bypasses the blister.