Design-Optimization of Dry Powder Inhalers: Selecting an Objective Function

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Summary

In passive dry powder inhalers (DPIs) drug is often stored in blisters incorporated in the device. The patient inhales through the device, forcing an airstream through the blister. Drug is entrained into the airstream for delivery to the lung. The entrainment and dispersion of drug depend on internal inhaler geometry. Relevant design features include the air path in the device and the blister. Two objectives were considered: A) DPI dose emission that is independent of the inhalation profile, such that the emitted dose reaches similar lung regions when two patients inhale with different inhalation profiles; B) Targeting of the emitted drug to specific pulmonary airways for therapeutic applications. For example, for some medical applications a 'bolus' delivery is desired, i.e. most of the drug should leave at a particular instant. We present an optimisation approach for DPI design for these objectives through simulation of dose emission using computational fluid dynamics (CFD). We demonstrate the approach by computationally optimizing a simple 2D DPI. The geometry considered is a blister where air enters through one hole, entrains drug, and exits through another hole. Three parameters characterised the geometry: the separation of the holes, *s*; the width of the outlet hole, d_1; and the width of the inlet hole, d_2. A gradient descent method was used to vary these parameters to optimise the DPI. Through the CFD studies a DPI air path geometry was optimised to achieve an ideal 'early bolus' drug delivery that was independent of the inhalation profile.

Introduction

Dry powder inhalers (DPIs) are easy-to-use and portable devices for pulmonary drug delivery. It is well-known that the performance of most passive DPIs is dependent on the airflow rate through the device[1, 2], and use of DPI devices has traditionally been associated with low lung deposition fractions[3]. The effect of flow rate on DPI performance is usually examined using a steady flow rate, for example the peak inspiratory flow rate achieved by patients through their device. However, it is increasingly understood that differences in the inhalation manoeuvre (inhalation profile) is of immense importance in determining pulmonary deposition from DPIs[4]. It would be desirable to engineer a device that provides delivery of a consistent dosage, and achieves high drug deposition in similar lung regions for patients with different inhalation profiles. Thus, high-performance drug delivery critically depends on the design of the inhalation device. In this study, we use design optimization to find a geometry that minimizes the patient-to-patient variability in dose emission performance.

The timing of drug release determines the region of the lungs that an aerosol bolus can penetrate[5]. For example, if the drug aerosol is of a suitable size-range and is released early in co-ordination with inhalation ('early bolus'), it will reach very deep parts of the lung[6]. The drug released in the middle of the inhalation will deposit in more proximal airway locations in the lung. This could be desired for the treatment of asthma or other diseases such as infections affecting the central conducting airways[7]. Drug released late might not reach the lung to any significant extent, and be exhaled during the expiratory period of the respiratory cycle[8]. A desired goal is to achieve similarity of drug delivery, i.e. the same fraction of the drug should deposit in the same lung regions for different patients with different inhalation profiles and inspiratory functions.

Zimarev et al.[9, 10] optimized a DPI by evaluating CFD simulations, and iteratively altering the geometry to improve performance. Zimarev validated his CFD simulation by comparing it with experimentally measured data from Tuley et al.[11]. For any given geometry Zimarev calculated the emitted dose, $M_1(t)$ and $M_2(t)$ for two patients with different inhalation profiles 1 and 2. To optimize for independence of the patient's inhalation profile, Zimarev minimised the aggregate difference between these profiles over the whole inhalation time. However, when two patients with different lung functions inhale through the device, the dose should ideally be emitted into an inhaled volume fraction such that the aerosol is transported to a similar lung depth for both patients [5]. Therefore, it is important when the drug is released with respect to the *inhaled volume*, not when it is released with respect to *time*. The aim of the current study is to develop an objective function that resembles the statement 'most similar drug delivery', and to demonstrate it by computationally optimizing a simple 2D DPI.

Methods

Objective function

The goal is to achieve the 'most similar drug delivery', i.e. drug should penetrate to the same pulmonary region for different patients, 1 and 2. In general, patients have different inhalation profiles; i.e. when they inhale through the device, they produce different volumetric flow rates $Q_1(t)$ and $Q_2(t)$ (see Fig. 1a) leading to different drug emission rates (dM/dt) (Fig. 1a). The integral (Equation 1) gives the inhaled volume as a function of time, t:

$$V_i(t) = \int_0^t Q_i(t')dt' \qquad \text{Equation 1}$$

The total inhaled volume (see Fig. 1b) is given by Equation 2:

$$V_{i,Tot} = \int_0^{\infty} Q_i(t')dt' \qquad \text{Equation 2}$$

After carrying out a CFD simulation of entrainment, we can calculate the emitted dose M_i. M_i is the mass of drug that has left the device and can be expressed as either a function of time $M_i(t)$ or inhaled volume $M_i(V)$ (see Fig. 1c). M_{Tot} is the total drug amount in the blister. We can scale $M_i(V)$ along the V-axis by defining the scaled volume (Equation 3):

$$x = \frac{V}{V_{i,Tot}}, \qquad \text{where } 0 \le x \le 1 \qquad \text{Equation 3}$$

This gives $M_i(V) = M_i(x \cdot V_{i,Tot})$, (see Fig. 1d).

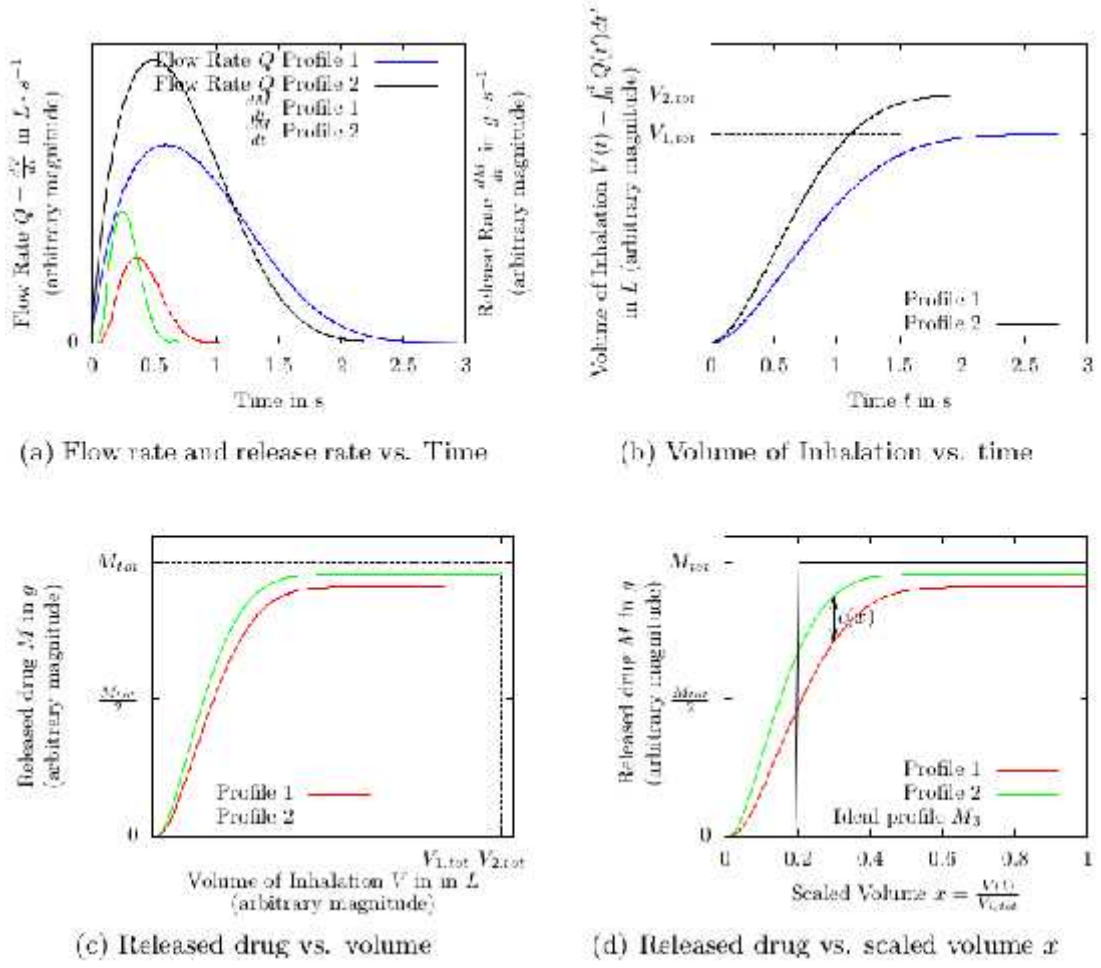


Figure 1: Idealized representations of inhalation flow rate (*Q*), inhaled volume (V_t), released drug (*M*) and scaled volume (*x*) as functions of time or each other. Sample data for clarification purposes only.

After a fraction x of the total inhaled air $V_{i,Tot}$ is inhaled, the device would ideally have released the same amount of drug. It follows that a criterion for similarity of dose emission can be represented by Equation 4, for all x.

$$M_1(x \cdot V_{1,Tot}) = M_2(x \cdot V_{2,Tot}) \qquad \text{Equation 4}$$

To achieve most similar dose emission, we wish, therefore, to minimize the difference (Equation 5) for all x:

$$c(x) = |M_1(x \cdot V_{1,Tot}) - M_2(x \cdot V_{2,Tot})| \qquad \text{Equation 5}$$

Fig. 1d shows the same release profile as in Fig. 1b, but as a function of scaled volume x. We want to achieve $c(x) = 0$ for all x. A possible cost-function to achieve this is therefore Equation 6:

$$C_A = \int_0^1 c(x)dx = \int_0^1 |M_1(x \cdot V_{1,Tot}) - M_2(x \cdot V_{2,Tot})|dx \qquad \text{Equation 6}$$

Note that since CFD solves discretized versions of the governing equations in practice we must approximate the integral (equation 6) as a summation.

Minimizing the cost function C_A guarantees a device airflow geometry that can achieve the highest similarity of emission-volume profile. However, it doesn't guarantee that this emission profile is also a desired one. It depends on the desired therapeutic application whether we require, for example, either an early bolus delivery or a continuous emission to achieve deposition throughout all airways. We should, therefore, consider scaling a desired, idealized release profile. As an illustration, if for a particular medical application an early bolus delivery of drug is desired, we can define an idealised early bolus profile (see Fig. 1d) using Equation 7:

$$M_3(x) = \begin{cases} 0 : x < 0.2 \\ M_{Tot} : x \geq 0.2 \end{cases} \qquad \text{Equation 7}$$

This is a step function that represents a profile which releases all the drug at a specific scaled volume, x=0.2.

To evaluate how closely the emitted dose profile from our device matches the idealised profile we can use the cost function given by Equation 8:

$$C_B = \int_0^1 | M_1(x, V_{I,Tot}) - M_3(x) | dx \qquad \text{Equation 8}$$

Minimizing this cost function gives a geometry with the desired release behaviour, but it doesn't ensure 'most similar drug delivery' for different patients.

To find a geometry that fulfils both objectives, we must solve the multi-objective optimization problem $min(C_A, C_B)$. We have initially assumed that both objectives are equally important and minimised the sum $C_{Tot} = C_A + C_B$.

Computational Fluid Dynamics

The CFD package *OpenFOAM* was used to simulate entrainment devices with geometries meshed by the *Snappyhexmesh* program (both open source and distributed by the *OpenFOAM* Foundation, version 2.4.0). The Eulerian-Eulerian *twoPhaseEulerFoam* solver was used for the simulations. This solver includes kinetic theory of granular flow (KTGF) models to capture the transport of, and interaction between, the gaseous and granular (drug) phases. At the outlet the unsteady pressure boundary condition applied was the same as that used by Zimarev[10]. This was a linearly increasing pressure difference (i.e. dP/dt = constant) for a fixed period of time (t = 0.3 s). Thus, only the first part of the inhalation profile that increases approximately linearly has been simulated. The objective function $C_{Tot} = C_A + C_B$ has been used to optimise for a most similar 'early bolus' drug delivery.

Design Optimization

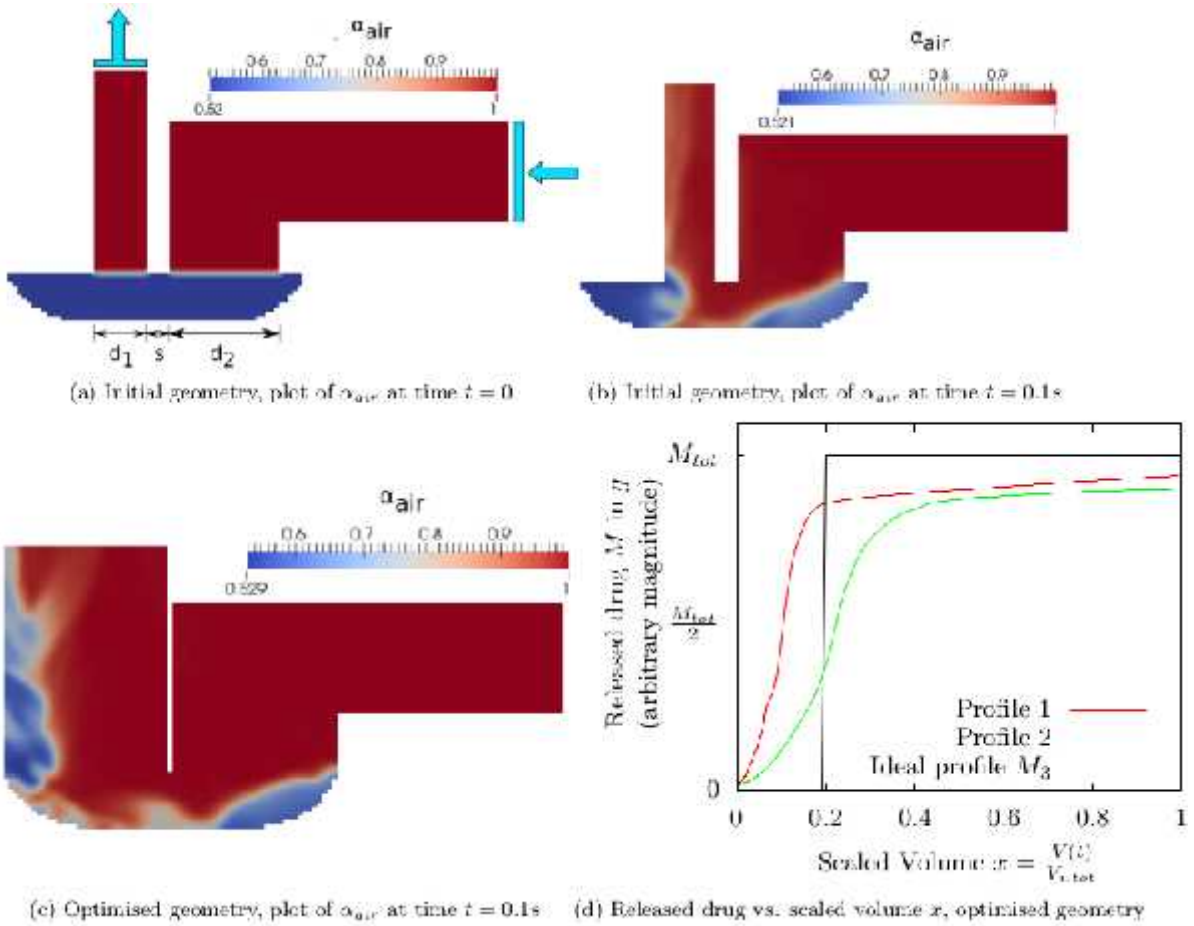
As a preliminary application of the proposed objective function, a simple, 2D blister DPI entrainment geometry was optimized following drawing and parameterization in *FreeCAD* (open source, version 0.15). In the geometry considered air flowed from the inlet, through the blister to the outlet. Three design variables were chosen to describe the geometry: the width of the outlet hole, d_1, the width of the inlet hole, d_2 and the separation of the holes s. A *python* script was created that ran a gradient descent optimization algorithm to minimize the cost function C_{Tot}. The script calculates the costs for a particular design in three steps. First, the script uses *FreeCAD* to change the design variables and to export the updated geometry into a *.stl* file. Second, the script uses *snappyhexmesh* to mesh the geometry, sets the initial conditions and runs the *twoPhaseEulerFoam* solver. In the final step the script carries out post-processing and determines the costs C_A and C_B from the output of the CFD simulation.

Results and discussion

Figure 2 shows the powder distribution in initial and optimized geometries for different times t. α_{air} is the local volume fraction of air compared to all other phases (drug + air). Fig. 2c shows the geometry with the lowest cost C_{tot} found in this study. It appears that the optimisation routine preferred a geometry with a low separation of holes and large width of the inlet and outlet holes d_1, d_2. Qualitatively, this design increases the 'area of attack', i.e. the airstream can easily pick up all drug in the blister, thus delivering an 'early bolus'. Fig. 2d is similar to Fig. 1d, but shows the simulated data for the optimised geometry. There is an overlap between the idealised 'early bolus' release profile and the simulated ones.

Conclusions

Through this work it has been shown that design optimisation techniques can be used with CFD to optimise DPIs for independence of patient's inhalation profile and to deliver an ideal bolus delivery. In contrast to previous work by Zimarev et al. [9, 10] an objective function that more closely resembles a realistic therapeutic optimisation goal has been presented. Our first results suggest that a design with large holes and small hole separation is desired to achieve these goals.



(a) Initial geometry, plot of α_{air} at time $t = 0$ (b) Initial geometry, plot of α_{air} at time $t = 0.1$s

(c) Optimised geometry, plot of α_{air} at time $t = 0.1$s (d) Released drug vs. scaled volume x, optimised geometry

Figure 2: Initial (arbitrary) geometry for different times (a), (b) and optimised geometry (c). Fig (d) shows released drug (*M*) as a function of scaled volume (*x*) for the optimised geometry.

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