Computational Modelling and Stochastic Optimisation of Entrainment Geometries in Dry Powder Inhalers

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Summary

Dry powder inhalers are one of the methods for the delivery of drug particles to the lungs. In addition to the influence of powder properties, their performance is dependent on the aerodynamics of the airpath and the user's inhalation characteristics. As a result, engineers have used computational fluid dynamics (often single-phase) to improve the aerodynamic performance of individual inhaler geometries. This paper attempts to extend this approach by using a stochastic optimisation algorithm coupled with a multiphase (air-powder) computational model to automatically evaluate multiple geometric iterations. Of the functional parts that make up the inhaler, entrainment geometries play an important role. They were therefore chosen as the focus of this optimisation study. The performance of the computational model used was in reasonable agreement with the experimental results found in the literature. Optimisation was therefore carried out for flow rate independence and dispersion of powder at the outlet – both desirable in efficient inhalers. The latter criterion appeared to be a harder optimisation problem than flow rate independence. The algorithm managed to produce plausible improved geometries (that utilised flow recirculations), although further validation studies would be needed.

Introduction

Dry powder inhalers (DPIs), together with metered-dose inhalers (MDIs) and nebulisers, are the main methods for controlled drug delivery to the lungs. DPIs and MDIs are small and portable, hence widely used by patients suffering from respiratory conditions like asthma and chronic obstructive pulmonary disease. Unfortunately, MDIs require the user to perform two operations simultaneously: both inhalation and activation of the propellant. If poorly coordinated, this increases the inter-sessional variability in the quantity of the drug delivered. Unlike MDIs, DPIs do not suffer from this issue. The single act of inhalation acts as the propellant, entraining (and to some extent breaking up) the particles. As a result, DPI performance is linked to the aerodynamics of the airpath and flow rates generated by the users. The study of flows in DPIs can potentially lead to the development of geometries that give improved performance. Traditionally this has been done by using single-phase computational fluid dynamics (CFD), applied to one or several specific geometries. What this paper proposes is the use of a multiphase model *directly* coupled with a stochastic optimisation algorithm, which explores multiple different geometries to find an improved one. The overall research aim was the development and testing of such a framework.

Optimisation of an inhaler entails the improvement of one or more of its functional components. In general, the DPIs appear to have three functions: they (i) store the powder, (ii) entrain and (iii) deagglomerate it. Functions *ii* and *iii* are key to inhaler performance. Entrainment geometries (Fig. 1) usually achieve both *ii* and *iii*. However, if *iii* is insufficient additional deagglomeration geometries may be used. Because inhalers cannot function without entrainment geometries, they were chosen as the focus of this optimisation study.

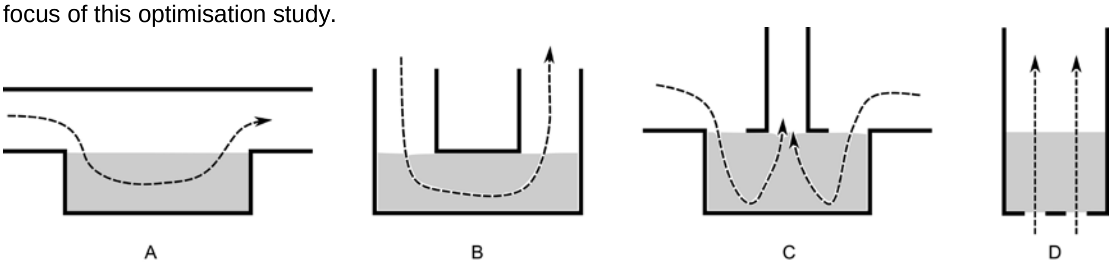

Figure 1 Simplified entrainment geometries encountered in industry and academic research: *A* – shear force entrainment [1]; *B*, *C* and *D* – gas-assisted entrainment [2 ,3, 4, 5]. Gray areas indicate the powder, arrows – direction of the flow.

Methods

The whole optimisation framework consisted of four components: an ICEM™ meshing application, FLUENT™ multiphase computational fluid dynamics (CFD), a shape parameterisation algorithm based on free form deformation (FFD) and a custom stochastic optimisation algorithm.

For initial validation a structured Cartesian mesh was used. Mesh independence studies were carried out for geometries *A* and *B* (Fig. 1). During optimisation meshing was executed as an automated batch process from a pre-defined script.

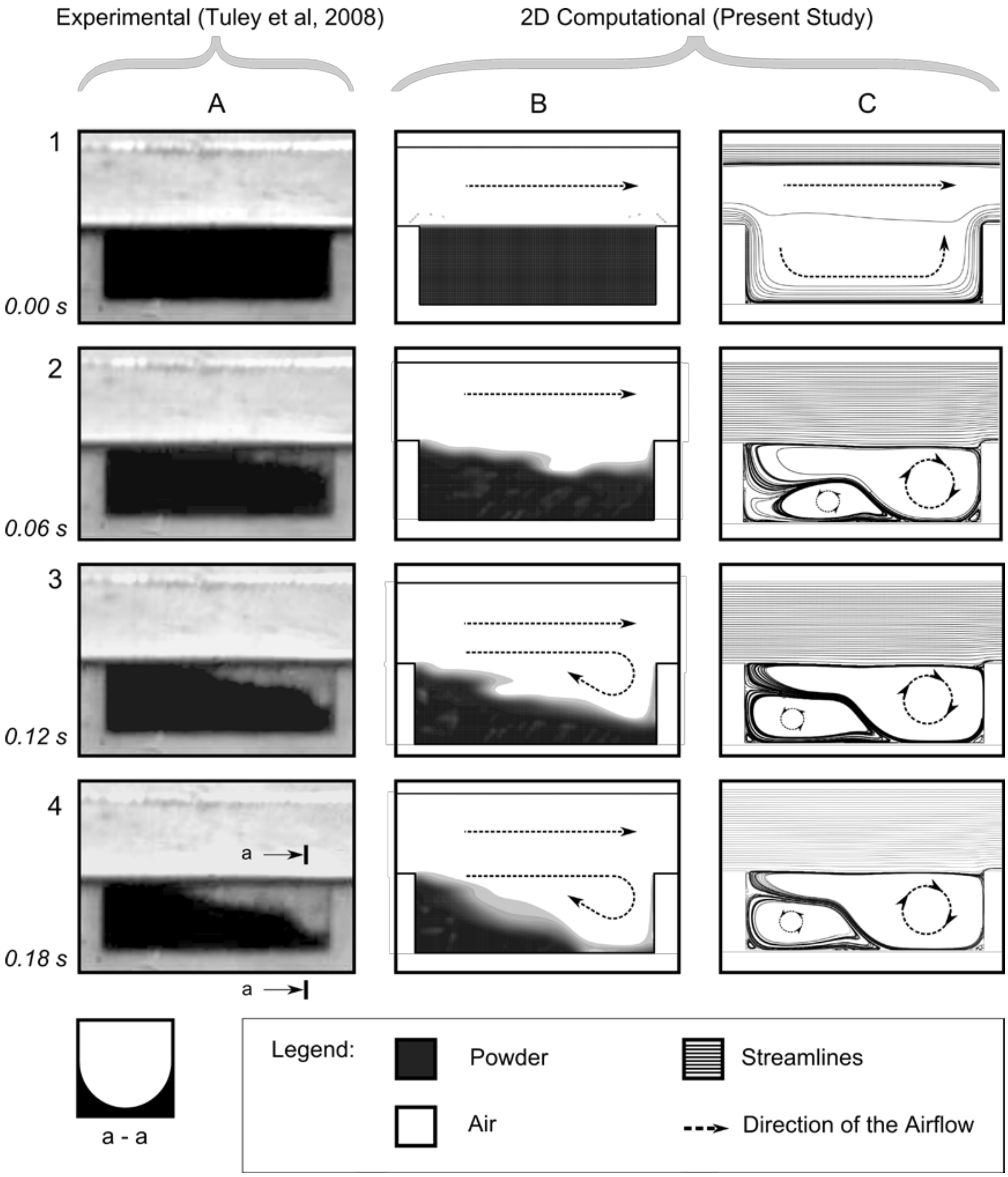

Figure 2 Comparison between experimental [3] and computational results for geometry *A*. Columns show different types of studies: A – experimental, B – computational multiphase (air and powder) and C – computational single-phase (air only). Rows correspond to different moments in time; experimental time before the start of evacuation was excluded.

An Euler-Euler multiphase model was used. It approximated the particulate phase as a continuum using the modified form of Navier-Stokes equations. After Tibbatts et al [6] and ANSYS [7] the granular bulk viscosity was treated using the Lun-et-al model; frictional viscosity was calculated using the Johnson-et-al model. An unsteady pressure boundary condition was applied at the outlet using a user defined function. Atmospheric pressure was applied at the inlet. After Wong et al [8] a shear stress transport k-ω turbulence model was selected: it incorporated the best features from the standard k-ω and k-ϵ models, yet remained computationally fast. Speed was critical for optimisation, as the algorithm had to evaluate multiple solutions. The CFD solver ran as a batch process controlled by a specialist script, that imported the mesh and exported solution data for processing by the optimisation algorithm.

A genetic optimisation algorithm (GA) was used. Unlike the more traditional gradient based methods, GAs are more likely to find a global minimum in the noisy cost functions associated with CFD problems. The method has already been applied to aerospace and structural optimisation problems. By using operators like *selection* and *crossover* the algorithm is able to select geometric features that are performing well with respect to the cost functions and combine them to form potentially better geometric solutions. By using the *mutation operator* the algorithm can continually develop new features, some of which will noticeably improve the performance [9].

Because optimisation is an iterative process, it requires a way of dynamically altering the shape, whilst preserving its overall architecture. An FFD algorithm, widely used in aerospace applications, was chosen. Using *Bernstein polynomials* it deforms the standard set of datum points using a number of control points [10].

Results and Discussion

The first part of this research involved the selection and validation of a multiphase computational model for the simulation of powder-air interactions in entrainment geometries. For qualitative validation geometry *A* (Fig. 1) was chosen for its characteristic entrainment pattern observed by Tuley et al [3] and Lastow and Remmelgas [1] – the formation of a recirculation at the trailing edge of the reservoir. The computational multiphase simulation (Fig. 2, column *B*) was in reasonable agreement with the experimental results found in the literature (Fig. 2, column *A*). However, the computational evacuation appeared to occur quicker. Because Tuley et al [3] recorded the side view of the 3D geometry only, the visible concentration of powder at the wall might have been greater than that at the centre of the profile as shown in detail *a* - *a* (Fig. 2). This would not have been captured by the computational model. A single-phase (air only) simulation was also carried out (Fig. 2, column *C*). It was in agreement with both experimental and multiphase computational data and helped to explain the powder evacuation mechanism (see the formation of a P-like re-circulation in rows 3 and 4, Fig. 2). The multiphase simulation was also compared to quantitative data by Tuley et al [3] for geometry *B* (Fig. 1). Both experimental and computational data showed the same logarithmic trend, although the experimental data was characterised by greater fluctuations in the volume fraction values and, like in the case of the qualitative validation study, longer evacuation times.

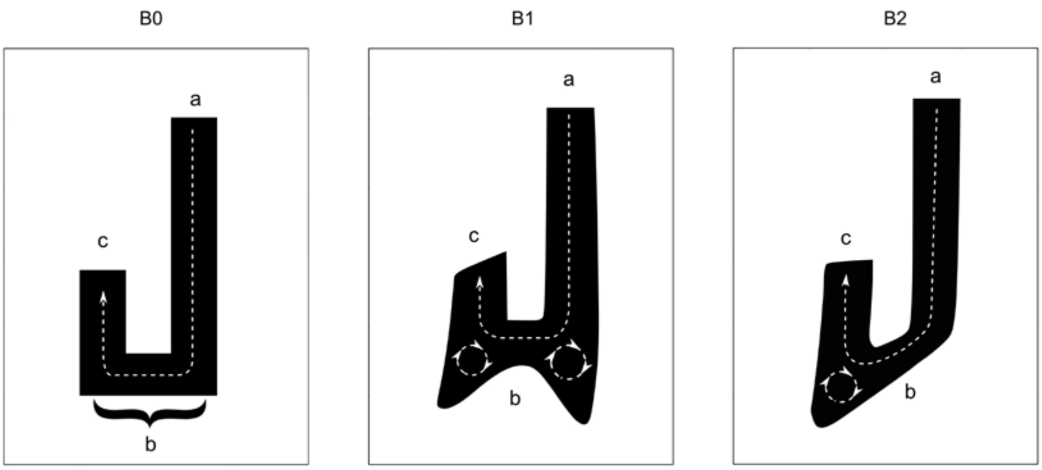

Figure 3 Standard (B0) and optimised for flow rate independence (B1 and B2) geometries. Detail a – air inlet, b – powder bed and c – outlet. Arrows indicate the direction of the airflow and recirculations.

After the validation study the model was coupled with a stochastic optimisation algorithm. The second part of this research focused on the optimisation of geometries *A* and *B* (Fig. 1). First of all, optimisation was carried out for flow rate independent performance. Average volume fraction of air was measured at the powder bed (Fig. 3, *d*) and plotted against time. Each geometry was tested at high and low flow rates and the similarity between the two volume fraction graphs was measured. The more similar the two graphs were, the better was the performance considered. Both optimised geometries B1 and B2 achieved improved performance by developing deep powder pockets. The evacuation of powder in the pockets was less dependent on the flow rate as was the case with direct *gas-assisted* entrainment in B0. In B1 and B2 the powder was evacuated more gradually by the mechanism of *saltation*, induced by the recirculating airflows. Optimisation was also carried out for high powder dispersion at the outlet (equivalent to FPF). However, it appeared to be a harder optimisation problem than flow rate independence; developing an effective cost function was difficult.

Conclusions and Future Research Directions

The main aim of this research was to investigate the effectiveness of the framework for computational modelling and optimisation of entrainment geometries. It was shown that the model was in reasonable agreement with experimental results and that it produced plausible improved geometries. Further work could include more extensive computational trials and experimental validation; 3D modelling could also be investigated. In addition to entrainment, geometries associated with deagglomeration (mesh, wedge and cyclone-like structures) could be studied.

Acknowledgements

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