Modelling Drug Entrainment in a Dry Powder Inhaler: Benchmarking and Sensitivity Analysis of a Multiphase CFD Approach

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Summary

Dry powder inhalers (DPIs) are used to deliver drug powder to the lungs. When a patient inhales through a DPI, air flows through the drug compartment and entrains drug. The rate of entrainment depends on a number of factors, including the inhalation flowrate, the geometry of the inhaler and physicochemical properties of the drug formulation. While the influence of each of these factors has been studied experimentally, a robust computational method to predict drug entrainment accurately for real world combinations of these parameters would be useful in the design and optimization of DPIs.

The objective of this study was to investigate the applicability of a multiphase computational fluid dynamics (CFD) simulation approach: Firstly, results of two different CFD solvers (ANSYS Fluent and OpenFOAM) were compared with experimental data. Secondly, the sensitivity of the drug release rate to variations of drug properties and CFD solver settings was investigated. Particularly, (a) the size of drug particles, (b) the density of particles, (c) the initial volume fraction, α, (d) the drag model, (e) the packing limit, α_{max}, and (f) the solids pressure were varied.

This investigation showed that the two different CFD solvers produced similar results and that these results were consistent with experimental data. The sensitivity analysis indicated that the simulated entrainment is not strongly dependant on either particle size or the choice of drag and solids pressure model. However, drug density, the initial volume fraction of drug, and the choice of the packing limit, do significantly influence the results.

Introduction

When designing dry powder inhalers (DPIs) it is desired to achieve a number of medical, manufacturing and commercial objectives. Possible objectives of optimizing DPIs include: (A) independence of the drug emission profile for different patients and (B) achieving a desired emission profile [1, 2]. To optimize DPIs in accordance with these objectives, it is necessary to predict how well a DPI can achieve them, as a function of the entrainment geometry and physical properties of the drug powder. Computational fluid dynamics (CFD) simulations are often used to assess DPIs [3, 4]. However, most of these approaches are either single phase simulations or particle-tracking (Eulerian-Lagrangian) approaches. Only a few studies exist where an Eulerian-Eulerian (EE) approach was applied [1, 5]. In EE approaches all phases are treated as continuous phases. When applied to the simulation of DPIs, one phase may represent air, while the other phase represents formulation components. In order to simulate a granular phase, like drug powder, with an EE approach, additional models are required to describe the interaction between the fluid (air) and the granular phase (drug formulation). The kinetic theory of granular flow (KTGF) was developed to describe the constitutive behaviour of granular material. In order to apply KTGF in EE simulations, sub-models have to be selected. For example, these include sub-models for the drag of air on particles (drag coefficient), for the probability of particle-particle collisions (radial distribution function) and for the solids pressure (the additional pressure due to the presence of the granular phase). See [6] for detailed description of these sub-models. Zimarev *et al*. applied EE CFD simulations to model the entrainment of drug in a DPI entrainment geometry and to optimize the entrainment part of a DPI [5]. The CFD solver used was ANSYS Fluent [6]. In this EE-model Zimarev *et al*. [5] compared CFD predictions with experimental results from Tuley *et al*. [7]. Kopsch *et al*. used a similar approach to optimize DPIs [1], but used OpenFOAM [8] as a CFD solver and improved objective functions. In both studies the DPI geometry was optimized for a given drug powder, with defined particle size, density and porosity. However, a direct comparison of these two CFD packages for DPI entrainment simulations has not been conducted. It is obviously desirable that simulation results should be independent of the particular CFD solver used.

There are two objectives of this study: Firstly, to investigate whether two different CFD solvers, *i.e*. ANSYS Fluent [6] and OpenFOAM [8], produce similar results and to compare these results to experimental data. Secondly, to analyse the sensitivity of the results when various settings were varied. In particular, the mass of entrained drug $M_{(t)}$ was plotted as a function of time t when six different powder properties and CFD solver settings were changed. Powder properties that were varied include (a) the size of drug particles, (b) the density of particles and (c) the initial volume fraction α. CFD solver settings that were varied include; (d) the drag model, (e) the packing limit α_{max} and (f) the solids pressure.

Methods

CFD Eulerian-Eulerian approach

The entrainment geometry considered was the 90° geometry chosen by Tuley *et al*. [7]. This geometry was drawn and meshed, Figures 1 & 2. An Eulerian-Eulerian CFD case was prepared with both ANSYS Fluent and OpenFOAM. In both CFD packages the boundary conditions of the problem had to be specified. The inlet boundary condition was a constant atmospheric pressure boundary condition. The outlet boundary condition was a transient pressure boundary condition. In ANSYS Fluent the time-dependant pressure boundary condition was specified with tabular data. In OpenFOAM the library swak4FOAM [9] was installed to specify the boundary condition.

The initial conditions of the problem had to be also specified. This included the location of the drug powder and the initial volume fraction α of the drug. Other physical conditions that were specified were the density of air and drug, the size of drug particles and parameters for the KTGF sub-models.

Comparison of the CFD approaches with experimental results

The entrainment of lactose (16% fines) and glass powder was modelled using the powder properties found in [7]. Initially, the KTGF models shown in Table 1 were chosen. Note that not all models were available in both Fluent and OpenFOAM.

Model	**OpenFOAM**	**ANSYS Fluent**
Viscosity Model / Granular Viscosity	Gidaspow	Gidaspow
Frictional Stress Model / Frictional Viscosity	Johnson Jackson	Johnson *et al*.
Conductivity Model / Granular temperature	Gidaspow	Algebraic
Granular Pressure Model / Solids Pressure	Lun	Lun *et al*.
Radial Distribution	Lun Savage	Lun *et al*.
Drag Coefficient	GidaspowErgunWenYu	Gidaspow

Table 1 - Initial selection of KTGF models

Sensitivity analysis

The sensitivity of drug entrainment to three drug properties ((a) size of drug particles, (b) particle density, (c) initial particle volume fraction) and three CFD model settings ((d) drag model, (e) packing limit, (f) solid pressure) was studied. This was performed in Fluent by varying one of these settings while keeping the other settings fixed.

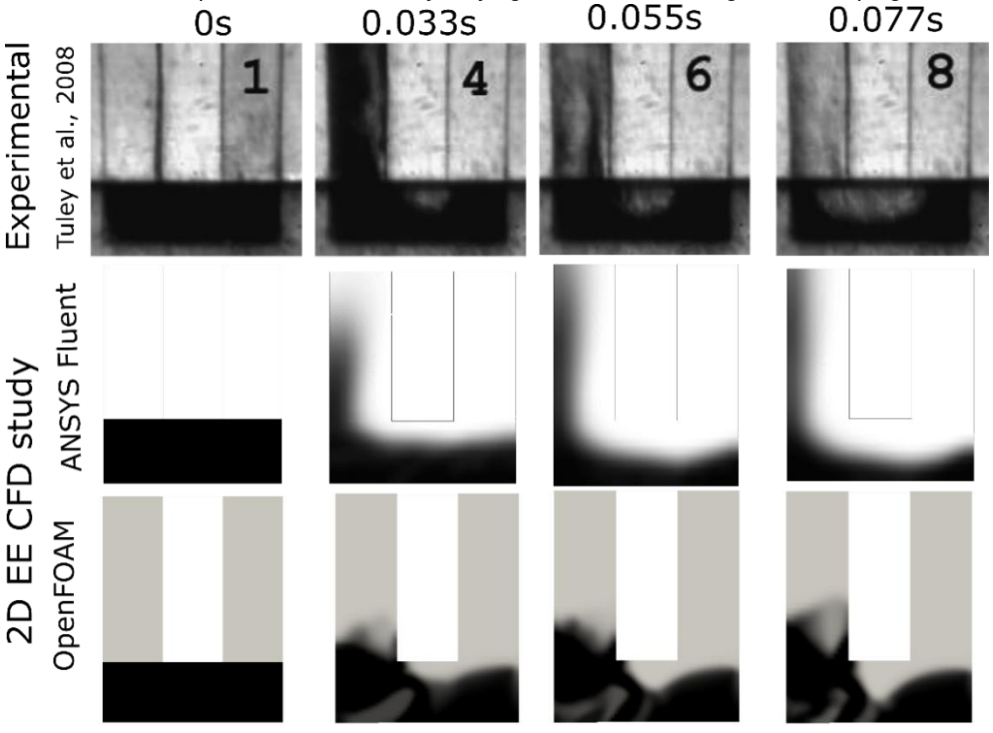

Figure 1 - Comparison of experimental results from Tuley *et al*. [7] with CFD simulation results from ANSYS Fluent [6] and OpenFOAM [8]. This comparison is for glass powder (mean particle *d = 45 μm*). Time before the beginning of emptying excluded.

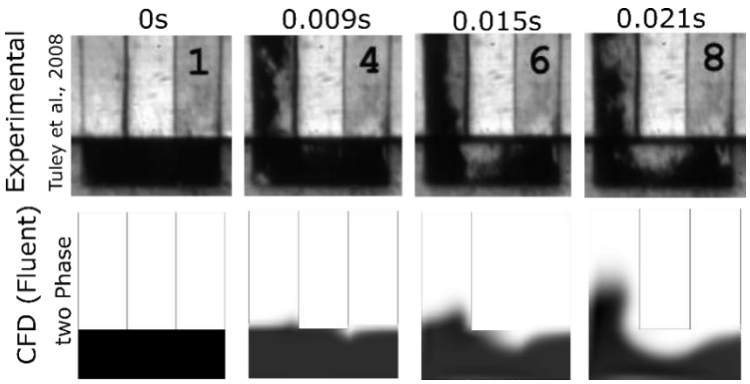

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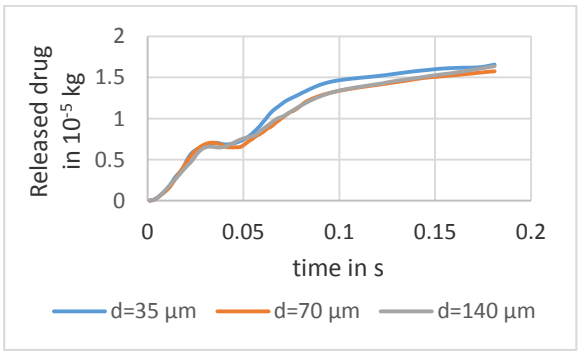
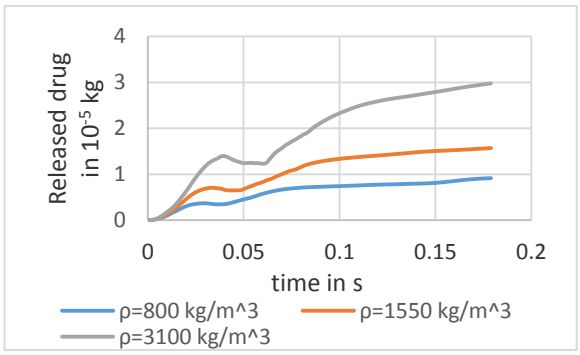
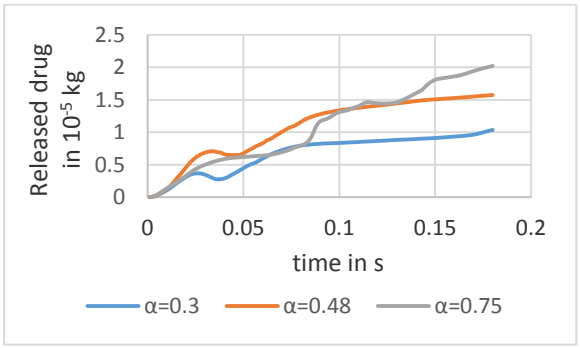
Figure 2 - Comparison of experimental results from Tuley *et al*. [7] with CFD simulation results from ANSYS Fluent [6]. This comparison is for lactose (16% fines) powder. Time before the beginning of emptying excluded.



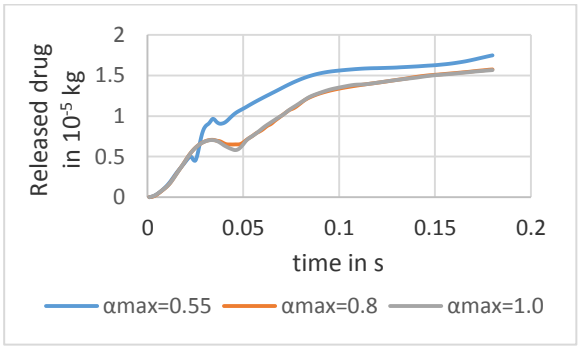
a) Size of particles *d*



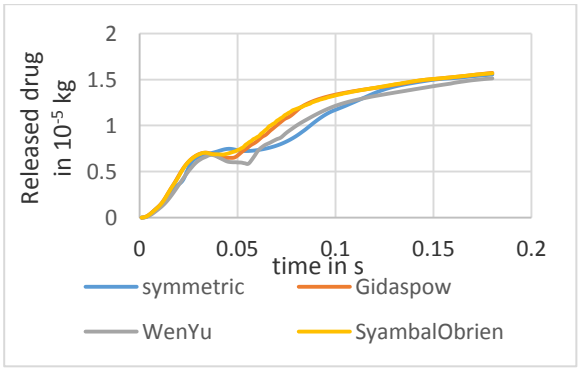
b) Solid density of drug *ρ*



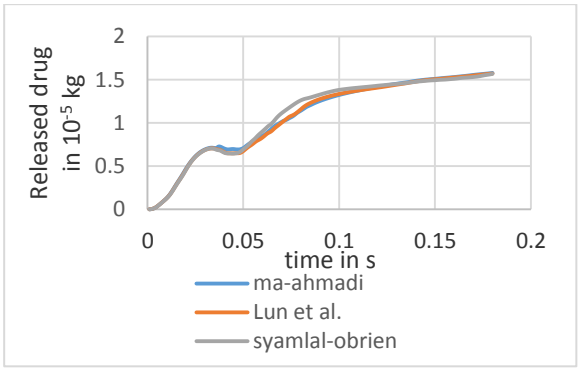
c) Initial volume fraction in powder bed *α*



d) Packing limit α_{max}



e) Model for drag coefficient



f) Model for solids pressure

Figure 3 - Drug emission profiles *M(t)*, when various particle properties or CFD settings were varied while all other properties and settings were kept the same. The CFD solver was ANSYS Fluent [6].

The default settings are: size of particles d = 70 µm, solid density of drug ρ = 1550 kg m^{-3}, initial volume fraction in powder bed α = 0.48, packing limit α_{max} =0.8, model of drag coefficient: Gidaspow, model for solids pressure: Lun *et al*.

Results and discussion

Figure 1 shows good agreement between experimental data and the CFD predictions from Fluent and OpenFOAM when glass powder was used. Not all KTGF sub-models were available in both Fluent and OpenFOAM and thus some differences in the results from these two solvers are to be expected. Similarly, Figure 2 compares experimental data and predictions from Fluent. These predictions can be compared to OpenFOAM results for the same geometry in [2] and are in good agreement. Figure 3 shows the mass of drug released $M(t)$, from the compartment as a function of time, t, when various settings were varied (sensitivity analysis with ANSYS Fluent). It was observed that; (a) the size of drug particles d, (e) the choice of the drag model, and (f) the choice of the solids pressure model had little influence on the release rate. Note that the EE approach used in this study is not capable of modelling cohesive forces between particles. For particles of small size (d < 15 µm) it is known that cohesive forces may significantly influence entrainment behaviour [10]. For this reason the EE approach tested in this study is only relevant for large particles d > 15 µm. Comparison of Figures 1 & 2 shows that the entrainment rate, in terms of (visible) volume fraction, is higher for the lower density lactose powder. This may appear to contradict the results shown in Figure 3b. However, in all of Figure 3 it is the **mass** of drug released that is plotted as a function of time. In the case of Figure 3b the increase in powder density dominates the lower **volumetric** release rate and therefore the rate of mass entrainment is actually higher for higher density powders. In Figure 3c the final total released mass reflects the different initial volume fraction in the powder bed (*i.e*. all powder has been evacuated). However, the results show that if the initial volume fraction α is close to the packing limit α_{max} then the release is somewhat delayed during the initial stages. Figure 3d shows that the mass release rate is only insensitive to the packing limit α_{max} when it is significantly higher than the initial volume fraction in the powder bed (α = 0.48).

Conclusions

In summary, it has been shown that two different CFD solvers can predict the rate of drug entrainment in the chosen geometry with similar accuracy and a preliminary sensitivity analysis has been conducted. It is hoped that these results may be useful in supporting the use of CFD to predict entrainment of drug to aid the design and optimization of DPIs.

References

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