

## A Population Balance Equation - Probability Density Function (PBE-PDF) model for the turbulent dispersion and deagglomeration of inhaled pharmaceutical powders

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### Abstract

A new model is developed for the turbulent dispersion and deagglomeration of aerosol powders. This model has wide application but has particular potential for understanding and improving the effectiveness of pulmonary drug delivery. The model uses a probability density function form of the population balance equation involving closed forms of the non-linear agglomerate birth and death terms thus eliminating the need for high resolution and making it a good candidate model for engineering design. Preliminary validation of the model is conducted against published experiments for the turbulent dispersion of powders in a specially designed deagglomeration rig.

### Introduction

Pulmonary drug delivery is commonly used for the topical treatment of lung diseases such as asthma, bronchitis, and chronic obstructive pulmonary disease. It is potentially an attractive delivery route for the systemic treatment of a much wider range of diseases including diabetes, cystic fibrosis and influenza and in the treatment of acute cancer pain [1]. The advantages of pulmonary delivery over oral and intravenous routes include reduced cost, improved patient safety and increased bioavailability. Among the pulmonary delivery technologies the dry powder inhalers (DPIs) have seen the greatest growth in recent decades driven largely by the simplicity of their operation and absence of harmful propellants. However, while much effort has been expended in designing, manufacturing and marketing novel, user-friendly and affordable devices which are widely used for topical treatments, DPIs continue to exhibit sub-optimum performance (e.g. the drug dispersion varies from 12% to 40% of the loaded dose [2, 3]). Not only do the current combinations of devices and drug formulations result in incomplete dose delivery, more concerning is the large variability in that delivered dosage (the fine particle fraction or FPF) from one use to the next or from one patient to another. While this variability can often be tolerated for drugs with broad therapeutic windows, it is unacceptable for potent systemic drugs; consequently the range of DPI application is severely limited.

The delivery of dry powder drugs to the lungs involves a number of complex and inter-related physical processes. The key processes are powder aerosolisation, deagglomeration (i.e. breakage) of active drug particles from larger carriers and/or drug-only agglomerates, dispersion of the drug aerosols through the airways, and deposition. The effectiveness of these processes in delivering maximum and repeatable dose delivery is dependent on the physico-chemical properties of the powder formulation, the design of the device and the strength of the patient's inspiratory air flow. Aerosolisation and dispersion of powders is quite well understood. Already complementary experimental and CFD research has identified critical design features which enhance those two processes and thus improve DPI performance [4, 5, 6, 7, 8, 9]. However, the process of deagglomeration is much less understood [10]. This is limiting improvements in DPI design; failure of the drug particles to break away from cohesive drug-only agglomerates or adhesive drug-to-carrier agglomerates directly leads to high rates of drug deposition on the DPI walls and in the throat and upper airways. Failure to enhance deagglomeration is a major factor in the observed low and variable rate of deep lung deposition from DPIs [11].

Quantitative experimental observation of deagglomeration is very difficult due to the small size (in the micron range) and short duration (microsecond range) of breakage processes. Discrete element numerical simulation is beginning to shed much needed light on the mechanics of drug powder breakage [12, 13]. But the cost of these simulations, which resolve individual micron sized particles, is very high and application to full scale simulations is not currently possible. For practical application and computational fluid dynamic informed design of DPIs it is necessary to model rather than resolve small scale breakage processes.

Breakage of aerosolised agglomerates occurs by two different mechanisms: i) application of a sudden accelerating force such as caused by collision with a wall; and ii) application of a shear force such as caused by a turbulent eddy. The relative importance of these mechanisms remains contested [1] and the issue can only be resolved by investigating each in isolation. The aim of the current paper is to formulate a CFD-based model for turbulent shear deagglomeration based on the population balance equation (PBE) [15, 16] and to perform preliminary validation against previous experimental data from a deagglomeration rig whereby wall impactions were specifically avoided [14].

The model

### The model

The system under consideration consists of air (the continuous phase) and solid powder particles/agglomerates (the discrete phase). The continuous phase is governed by the well known equations for conservation of mass and momentum. Reynolds average forms of those along with equations for turbulence kinetic energy,  $k$ , and its rate of dissipation,  $\epsilon$ , are solved by a finite-volume method. For the discrete phase we follow the PBE approach to model the number density of particles at each location and time. In general the number density field can be classified according to particle size (volume or length), shape, surface area, etc., but in this work  $N$  is classified according to volume,  $v$ , only. We define  $N(v)$  as the number of particles per unit volume of the continuous phase per unit volume of the discrete phase (dimensions of  $L^{-6}$ ). The zeroth moment of  $N$  is simply the number density of particles across all sizes (dimensions of  $L^{-3}$ ):

$$M_0 = \int_v N dv = N_p \quad (1)$$

while the first moment is the volume fraction of the discrete

phase:

$$M_1 = \int v N dv = v_f. \quad (2)$$

The normalised particle size distribution (PSD), which is of interest to our deagglomeration modelling, is given by  $N(v)/N_p$ .

Although the powder particles are a discrete phase, their number density is a continuous function which is modelled as a continuum according to the population balance equation [15]

$$\frac{\partial N}{\partial t} + \frac{\partial}{\partial x_i} \left( V_i N - D_p \frac{\partial N}{\partial x_i} \right) = \frac{\partial}{\partial v} (GN) + W_{BD}. \quad (3)$$

In the above  $x_i$  is the spatial coordinate,  $V_i = V_i(v)$  is the particle velocity in the  $i$  direction,  $D_p = D_p(v)$  is the Brownian diffusion coefficient,  $G = G(v)$  is the rate of growth of volume due to continuous surface phenomena such as evaporation and condensation ( $G = 0$  for our case), and  $W_{BD} = W_{BD}(v)$  is a source term accounting for discontinuous particle births and deaths due to agglomeration and deagglomeration. A particle of volume  $v$  is born when a larger particle breaks into a number of smaller particles or upon agglomeration of two smaller particles. Similarly a particle of volume  $v$  dies when it breaks or when it agglomerates with another particle. Thus  $W_{BD}$  is the net outcome of births plus deaths due to deagglomeration and births plus deaths due to agglomeration:

$$W_{BD}(v) = W_B^d(v) - W_D^d(v) + W_B^a(v) - W_D^a(v). \quad (4)$$

For dilute powder flows the rates of agglomeration are small and can be safely ignored [18]. The deagglomeration functions are further modelled as [15]

$$W_B^d(v) = \int_v^\infty b(\hat{v}) \mu(v|\hat{v}) N(\hat{v}) d\hat{v} \quad (5)$$

$$W_D^d(v) = b(v) N(v) \quad (6)$$

where  $b(\hat{v})$  is the deagglomeration kernel representing the frequency of breakages of particles of size  $\hat{v}$  and  $\mu(v|\hat{v})$  is the number of particles of size  $v$  resulting from breakage of a larger particle of size  $\hat{v}$ . For the size range of particles considered here, deagglomeration forces are caused by a combination of turbulent shear, drag due to the slip velocity between the discrete and continuous phases and transient acceleration. For particles smaller than the Kolmogorov length scale turbulent shear forces dominate while drag and transient acceleration forces become more important with increasing particle inertia. Initially we make a simplifying assumption that the powders consist of non-inertial particles (Stokes number  $\ll 1$ ) but return to discussion of inertial particles in the final section of the paper. The turbulent shear rate for an eddy of size  $l$  scales as  $\gamma = (\varepsilon/l^2)^{1/3}$ . The peak turbulent shear occurs at the Kolmogorov scale  $l = \eta = (v^3/\varepsilon)^{1/4}$  leading to  $\gamma = (\varepsilon/v)^{1/2}$  ( $v$  is the kinematic viscosity). We use the power-law deagglomeration kernel [19]

$$b(v) = k \gamma^y v^{1/3} \quad (7)$$

where  $k$  and  $y$  are material dependent empirical constants. Simulations are performed for  $y = 0.71$  and  $1.85$  (extreme bounds suggested in the literature [19, 21]) and  $k$  is found by fitting to the experimental data at one flow condition.  $\mu(v|\hat{v})$  is modelled probabilistically according to

$$\mu(v|\hat{v}) = \mu' P(v|\hat{v}). \quad (8)$$

where  $\mu'$  is the number of daughter particles of all sizes and  $P(v|\hat{v})$  is the probability density of the daughter particle size distribution. The literature provides various models for  $\mu'$  and

$P(v|\hat{v})$  [19, 20]. The powder agglomerates considered in this work consist of a large carrier coated by many similar sized fines [14] which we assume break individually by erosive shear rather than a major fracture. We therefore set  $\mu' = 1$  and determine  $P(v|\hat{v})$  by mass and volume conservation constraints. Future work will consider more realistic models.

The PBE holds for either laminar or turbulent flows although any numerical method which attempts to directly solve (3) in a turbulent flow must resolve all the spatial and temporal scales. For most flows of practical relevance full resolution is not computationally affordable and some form of averaging or statistical emulation of the turbulent field is required. Reynolds averaging or spatial filtering of the PBE leaves the non-linear terms unclosed; specifically this affects the terms involving advection, continuous growth and discontinuous births and deaths. It is common to close mean/filtered advection terms using a turbulent diffusivity model. Closure models for the birth and death terms are less obvious. A naive turbulence closure would simply use the mean shear rate based in turn on the mean of  $\varepsilon$ . The effect of this is hard to determine quantitatively without doing detailed modelling, however, given the highly intermittent nature of  $\varepsilon$ , a closure based on its mean value is unlikely to be accurate. An alternative approach to modelling the moments of  $N(v)$  is to model its full probability distribution and in so doing alleviate the closure problem. This method has long been applied to other fields of fluid mechanics such as combustion [22] and has recently been extended to the modelling of population balances by Rigopoulos [16].

We start by approximating the number density as a set of discrete nodal values rather than a continuous function:

$$N(v) = \{N(v_1), \dots, N(v_\alpha), \dots, N(v_M)\} \quad (9)$$

where  $M$  is the number of particle volume classes. The turbulent fluctuations of  $N$  are represented by the one-time, one-point joint probability density function (PDF),  $f_N(n)$  where  $n = \{n_1, \dots, n_\alpha, \dots, n_M\}$  is the sample space of  $N$ . As usual the PDF is normalised so that the integral over all volume classes is unity. The moments of the PDF are useful statistical measures, for example the mean and variance:

$$\langle N \rangle = \int_0^\infty n f_N(n) dn \quad (10)$$

$$\langle N^2 \rangle = \int_0^\infty (n - \langle N \rangle)^2 f_N(n) dn. \quad (11)$$

The advantage of using a PDF method becomes apparent from its transport equation [16]

$$\begin{aligned} \frac{\partial f_N}{\partial t} + V_i \frac{\partial f_N}{\partial x_i} + \frac{\partial W_{BD} f_N}{\partial n_\alpha} = & - \frac{\partial}{\partial x_i} (\langle V_i | n \rangle f_N) \\ & + \frac{\partial}{\partial n_\alpha} \left( \left\langle \frac{\partial}{\partial x_i} \left( D_p \frac{\partial N_\alpha}{\partial x_i} \right) | n \right\rangle f_N \right) \end{aligned} \quad (12)$$

where  $W_{BD}$  is not averaged but instead appears in its exact form. Note that full closure of  $W_{BD}$  requires a model for the instantaneous value of  $\varepsilon$  in order to determine  $\gamma$  in Eq.(7) and this is discussed in the next section. The Brownian diffusive transport has been omitted from Eq.(12) on the assumption that it will be small compared to turbulent mixing. The symbol  $\langle \cdot | \cdot \rangle$  denotes a conditional average. The terms on the right hand side of Eq.(12) need to be modelled and the usual PDF closures suggested in the literature are used here [22, 16]. We draw attention only to the conditional dissipation term which does not have a corollary in the PBE. It represents the molecular dissipation of turbulent variance and is modelled with a mixing model discussed below in the context of the Monte Carlo implementation.

## Monte Carlo implementation

Since the PDF dimension  $M \gg 1$ , in general, solving Eq.(12) via a finite-difference/finite-volume formulation would be prohibitively expensive. Instead a Monte Carlo approach is used whereby  $f_N$  is emulated using an ensemble of statistically independent notional particles each of which represents a single turbulent realisation of the number density,  $N(v)$ . Based on concepts of equivalent systems each particle,  $p$ , in the ensemble is governed by the Ito stochastic differential equations

$$dx_i^{(p)} = \left( \langle V_i \rangle^{(p)} + \left( \frac{\partial D_t}{\partial x_i} \right)^{(p)} \right) dt + \sqrt{2D_t^{(p)}} dw_i \quad (13)$$

$$dN_\alpha^{(p)} = \left( \frac{1}{2\tau_m} \left( N_\alpha^{(p)} - \langle N_\alpha \rangle \right) + W_{BD}^{(p)} \right) dt. \quad (14)$$

In the above  $dw_i$  is a Weiner process (random walk); over a time-step of duration  $\Delta t$  the Weiner increment is  $\Delta w_i = \sqrt{\Delta t} \zeta$  where  $\zeta$  is a normally distributed random variable with a mean of zero and variance of unity. In this work the conditional dissipation on RHS of Eq.(12) is modelled by a simple linear relaxation to the mean mixing model where  $\tau_m$  is mixing time-scale with  $\tau_m^{-1} = 2\langle \varepsilon \rangle / k$ .

The source term  $W_{BD}$  for births and deaths due to deagglomeration is modelled according to Eq.(5) and (6) where the deagglomeration kernel  $b(v)$  is a function of the shear rate  $\gamma = (\varepsilon/l^2)^{1/3}$ . Since the CFD provides only the mean energy dissipation,  $\langle \varepsilon \rangle$ , a model is required for its instantaneous value along trajectories of the Monte Carlo notional particles. In a turbulent flow  $\varepsilon$  is highly intermittent and assumed here to have a lognormal distribution. Following Koch and Pope we model the logarithm of the  $\varepsilon$  as the sum of two independent Orstein-Uhlenbeck (O-U) processes [23]:

$$\ln \left( \frac{\varepsilon(t)}{\langle \varepsilon \rangle} \right) = \phi(t) + \theta(t) \quad (15)$$

$$d\phi = - \left( \phi + \frac{1}{2} \sigma_\phi^2 \right) \frac{dt}{\tau_\phi} + \left( \frac{2\sigma_\phi^2}{\tau_\phi} \right)^{1/2} dw_\phi \quad (16)$$

$$d\theta = - \left( \theta + \frac{1}{2} \sigma_\theta^2 \right) \frac{dt}{\tau_\theta} + \left( \frac{2\sigma_\theta^2}{\tau_\theta} \right)^{1/2} dw_\theta \quad (17)$$

where  $\sigma^2$  are the variances,  $\tau$  the timescales and  $w$  the independent Weiner processes.  $\sigma^2$  and  $\tau$  can be selected (e.g. using DNS data) to match the turbulence characteristics along Lagrangian trajectories. For isotropic, homogeneous turbulence Koch and Pope find the following values [23]:

$$\sigma_\phi = 0.55 \quad (18)$$

$$\tau_\phi = \frac{6.2 \langle k \rangle}{R_\lambda \langle \varepsilon \rangle} \quad (19)$$

$$\sigma_\phi^2 + \sigma_\theta^2 = -0.15 + 0.25 \ln \left( 3.1 R_\lambda^{1/2} + 0.1 R_\lambda^{3/2} \right) \quad (20)$$

$$\tau_\theta = \left( \frac{0.19}{1 + 4/R_\lambda} + \frac{6.8(1 + 4/R_\lambda)}{R_\lambda \ln(0.1 R_\lambda)} \right) \frac{\langle k \rangle}{\langle \varepsilon \rangle}. \quad (21)$$

where the Taylor scale Reynolds number can be modelled as

$$R_\lambda = \frac{u' \lambda}{v} = \frac{2 \langle k \rangle}{3} \left( \frac{15v}{\langle \varepsilon \rangle} \right)^{1/2}. \quad (22)$$

The application of the above to our heterogeneous case (see below) requires greater justification but as will be seen the major characteristics of the energy dissipation field are qualitatively correct.

## Results

Preliminary validation of the new model is performed for the breakage of powder agglomerates comprised of silica primary fines (mean size  $2.5 \mu m$ , 1wt%) and borosilicate glass carriers (mean size  $138 \mu m$ , 99wt%) in the deagglomeration rig reported in Kurkela et al. [14]. The rig incorporates a steady rate powder feeding mechanism with air flows through the walls of the device to minimise wall impactions and agglomerate settling. The dominate breakage mechanism is by turbulent shear with turbulence provided by a central jet of air (an orifice around the power feeder with OD=3.7 mm and ID=1.9 mm); results are reported for jet Reynolds numbers ranging between 7700 and 46000. In the Reynolds averaged flow field is generated by an in-house CFD code [24] while the PDF-PBE equations are solved in a new code developed for this work [18]. As yet two-way momentum coupling between the codes has not been considered.

An important aspect of the method is that the modelled turbulent shear rate characteristics match those of real turbulence. The shear rate is a function of the rate of kinetic energy dissipation,  $\varepsilon$ , which is known to be highly intermittent. Figure 1 (top) shows the instantaneous value of  $\varepsilon$  normalised by the mean value,  $\langle \varepsilon \rangle$ , taken from the CFD solution. The values are for a single Monte Carlo particle over a time of 0.14ms. The intermittency is clearly captured; over most of the time range shown  $\varepsilon/\langle \varepsilon \rangle < 1$  although there are rare extreme values greater than 20. The strong correlation between deagglomeration and extreme values of the shear rate is evident from Fig. 1 (bottom) which shows the mass of powder deagglomerated (for that Monte Carlo particle) normalised by the total powder mass in the system. The gradual period of declining deagglomeration at early times corresponds to the region near the inlet jet where most agglomerates are large and so are easily deagglomerated by the mean flow. Later on the particle sizes are reduced and deagglomeration only coincides with high values of the shear rate.

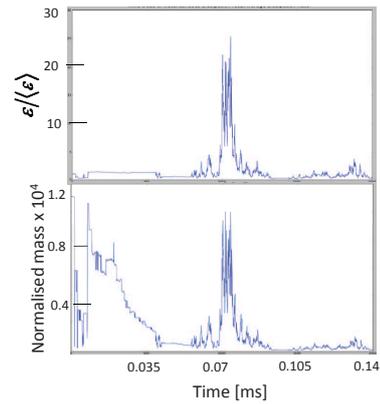


Figure 1: Top: normalised dissipation for a single Monte Carlo particle; Bottom: normalised mass deagglomerated for a single Monte Carlo particle.

The modelled and experimentally observed [14] fraction of primary fines sampled at the exit of the deagglomeration zone of the rig are shown in Fig.2. The experimental data clearly shows the increased fraction of fines due to enhanced deagglomeration at higher turbulence levels (characterised by Reynolds number). Model results are for two different values of the exponent  $y$  in Eq.(7). For each value of  $y$  we tuned the coefficient  $k$  in Eq.(7) to match the experimental data for the Re=46000 flow then maintained the same values of  $y$  and  $k$  for the lower Reynolds

number conditions. We note that these results are preliminary and further analysis is required to fully test model and numerical sensitivities. For  $y = 0.71$  there is a very good match with experimental data although the result obtained for the lowest Reynolds number case has been omitted due to some uncertainty about numerical convergence. For  $y = 1.85$  the model underpredicts the fines fraction by a significant margin.

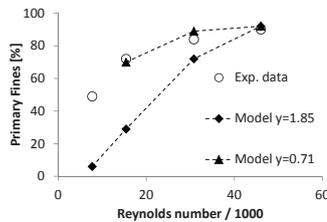


Figure 2: Fine particle fraction as a function of jet Reynolds number.

### Conclusions and extensions

The probability density function form of the population balance equation has been extended to incorporate turbulent deagglomeration of aerosolised powders. The model will have a wide range of application especially in the field of pulmonary drug delivery. The major features of the model are reported along with its Monte Carlo implementation and the model for the intermittent rate of turbulence energy dissipation. Preliminary validation against experimental data shows that the model can accurately predict deagglomeration provided empirical constants for the breakage kernel are properly selected.

A major simplification in this modelling is the assumption of non-inertial powder particles. However, most drug formulations developed for dry powder inhalers contain agglomerates of sufficient size to guarantee that the Stokes numbers  $\gg 1$ . Therefore inertial effects should be considered and this is the subject of ongoing research. Whereas the PDF of number density for non-inertial particles has been given the phase space  $n = \{n_1, \dots, n_\alpha, \dots, n_M\}$ , for inertial particles we will extend that space to include both particle velocity,  $V_p$ , and fluid velocity seen along the particle trajectories,  $U_s$ , i.e. the PDF to be solved is  $f_N(n, v_p, u_s; x, t)$ . The PDF transport equation then becomes [25]

$$\frac{\partial f_N}{\partial t} + V_i \frac{\partial f_N}{\partial x_i} + \frac{\partial W_{BD} f_N}{\partial n_\alpha} = \frac{\partial}{\partial n_\alpha} \left( \left\langle \frac{\partial}{\partial x_i} \left( D_p \frac{\partial N_\alpha}{\partial x_i} \right) \right| n, v_p, u_s \right\rangle f_N \right) - \frac{\partial}{\partial v_{p,i}} \left( \langle A_{p,i} | n, v_p, u_s \rangle f_N \right) - \frac{\partial}{\partial u_{s,i}} \left( \langle A_{s,i} | n, v_p, u_s \rangle f_N \right) \quad (23)$$

where  $A_p$  and  $A_s$  are the particle and "seen" fluid accelerations, respectively.

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