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On computational control of flow in airblast atomisers for pulmonary drug delivery

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Abstract

Among different approaches to successful pharmacotherapy the pulmonary drug delivery (PDD) mode plays an increasingly important role. In this paper PDD systems based on air-blast atomisation have been analysed mathematically. In order to allow the bioengineer to estimate the degree of effectiveness of a specific system prototype and to lay the basic principles for design, a conservation-law-based mathematical model is discussed. Key control parameters that allow improvement in the efficiency of the system have been identified and main characteristics of the system have been analysed numerically as functions of these parameters.

Keywords: Pulmonary drug delivery systems; Airblast atomisation; Mathematical models

1. Introduction

Pulmonary drug delivery (PDD) has fundamental advantages for therapy of diseases of the respiratory tract, including asthma and chronic obstructive pulmonary diseases (COPD), because it is site-directed (Gonda et al., 1998; Mather et al., 1998; Taylor and McCallion, 1997; Waldrep, 1998; Ward et al., 1997; Yu and Chien, 1997). In the treatment of respiratory diseases in particular, the lung is a natural portal and inhalation drug therapy (IDT) is widely accepted by patients and has proven effective. Moreover, due to its ability to provide a huge but extremely thin absorptive 'viscous' membrane, the lung is also a very promising portal for non-invasive means for systemic delivery of peptide/protein-based therapeutic agents into bloodstream. As a result, biotherapeutics for delivery of drugs via pulmonary route undergo extensive controlled clinical trials worldwide and patient-friendly administration of these drugs remains one of the greatest challenges facing the pharmaceutical and biotechnology industries (Adjei and Gupta, 1997). Since drugs delivered to the lungs can normally achieve a rapid therapeutic effect with the potential for minimising adverse side effects, there is clear evidence to suggest that potentially PDD

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can be seen as an alternative way to deliver unstable, peptide-based bio-technology delivered drugs which are typically delivered by injection (Ward et al., 1997).

In addition to clinical trials for needs of the diabetes market (dominated currently by the insulin administration), inhaled drugs have been tested for treatment of emphysema, cystic fibrosis, multiple sclerosis, side effects of cancer thermotherapy, for reduction of the symptoms of influenza, chronic persistent pain, as well as for pain management including the non-invasive systemic administration of morphine for patients with cancer, headache, for post-operative and organ-transplant patients (Ward et al., 1997). Moreover, even some vaccinations might be in future replaced by inhaled formulations. Although other modes of drug delivery (in particular, the oral mode) still dominate the market, current scientific studies (Yu and Chien, 1997) have led to growing attention to the potential of a pulmonary route in the scientific communities of medical professionals and bioengineers, as well as to an increasing interest from pharmaceutical companies. This attention and the interest are not surprising if we recall that, taken the United States alone, pneumonia, chronic bronchitis, and asthma account for more than 30 million visits a year to practitioners, and about 27% of the current drug delivery market in the country comes from inhalation of drugs for lung diseases. It is estimated that the worldwide market of drugs to treat just respiratory diseases, not to mention others, will exceed US$21 billion by the year 2005.

The rapid growth of pulmonary delivery of drugs is facilitated by many advantages of drugs inhaled into the lungs over other delivery methods such as oral (i.e. tablets, capsules), injections, etc. These advantages include (a) quick and effective access to the lung and bloodstream; (b) smaller doses due to direct delivery, and therefore fewer side effects compared to other delivery methods, in particular, oral; (b) non-invasiveness, unlike injections; (c) suitability for a wide range of molecules; (d) patient convenience. Although experimental work has been extensive and clinical needs in pulmonary delivery is well recognised, bioengineering aspects of PDD systems have not been addressed in the literature with the vigour they deserve. Due to technological advances PDD systems become smaller (Keller, 1999), and further minuaturisation of such systems leads to the situation where the evaluation of their effectiveness at the development stage with simple and robust mathematical models becomes an important direction in bioengineering research.

2. Pulmonary drug delivery systems

In most cases the operation of a PDD system is based on the fact that a vapour, droplets, or a powder composition of medicine is inhaled and transported by the air stream to the lung. The lung takes inhaled breaths of air and distributes them deep into the tissue to a very large surface consisting of a series of sacs of the order of one-half billion, and known as alveolar epithelium, which is ~ 100 m^2 for an average adult. This very large surface of sacs (alveoli) are enveloped by an equally large capillary network. As a result of high drug absorption through the deep lung into the bloodstream, the lung is a natural target for a number of useful drugs including biomolecules. Note that is an essential advantage compared to other routes of delivery of drugs, such as oral, transdermal and nasal which have not generally been very effective in delivering large molecules therapeutics.

Generation of therapeutic aerosols producing particles targeting the lungs can be achieved by various types of PDD systems including (Keller, 1999)

- ultrasonic nebulizers;
- metered dose inhalers (MDI);
- dry powder inhalers (DPI);
- airblast atomisers;
- smart ('droplet-on-demand') inhalers, etc.

MDIs were first to come to the market of IDT. Originally developed in the 1950's MDIs have been continuously evolved into newer generations of the aerosol drug delivery systems (Keller, 1999) and they continue to dominate the market of delivering medication to the lungs, in particular for asthma and COPD patients (Clark, 1996). As a rule, the patient using these devices must coordi-

nate inhalation to achieve an optimal treatment. However, a major problem with current MDIs lies with the fact that using them we cannot go deep into lungs due to insufficient minimisation of deposition in the upper airways leading to a situation where typically about 20% of the MDI output only reaches the lungs. Not only do the wasted amount, typically deposited in the throat and mouth, costs to the pharmaceutical industry estimated $750 million per year, but it also can cause some side effects. Therefore, MDIs are still far from optimal, to say the least. Moreover, in some case in the design of MDIs the industry uses environmentally unfriendly aerosol propellants, such as CFC, which in addition are often inefficient in mixtures with biomolecules such as peptides and proteins.

Due to the fact that without any use of CFC DPIs can deliver (dry powder) formulations for peptides and proteins, these PDD systems have become quite popular in recent years. However, since in DPIs, typically based on spray-drying process technology, the solid form of drugs must facilitate rapid and complete deployment as an aerosol at the point of delivery it is very difficult to achieve high efficiency of such systems, because in order to achieve high efficiency this dry powder aerosol should be quickly dissolved in the liquid. Moreover, since there is not enough energy in a human inhalation to efficiently break apart very fine powder clumps, this leads to different velocity of particles and hence dosing variabilities etc. As a result, similar to MDIs, in applications of DPIs only $5-30\%$ of the total aerosol dose can be deposited in the lower respiratory track.

In many cases generation of therapeutic aerosols producing particles targeting the lungs can be achieved effectively using nebulizers (Waldrep, 1998). These PDD systems are usually based on ultrasonic technology and are typically fed with the *liquid* drug. In addition to traditional pharmaceutical applications these systems have now been developed for delivery of proteins, peptides and other large molecules to the lungs for absorption into the bloodstream. However, they often produce a large range of droplet sizes which could be too large to reach the deep lungs efficiently (Waldrep, 1998).

The last, but not the least in our short survey of PDD systems is the airblast atomisers. Due to their huge potential PDD systems based on airblast atomisation become very popular in practice and theory of bioengineering applications of IDT. Such systems will be the main topic of discussion in the remaining sections of this paper. The recent analysis (Dunbar et al., 1998) revealed that over a wide range of atomiser operating conditions the airblast atomiser produce droplet sizes 4–10 times smaller compared to its ultrasonic nebulizer counterpart. The reported droplet size was under 5 μm range at about $d = 4.5–4.8$ μm, where d denotes the Sauter mean diameter. Note that in traditional applications of IDT such as asthma and COPD medicine should be delivered to the lungs as aerosols up to 6–10 μm (Keller, 1999). The reduction of this size even further is not impossible and would help to deliver high number density macromolecules to the systemic circulation by inhalation. Such inhalation therapies are currently under investigation (Edwards et al., 1998) and for most of them aerosols have to be designed to comprise of small droplets of approximate density 1 g/cm^3 and the mean geometric diameter of 1–3 μm in order to achieve penetration into the airways or lung periphery. This density, equal to the density of water, and the 3 μm diameter of droplets were chosen for all our computational experiments reported in this paper.

The design of new PDD systems that may allow targeting the deposition of fine drug droplets to specific sites into the lungs at predetermined inhalation flow rates can be facilitated with the development of mathematical models allowing estimation of the key characteristics of liquid flow including its rate and velocity at the point of drug release. Some aspects of mathematical modelling of such traditional PDD systems as ultrasonic nebulizers, MDI, and DPI have received an increasing interest in pharmaceutical and bioengineering literature (see, e.g., Clark, 1996; Keller, 1999; Taylor and McCallion, 1997; Dunbar et al., 1998 as well as references therein). Although, as we have mentioned above, there is evidence to suggest that air-blast atomisers can outperform such traditional devices, results on mathematical modelling of PDD systems based on air-blast

atomisation are practically absent. It is a major goal of the sections that follow to fill this gap and to present both general principles of modelling of such systems, as well as a simple mathematical model that allows to estimate the degree of effectiveness of a specific PDD air-blast atomiser.

3. Airblast atomisers in inhalation drug therapy: principles of operation

The effect produced by the kinetic energy of a flowing airstream to shatter the liquid jet or sheet into droplets has been used for a long time in many different applications with a growing interest since the mid-1960s, facilitated by airblast and air-assist atomisers used in energy and aerospace industries (El-Shanawany and Lefebvre, 1980; Lefebvre, 1989). Due to many advantages of airblast atomisers over their counterparts, i.e. pressure atomisers, airblast atomisation of liquid has been used in such diverse areas as deposition and coating processes, evaporative cooling and drying processes, energy conversion systems, etc. (Lefebvre, 1989; Perry, 1984). Nevertheless, applications and especially rigorous studies of airblast atomisers for delivery of drugs are of relatively recent origin. In contrast to other applications of droplet-laden flows (Noymer, 2000) where much larger scales have to be considered, in PDD applications we often have to create and transport sufficiently *small droplets deep into the lungs by using a small, effective, and patient friendly breath-actuated system* (Keller, 1999).

In this paper, we limit ourselves by a specific class of airblast atomisers. However, the mathematical technique developed in the next sections could be useful for other PDD systems, such as plain-jet, venturi, thermal or piezoelectric drop-on-demand systems, etc, which are different from the considered systems in such elements of design as (a) the breakup mechanism of the liquid into droplets, and/or (b) the method by which the liquid is drawn into the air stream. Indeed, conceptually all these atomisers are similar. They can operate efficiently only under relatively slow liquid flow rates (Dombrowski and Munday, 1968), and from a physical point of view in all these cases we have to deal with mass transfer due to the liquid-in-air dispersion. Moreover, PDD systems based on venturi, nozzles, orifices 'obstructions' are identical from an operational point of view in a sense that the velocity of flow upstream and downstream is found as a function of the pressure change across a section of the system (Kenyon, 1960, p. 191) with a decrease in pressure accompanied by an increase in speed and governed by the Bernoulli law. Having said that and given the requirement that the design of airblast atomisers for PDD should be kept simple, we consider a typical design block consisting of a cylindrical tube with a central reservoir inside containing *liquid drugs* (Fig. 1). Such design configurations can be used for PDD prototype devices, as well as for components in designing electronic lung devices and simulators, allowing simulations of different flow rate conditions (e.g. Brindley et al., 1994; Burnell et al., 1998). Recall that the inability to vary flow rates is considered to be one of the major drawbacks in the current designs of electronic lung simulators (see, e.g. Finlay and Gehmlich, 2000). The cylindrical tube that we use as a basic element in the design can be made as clear in order to allow the patient and practitioner to know immediately whether a full dose of medicine has been inhaled (of course, where appropriate, the system could be supplemented by electronic control of the total dispensed volume (Gonda et al., 1998)). The reservoir has a slot for release of liquid droplets due to Bernoulli's principle, provided the sufficient kinetic energy of the air-stream. If the slot is

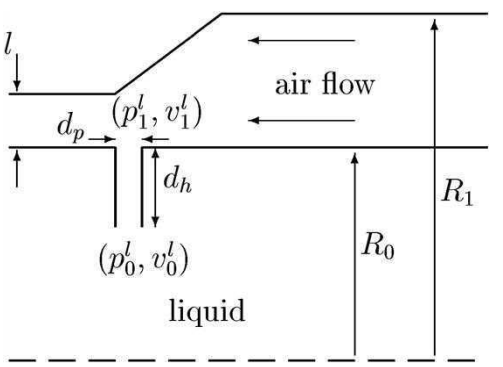

Fig. 1. Schematic of a typical airblast atomiser geometry.

sufficiently thin one can consider it as a prefilming tool for the liquid jet that allows first to spread out the liquid in a thin continuous sheet before it is impacted by the inhaled air stream. Our analysis covers also the situation where the 'slot' serves as a multi-hole nozzle with the liquid flowing through a number of radially drilled plain circular holes, located all around the circumference of the slot. The liquid is ejected from these holes from which it emerges in the form of many small discrete jets merging together in a 'sheet' that enters an inhaled airstream, and then undergo in-flight disintegration without any further preparation such as filming (Lefebvre, 1989).

Due to its inherent simplicity, the airblast concept lends itself to a wide variety of design configurations with the same basic objective, that is to deploy the available inhaled air in the most effective manner to achieve the best possible level of atomisation (Lefebvre, 1989, p.142). Of course, due to an enormous diversity of possible designs (caused, for example, by the use of nozzles different from those described above (Schmidt and Sojka, 1999; de Heij et al., 1999) it is possible that a slight change in geometry may lead to substantial differences in the characteristics of the PDD system. In such a situation it is more natural to provide the bioengineer with a comprehensive mathematical model that gives some general guidelines for modelling and design of these PDD systems rather than to try to cover in details all possibilities in an attempt to develop design rules for all PDD airblast atomisers. Therefore, in what follows we concentrate on a representative example of PDD airblast atomisers where we have to deal with the flow through orifice obstacles or venturi tubes or combination of both (Bird et al., 1960, p. 470). Since air-blast PDD systems have typically to be tested over a wide range of drugs with different viscosities and surface tensions, we aim at the development of a *simple* mathematical model that will allow to assist quickly such testing procedures.

As a first step, we formulate a simple criterion in order to verify operating conditions of the system. After the liquid appears from the slot in the form of a sheet (or in the form of sufficiently many jets that can be well approximated by a sheet (Lefebvre, 1989, p. 59), it emerges into the flowing air stream, and its subsequent development depends very much on its initial velocity, as well as the velocity and the flow rate of the air. It is natural, therefore, to consider these parameters as key control variables in the analysis of operating characteristics of the system. In the general case there are many different mechanisms involved in expanding the sheet against the contacting surface tension force, for example by using pressure forces in pressure-swirl atomisers or centrifugal forces for rotary atomisers. The breakup of a sheet of liquid into droplets in this case is due to a competition between air forces and surface tension (Lefebvre, 1989). Surface tension forces try to return a perturbation of the liquid sheet, arisen due to Bernoulli's principle, back to its original position. However, the air experiences a local decrease in static pressure, corresponding to the local increase in velocity, that tends to expand the perturbation farther outwards.

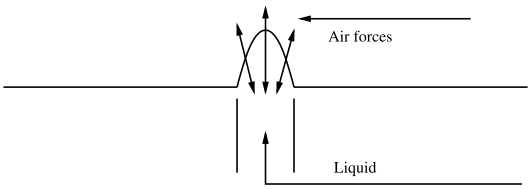

Fig. 2. Forces at the interface of a liquid sheet moving in air.

Mathematically, this means that if we assume for a moment that the sheet of liquid is 'flat' we can write a balance equation at the boundary between the liquid and the air (Fig. 2) connecting the displacement of liquid from the equilibrium position, the difference between liquid and air pressures, p^{l} and p^{a}, respectively, and the liquid surface tension, σ. The main prerequisite for the system to operate is to generate enough pressure to break fluid into droplets efficiently, that is to ensure that

$$\frac{1}{2}\rho_{\mathrm{l}}([v_1^{\mathrm{l}}]-[v_0^{\mathrm{l}}]^2)=p_0^{\mathrm{l}}-p_1^{\mathrm{l}}\gg p_{\mathrm{int}}, \tag{1}$$

where $\Delta=p_1^{\mathrm{l}}-p_0^{\mathrm{l}}$ is the liquid pressure drop ($\Delta p<0$) due to Bernoulli's principle, and p_{int} is the total internal pressure of the liquid. As we show in Section 4, by estimating the average

number of droplets generated on a specified time scale (say, in 1 s), and the desired average diameter of droplets (assuming their spherical shape) the surface energy of these droplets can be easily calculated. Then the key control parameters in the process of PDD will be the air flow rate W_0^a and *the exit area of the flow* into the droplet formation region, bounded by the edge of the orifice and the reservoir. Hence, having computed the surface energy, the plot of kinetic energy of the air as a function of the air flow rate and the flow exit area becomes a useful visualisation tool in determining the productivity of PDD systems in breaking surface tension of liquid drugs. A typical dependency is given in Fig. 3 where for the upper left graph W_0^a was taken at 0.55×10^{-3}m^3/s The inclusion of the air flow rate into the set of parameters under investigation is due to the fact that, contrary to other routes of applications, in IDT the patient usually plays an active role and in some cases successful lung delivery depends on the patient's ability to operate the air flow system, which may be by inhalation (Keller, 1999).

An important comment should be made in favour of tools of mathematical modelling in this field. The current methodologies used in aerosol medicine and pharmaceutical industry to compare the performance of different PDD devices have a typical drawback that different devices are compared at the same flow rate (e.g. Brindley et al., 1994 and references therein). Certainly, this could be far from correct in realistic medical trials, and more and more authors agree that the requirement of a constant air flow rate has been viewed as a principle drawback (Finlay and Gehmlich, 2000). Nevertheless, many interesting results are currently available on comparison characteristics of different devices obtained by using different types 'electronic lung' simulators (e.g. Burnell et al., 1998). What is important to understand is that by using mathematical models the performance of prototype devices can often be evaluated over a

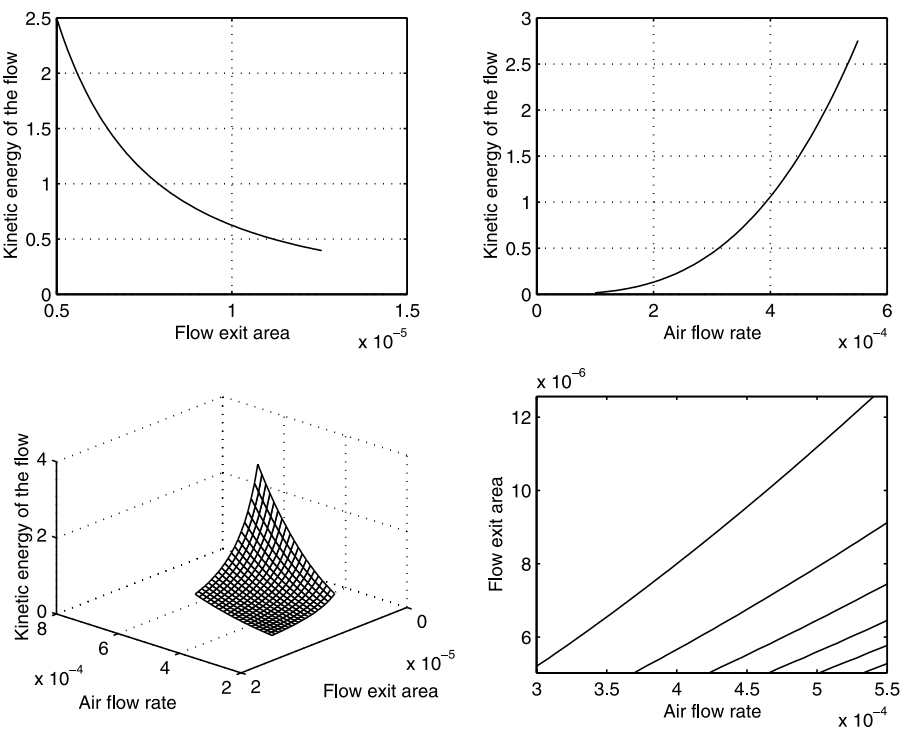

Fig. 3. Kinetic energy for breaking surface tension of the liquid as a function of the inhalation rate and the exit area of the flow into the droplet formation region.

wide range of conditions, allowing to remove the assumption of constant flow rates. Such mathematical models can help also in designing inhalation simulators themselves. To vary parameters in mathematical models much easier compared to prototype devices and simulators.

The physical processes involved in atomisation are not yet sufficiently well understood for mean diameters of droplets to be expressed in terms of equations derived from first principles (Lefebvre, 1989, p. 201). Nevertheless there exist quite efficient empirical formulae for approximating the effective droplet size in specific situations. In particular, in the situations analogous to those described above we can assume that the effective droplet size generated by the airblast atomiser for PDD applications can be determined by the normalised Sauter (surface mean) diameter using the following approximation (in the dimensionally correct form)

$$\frac{d}{l_c} = \alpha_1\left[\frac{\sigma}{\rho_a[v_1^a]^2 d_p}\right]^{\beta_1}\left[\frac{\rho_1}{\rho_a}\right]^{\beta_2}\left[1+\frac{W_1^l}{W_1^a}\right] + \alpha_2\left[\frac{\mu_1^2}{\sigma\rho_1 d_p}\right]^{\beta_3}\left[1+\frac{W_1^l}{W_1^a}\right], \quad (2)$$

where ρ_1 and ρ_a are the densities of the liquid and the air, respectively, $\mu_1 = \rho_1 v_1$ is the dynamic viscosity of the liquid, $v_1{}^a$ is the velocity of the air in the flow exit point (FEA), l_c is the characteristic dimension of the system, d_p is the 'prefilmer' diameter, set 1 for plain-jet designs (Lefebvre, 1989, p. 238), $W_1{}^a$ and $W_1{}^l$ are the mass flow rate of air and liquid in the FEA, respectively. One term in the sum in the right hand side of (Eq. (2)) is dominated by the relative velocity and surface tension and the other by viscosity. For liquid of low viscosity this expression shows that the mean droplet size is inversely proportional to the relative velocity between the air and the liquid, while for large values of air/liquid ratio the influence of viscosity on SMD becomes negligibly small. The choice of α_i, $i = 1, 2$ and β_j, $j = 1, 2, 3$ in (Eq. (2)) is made from fitting experimental data. Since most of experimental studies to validate empirical formulae such as (Eq. (2)) reported in the literature are typically conducted for a single atomiser with fixed size and geometry (Dunbar et al., 1998), we do not pursue these issues further in this paper. We note only that the effective droplet size for most of PDD airblast atomisers including the types of designs analogous to those of the Nukiyama–Tanasawa, the Lorenzetto–Lefebvre, Jasuja–Cranfield designs (Dombrowski and Munday, 1968; Lefebvre, 1989) can be well approximated by formula (Eq. (2)). Furthermore, since small droplets might not be deposited because they might stay airborne, and since large droplets might hit the wall too early, in order to estimate the amount of medicine that can be carried out to the alveoli by the inhalation air stream, the primary role in the design of PDD systems will play such characteristics of the flow as *the flow rate and its velocity*. Indeed, given $W_0{}^a$, the efficiency of liquid atomisation is determined by the geometry of the capillary slot and the FEA. The latter changes the initial air flow rate from $W_0{}^a$ to $W_1{}^a$. The dependency of the general performance of PDD systems on these parameters will be analysed in the next sections.

Finally, we mention that the characteristic length in (Eq. (2)) can be chosen in terms of the dimensions of the slot. In some cases, the length can be chosen in terms of dimensions of the nozzles, although we note that for the liquid of low viscosity the latter choice seems to have little influence on some key performance characteristics of the system (Lefebvre, 1989, p. 240). Alternatively, l_c can be taken in terms of the dimensions of the exit area of the air flow, i.e. l where $0 \leqslant l \leqslant R_1 - R_0$. As far as we know there has been no comprehensive experimental test results published for PDD airblast atomisers over wide range of design and operating variables. Some aspects of such studies and comparison with other technological ideas, such as those implemented in ultrasonic nebulizers and drop-on-demand devices, can be found in Dunbar et al. (1998), de Heij et al. (1999).

The design of PDD devices can be affected by the velocity in the air flow and by those characteristics of the flow that we have already discussed. However, there are other characteristics and effects that have remained unattended so far, e.g. the settling effects of the particles, in particular gravitational and electrostatic effects, and other

losses, not only in the airways to specific sites, but also to the walls of the device (see Section 2, and Haber et al., 2001). Particle size distributions are important in discussing these effects. The aerolisation of the drug depends upon the energy input by the patient (Brindley et al., 1994), and we account for this by introducing a parametric dependency related to the air flow rate, W_0[a], into the model. The deposition patterns of aerolised drugs may be also effected by this parameter (see also Brindley et al., 1994). The deposition of particles can be evaluated by using several known techniques, e.g. those described in Burnell et al. (1998). In its general setting, the problem of the particle losses should be considered in conjunction with a more general problem of assessing lung deposition of inhaled medications. It is a complicated problem because surface tension in the thin liquid film lining the airways and walls can cause an instability in the film which, in the case of airways, may lead eventually to closure of the airways. To evaluate this properly one needs to couple our model with a model based on lubrication theory (e.g. Cassidy et al., 1999). A detailed discussion of this issue lies outside the scope of the present paper, and we refer the interested reader to a recent survey (Snell and Ganderton, 1999) where several techniques for evaluating the loss/deposition of particles can be traced down, as well as to Burnell et al. (1998) for further discussions and references.

In what follows, we perform a mathematical analysis of the processes involving PDD systems using the key control parameters identified above.

4. Mathematical model for mixed air-fluid flow in PDD systems and computational experiments

Computational models based on mathematical equations describing various transport processes and pulmonary flows provide an indispensable tool in respiratory medicine. In its essence, most such models originate from conservation laws which provide also a firm foundation for an efficient treatment of many problems in biophysics, mathematical biology, bioengineering, and medicine. Based on this foundation, we derive a robust mathematical model that should be helpful in estimating the degree of effectiveness of PDD prototype systems based on air-blast atomisation principles. A range of issues connected with the construction of mathematical models for such air-blast systems, the definition of key control parameters, and the application of the models for evaluating the effectiveness of the systems have not received due attention in the existing literature. In its general setting, the problem we are dealing with in this paper is fairly complex. Indeed, the PDD system cannot be considered in isolation with respect to the patient. Therefore, many complex phenomena and effects are coming into plays such as those related to extremely complicated geometry of the lung airways (Section 2), wall uptake, both in the device due to particle losses and in the lung airways, the surface tension arising at the interface between the liquid lining and the air within the lung. Mathematical modelling of these phenomena and effects lie outside the scope of the present paper. Neither we do study any transport phenomena related to the path of inhaled particles to the upper airways and then to the tracheo–bronchial tree. These issues received a comprehensive attention in the recent publications found in a comprehensive survey by Grotberg (2001). Our main focus in this paper is on basic principles for design of PDD air-blast atomisers, and on constructing a conservation-law-based mathematical model that would allow to estimate the degree of effectiveness of such devices.

The dynamics of flow in PDD systems is governed by the three energy balance equations written below in the differential form (Slattery, 1999);

momentum balance

$$\rho\left[\frac{\partial v}{\partial t}+(\nabla\mathbf{v})\cdot\mathbf{v}\right]=-\nabla p+\mathrm{div}\mathbf{s}+\rho\mathbf{f}; \tag{3}$$

mass balance

$$\frac{\partial\rho}{\partial t}+\mathrm{div}(\rho\mathbf{v})=0; \tag{4}$$

and energy balance

$$\rho\frac{\mathrm{d}_{\mathrm{m}}e}{\mathrm{d}t}=-\mathrm{div}\mathbf{q}-p\,\mathrm{div}\mathbf{v}+\mathrm{tr}(\mathbf{s}\cdot\nabla\mathbf{v})+\rho Q; \tag{5}$$

where $\mathbf{s}$ is the viscous part of the stress tensor $\boldsymbol{\sigma} = -p\mathbf{I} + \mathbf{s}$, p is the mean pressure, e is the internal energy per unit mass, ρ, $\mathbf{v}$ are the density and velocity of the flow, respectively, $\mathbf{f}$ is the external and mutual forces per unit mass, $\mathrm{d_m}/\mathrm{d}t$ denotes the material time derivative, Q is the external and mutual energy transmission rates per unit mass, $\mathbf{q}$ is the energy flux function, and the term $\mathrm{tr}(\mathbf{s}\cdot\nabla\mathbf{v})$ models a dissipative function due to irreversible work of viscous forces.

The Eqs. (3)–(5) provide us with a starting point in deriving simple and robust mathematical models in specific cases of PDD applications. For example, in a number of PDD applications it is reasonable to assume a constant density flow, in which case the equation for balance of mass (Eq. (4)) can be written in the form

$$\frac{v_1^{\mathrm{a}}}{v_0^{\mathrm{a}}} = \frac{1}{\beta}, \tag{6}$$

where $\beta = A_0/A_1$ with A_0 and A_1 being cross section areas of initially inhaled air flow and the flow at the exit point. Then, the macroscopic balances can be considered for time-independent iso-thermal flow behaviour. In this case of steady isothermal systems we can follow (Bird et al., 1960) to reduce the energy balance Eq. (5) for the air component of the flow to the (mechanical) energy balance in the form of generalised Bernoulli equation

$$\frac{1}{2}([v_1^{\mathrm{a}}]^2 - [v_0^{\mathrm{a}}]^2) + \frac{1}{\rho_{\mathrm{a}}}(p_1^{\mathrm{a}} - p_0^{\mathrm{a}}) + \hat{Q}_{\mathrm{v}} = 0, \tag{7}$$

where $\hat{Q}_{\mathrm{v}} = Q_{\mathrm{v}}/w$, w is the mass rate of flow, and Q_{v} is the rate at which mechanical energy is irreversibly converted to thermal energy (i.e. 'friction loss') determined as

$$Q_{\mathrm{v}} = -\int_V (\mathbf{s}:\nabla\mathbf{v})\mathrm{d}V, \tag{8}$$

i.e. (Eq. (8)) is the integral of the local rate of dissipation of mechanical energy over the volume of the entire system. Since in most PDD applications its contribution can be neglected, we arrive at the classical Bernoulli equation. In particular, we can find the flow pressure drop (Δp) in the flow exit area (Section 3) using the following formula

$$\frac{\Delta p}{\rho_{\mathrm{a}}} = \frac{1}{2}([v_1^{\mathrm{a}}]^2 - [v_0^{\mathrm{a}}]^2). \tag{9}$$

As expected, the momentum equation confirms a decrease in the pressure (Bird et al., 1960). The velocities of flow present in Eq. (9) can be determined by the ratio between $W_0{}^{\mathrm{a}}$ and the corresponding cross-section areas to give

$$\frac{\Delta p}{\rho_a} = \frac{(W_0^a)^2}{2\pi^2}\left[\frac{1}{4R_0^2 l^2} - \frac{1}{(R_1^2 - R_0^2)^2}\right] \tag{10}$$

Finally, we consider the momentum equation for the liquid component of the flow in the slot. Since for Newtonian fluids (Slattery, 1999) we have

$$\mathbf{s} = \lambda \mathrm{div}\mathbf{v}\mathbf{I} + 2\mu\mathbf{D}, \tag{11}$$

the momentum balance Eq. (3) written for the liquid component of the flow can be reduced in this case to the Navier–Stokes equation which for incompressible fluids ($\mathbf{s} = 2\mu\mathbf{D}$) in the steady-state case has the form

$$\rho\,\mathbf{v}\cdot\nabla\mathbf{v} = -\nabla p + \mu\nabla^2\mathbf{v} + \rho\mathbf{f}. \tag{12}$$

In Eq. (11) and Eq. (12), we use the standard notation that is $\mathbf{D} = [\nabla\mathbf{v} + (\nabla\mathbf{v})^{\mathrm{T}}]/2$ for the rate of deformation tensor, μ for the shear viscosity of the fluid, and $\lambda = k - 2\mu/3$ where k is the bulk viscosity. Note that the efficiency control of PDD systems can be determined through the analysis of how the initial rate and the velocity of the flow change in the presence of a capillary slot that releases the liquid drugs. These two characteristics can be obtained as functions of geometric parameters of the systems such as slot dimensions, i.e. d_{p} and d_{h} (Fig. 1), and the cross-sectional exit area. In some cases the general 3D Eq. (12) can be reduced to a one-dimensional one by assuming that $\mathbf{v} = \mathbf{v}(0,0,u(x))$ and using a standard procedure described in Bird et al. (1960) p. 299. This procedure was applied in the case of cylindrical coordinates to yield plane Poisselle flow in the slot (e.g. Jenkins, 1999), which gives the following simple expression for the liquid flow rate in the slot:

$$W_1^l = \frac{\pi\Delta p}{6\mu_l p_l}\frac{(R_0 - d_h)}{d_h}d_p^3 \tag{13}$$

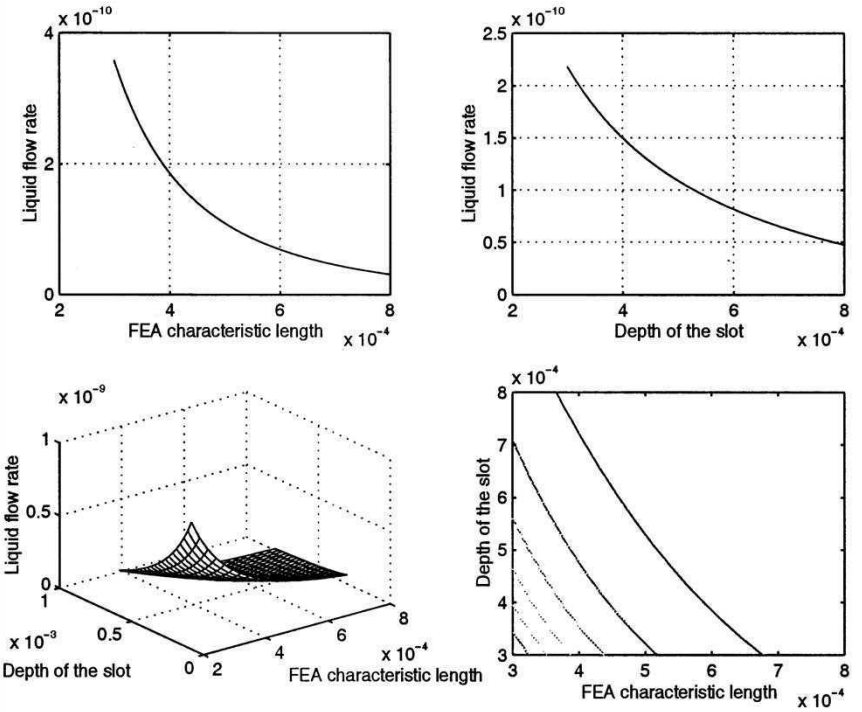

Fig. 4. Flow rate of the liquid as a function of the characteristic length of the exit area and the slot dimensions.

In the above expression we assume that the slot goes all around the circumference of the reservoir, and has therefore a ring-shaped cross-sectional area with parameters R_0 and d_h (Fig. 1). Finally, having W_l^1, the velocity in the capillary slot can be found as the ratio between W_l^1 and the corresponding (in our case the ring-shaped) cross-sectional area. This strategy allows one to control the system efficiency via the dimensions of the slot and the cross-sectional exit area of the flow.

It can be seen that under the simplifying assumptions discussed above if we vary the diameter of the slot while leaving all other parameters fixed, then the dependency of the flow rate on this diameter is cubic, that is $W_l^1 = A\ d_p^3$. So the amount of liquid delivered increases as d_p is increased, although this will result in correspondingly larger drops. On the other hand, if we vary the 'depth' of the slot, while leaving all other parameters fixed, we have the inversely proportional dependency of the flow rate on this 'depth', that is $W_l^1 = B/d_h + C$, where A, B, and C are constants. In this case the dependency of the flow rate on the dimensions of the slot, in particular d_h, and the dimensions of the cross-sectional exit area of the flow, in particular l, is demonstrated by Fig. 4. Typical data for our computational experiments is given in Table 1. For example, taking all parameters from this table and using the developed strategy we can estimate that $\Delta p \approx 3.87 \times 10^3$Pa, $W_l^1 \approx 109 \times 10^{-12}$m^3/s, and $v_l^1 \approx 5.78 \times 10^{-3}$m/s. Since the average radius of droplets is 3μm and hence the volume of 1 droplet is esti-

Table 1
Values of parameters

Parameter	Value	Parameter	Value
ρ_a	1 kg/m^3	ρ_l	10^3 kg/m^3
R_0	1.5×10^{-3} m	R_1	3×10^{-3} m
l	0.5×10^{-3} m	W_0^a	0.5×10^{-3} m^3/s
d_p	3×10^{-6} m	d_h	0.5×10^{-3} m
v_l	10^{-6} m^2/s	σ	7.3×10^{-2} N/m

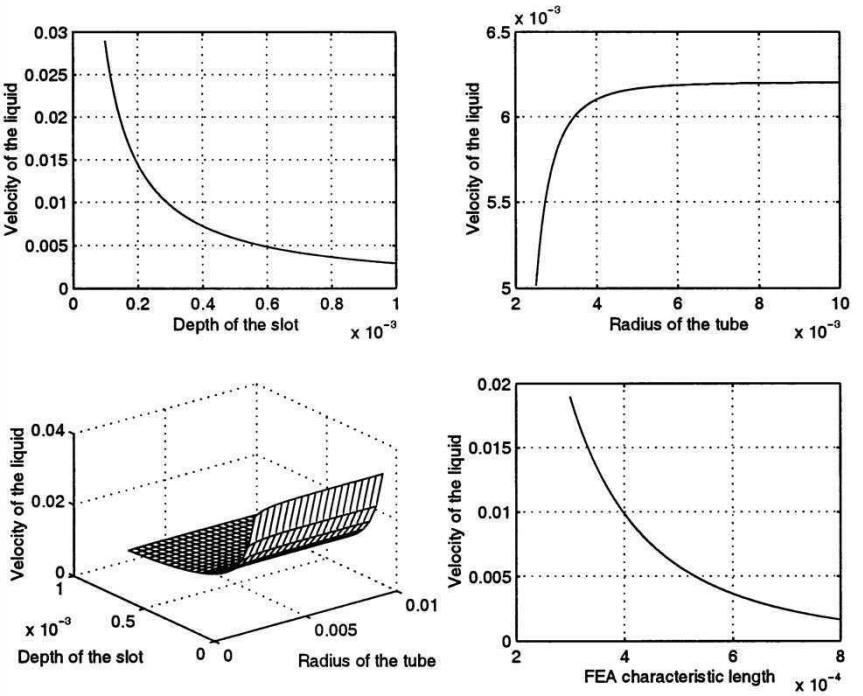

Fig. 5. Velocity of the liquid as a function of the characteristic length of the exit area, the slot dimensions, and the radius of the tube.

mated at $4\pi r^3/3 \approx 14.13 \times 10^{-18}\mathrm{m}^3$, the estimated number of droplets ejected per second in this case is approximately 8 million. Of course, this calculation assumes that the air flow rate is sufficient to generate the pressure drop that exceeds the surface energy criterion given in Section 3.

Finally, it should be emphasised that in addition to the parameters considered above the velocity of the flow is dependent on the system size as demonstrated by Fig. 5. In particular, it shows that the liquid velocity *increases* to some limiting value as the tube radius R_1 is increased, since the inlet velocity v_1^a decreases. However, the liquid velocity *decreases* as the length l is increased.

5. Concluding remarks and future directions

In this paper we have analysed mathematically a generic design block of PDD systems based on airblast atomisation. Using general equations of conservation laws, an efficient strategy has been suggested in order to assist the bioengineer to estimate the degree of effectiveness of a specific system prototype as a function of geometric characteristics. We have presented results of numerical experiments demonstrating typical dependencies of system performance on the identified control parameters.

One of the important issues to be discussed in future is the analysis of performance of PDD systems for liquids of high viscosity (which are known to be difficult atomised efficiently) and the comparison of the methodology used in this paper with other techniques of liquid atomisation (Das, 1997; Sindayihebura and Bolle, 1998) that are potentially useful for PDD systems including generation of droplets 'on demand' with high actuation frequency piezoelectric (plate or disc) generator (de Heij et al., 1999). When employing thermal techniques by heating directly the liquid

and/or piezoelectric drop-on-demand techniques (de Heij et al., 1999), the analysis of liquid droplets ejected into the inhaled airstream should be coupled to the analysis of appropriate thermal and/or piezoelectricity models (Melnik and Melnik, 2000). Since these techniques can help to overcome some side effects in patients treated with IDT, the development of mathematical models for such situations represent a challenge for future work. Moreover, progressing in the pulmonary delivery of biomolecules with high number density and moving towards generation smaller droplet sizes (sub 3 μm) we need more detailed analysis of transport-chemical deposition. In such cases the role of mathematical modelling in this field will increase.

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