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Drug Delivery by Inhalation of Charged Particles

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Abstract

All solid and liquid particles produced naturally or by energetic industrial processes are electrically charged. Although the natural levels of charge are normally insufficient to influence the deposition of inhaled particles in the lung it is possible to increase charge levels so that a significant increase in lung deposition is caused. By careful control of breathing, particle size and charge it is possible to target specific regions of the lung. Predictions of targeted deposition using the Southampton lung model are presented and a brief description of complementary clinical studies is given.

1. INTRODUCTION

Aerosols which consist of solid or liquid particles dispersed in the atmosphere are invariably electrically charged. Naturally occurring sprays and aerosols of water, such as sea and waterfall spray and aerosols of other liquids, are composed of electrically charged droplets and in many cases free ions as well. In nature the dust clouds produced by winds or the ash emitted during volcanic eruptions consist of solid particles charged by triboelectrification. In industrial situations it is generally found that during powder handling the greater the energy of the operation the greater is the observed triboelectric charging, for example the relatively feeble operations of powder sieving and pouring charge powder up to between 10^{-11} and 10^{-9} Ckg^{-1}. Energetic operations such as micronizing and pneumatic transfer generate charge levels in the range 10^{-7} to 10^{-4} Ckg^{-1} for particles of about 50 μm in diameter.

Some researchers, notably Vincent *et al*[1] and Johnson *et al*[2] have carried out measurements to evaluate the static electrification of workplace aerosols in textile, extraction and manufacturing industries. Generally the findings are that in the case of workplace aerosols charge levels are substantially above the Boltzmann equilibrium values. Although individual levels of charging vary markedly from factory to factory and from process to process within a given factory, they are invariably distributed symmetrically between positive and negative polarity.

The generation of therapeutic aerosols from devices such as nebulizers, metered-dose inhalers and dry powder dispensing systems always results in charged aerosols. In comparing the charge on air-blast and ultrasonic nebulizers, Lewis *et al*[3] showed that there were significant differences between the two types of device and demonstrated that fairly high levels of charge on inhaled aerosol particles could reduce coughing in patients. Other workers have

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shown that electrostatic charge develops on the nozzles of aerosol delivery devices and also on the walls of plastic spacer devices which are sometimes used for treating asthma and other respiratory problems. For example, O'Callaghan *et al* [4] and Wildhaber *et al* [5] showed during *in vitro* experiments that plastic spacer devices reduced the delivery of inhaled asthma medications. Later measurements by Kenyon *et al* [6] showed that there is a reduction in lung deposition of therapeutic drug from pressurized aerosol dispensers resulting from the static charge in plastic spacer devices.

The objective of this paper is to illustrate how electrical charge on inhaled particles may increase particle retention in the lung. A brief outline of the Southampton computer model of lung deposition is given and some of the supporting clinical work is referred to. It is shown how charged particle deposition, for the administration of therapeutic aerosols, can be controlled by adopting various strategies. These include prescribed breathing patterns, pulsing of aerosol during inhalation and by control of particle size and charge.

2. LUNG DEPOSITION OF INHALED CHARGED PARTICLES

Enhanced deposition of particles after inhalation and due to electrical charge was first suggested by Wilson [7]. Animal studies by Fraser [8] and Ferin *et al* [9] in which charged polymeric spherical particles were inhaled have shown that particle retention in the lung may be considerably enhanced by electrostatic charge. A considerable electrostatic enhancement of lung deposition was found when rats inhaled fibrous asbestos dust which had been charged to relatively modest levels during mechanical dispersion, Vincent *et al* [10]. Clinical measurements on human volunteers have also shown that the deposition of inhaled aerosol may be significantly increased by charging the individual aerosol particles, Melandri *et al* [11,12], Prodi and Mullerony [13]. Since then the role of charge on the deposition of charged particles within the respiratory system has been studied theoretically in physical lung models by Yu [14] and Hashish *et al* [15].

During inhalation the incoming air must negotiate a series of direction changes as it flows from the nose or mouth down the branching airway structure of the lungs. To model depositional processes within this structure it is essential to have a precise knowledge of lung morphology. It is then necessary to consider the following particle depositional processes: inertial impaction, sedimentation, diffusion, interception and electrostatic enhancement. Within the lung there is no electric field even if the human body is raised in potential above ground. Two depositional processes due to electrostatic charge may be considered. Firstly space charge effects may arise if dense charged aerosols are inhaled but this effect is usually unimportant. The second mechanism is one in which a charged particle induces an image charge on any grounded nearby surface. During image charge attraction a particle always induces an equal and opposite charge to itself on a surface such as a airway wall and the process is therefore always an attractive one regardless of particle polarity.

The application of drugs in aerosol form is a convenient treatment in many lung diseases. However, utilization of the inhalation route for rapid drug absorption in the lung and subsequently systemic transport to bodily organs other than the respiratory tract is now also being considered. This can be achieved efficiently by administering medication in the form of a charged aerosol which may be pulsed into the air flow during inhalation.

3. LUNG MODELS

The University of Southampton lung model of Hashish *et al* [15], assumes the lung structure and airway dimensions as published by Weibel[16]. For particle deposition each airway generation is represented by a cylinder whose length decreases and diameter increases with penetration into the lung, Shearer *et al* [17]. The cross-sectional area of each cylinder is representative of the total surface area of all the airways associated with a particular generation resulting in a trumpet-like profile. To determine the deposition of particles during a respiratory cycle the particle loss over the entire airway length and for the residence time involved is determined by integration. Mathematical expressions for the deposition mechanisms of impaction, sedimentation, diffusion and image charge are applied as appropriate depending on particle size, charge and flow rate. Expressions given by Yu and Diu [18] and Yu and Chandra [19] are used in the model. The model is set up on a personal computer and the total and regional deposition of particles of various sizes inhaled at different flow rates can be determined. The computer predictions have been shown to be in good agreement with experimental clinical data. In recent studies by Camner *et al* [20] the Southampton mathematical model has been compared with two other mathematical models from the Karolinska Institute in Sweden and from the National Radiological Protection Board in the UK. In these comparisons a selected range of the airways was restricted in diameter to simulate a diseased condition and it was shown that the three models produced predictions of deposition that were very close. It was assumed that the inhaled particles during these comparative studies were uncharged as the Southampton model is the only one in which particle charge may be accounted for.

4. CLINICAL ASSESSMENT OF DEPOSITION

Any computer models of particle deposition within the respiratory system must be validated by clinical data. Comparing computer predictions with clinical data is very difficult as the two sets of data are in totally different forms. The computer predictions are for particles distributed throughout the branching tree-like structure of the lungs, and so deposition of particles is presented as a function of generation number. The throat is the top part of the trachea, which leads into the lungs by branching out in a tree-like manner to the deepest parts of the lung, known as the alveolar region. The trachea, which is approximately 9cm long and 1.7cm in diameter, is designated as generation 0. It bifurcates into two generation tubes or bronchi. Bifurcations continue leading to 23 generations of branching. Generations 0-15 are classified as the tracheo-bronchial region and regions beyond this [16-23] are the alveolar region where gas exchange takes place.

On the other hand clinical data which is obtained by radio labelling inhaled aerosols enable the location of deposited aerosol to be determined spatially, that is particle concentrations may be determined at the centre part of the lungs and then outwards from that location to the lung periphery. To do this in our clinical studies at Southampton [21,22] we use a gamma camera which has twin detectors. It is rotated around each volunteer human subject after inhalation of the radio-labelled aerosol. The detected gamma rays by the rotating camera system enables a three-dimensional picture of particle deposition within the lungs to be determined. As there may be considerable intersubject variability we use a procedure to normalize the data and transform it from the actual lung shape into a hemisphere. The final

data set shows deposition at the centre of the lungs and then in a series of hemispherical shells about this central point outwards to the periphery. We split the lung into 10 shells. It is then necessary to relate the particle deposition data within each shell to distribution within the airway tree as predicted by the mathematical model. Each shell will contain portions of airway from the different generations rather than correspond to a single airway. It is necessary to know the spatial position of all elements of the airway tree with respect to the 10 shells that are measured by the gamma camera.

At Southampton [23] we have carried out clinical studies on 12 healthy subjects inhaling fine and coarse aerosols. The amount of particle deposition in the head and the total deposition were in reasonable agreement with our computer predictions. However, the distribution within the lungs showed more peripheral deposition than expected. We are presently refining our data analysis to resolve this problem. Future work will be carried our using pulsed aerosol delivery to volunteers and particles will be charged for some of this work.

5. OPTIMISATION OF PARTICLE DEPOSITION IN THE LUNG

In order to maximise the deposition of particles within the respiratory system and to perhaps selectively target certain regions of the lung, various strategies may be adopted. To understand these an appreciation of the competing mechanisms of deposition is required. Breathing may be either via the nose or the mouth or a combination of the two, and so before an aerosol is even presented to the lungs a considerable amount of filtering occurs. Mathematical models for deposition of particles within the head are empirical. Airflows through the respiratory system are complex and are turbulent in some regions and laminar in others. Larger particles, say, above about 5μm in diameter tend to be trapped by impaction and sedimentation in the head and tracheo-bronchial region, i.e. the upper part of the respiratory system. A considerable amount of particle impaction on the back of the throat may occur leading to swallowed drug. For these larger particles electrostatic charge has no significant effect upon the depositional process.

As particle size decreases below 5μm in diameter particles are able to penetrate deeper and deeper into the narrower airway sections and even the alveolar regions of the lung. Due to the smaller dimensions in these regions, particles are relatively close to airway and alveolar walls and so electrostatic charge becomes important and may considerably enhance deposition. As particle size is decreased into the submicron range, diffusion increases the probability of collision of particles with walls even in the upper airways. Deposition thus increases and again charge may enhance this process in the upper airways, where it is generally not desirable for therapeutic purposes but, of course, may be desirable if one is attempting to remove pollutant particles by means of electrostatic charge.

Considering now strategies which may be adopted to increase particle deposition and in some cases to selectively deposit particles, the importance of particle charge, breathing rate, i.e airflow rate, may first be discussed. Fig 1 shows how electrical charge on 0.5μm diameter water droplets or solid particles, inhaled during normal breathing, deposit in the lungs as droplet charge is varied. Deposition is defined as the fractional number of inhaled particles that are deposited. Note that as charge is increased to the relatively low level of 200 electrons [Rayleigh Limit = 44,000e] the deposition in the alveolar region increases dramatically. This moderate charge level corresponds to a charge-to-mass ratio of about 0.5 Ckg^{-1}. The effect

of charge is also to increase deposition in the upper airways [0-3] and this effect increases with charge level. Similar effects occur as particle size is increased but more and more charge is required to achieve a desirable effect. For example, for 5μm diameter particles shown in Fig 2 charging up to levels of about 200e has no effect. The higher charge level of 3000e causes a significant deposition of particles in the upper airways with reduced penetration into the lungs. Charge can be controlled and could theoretically be increased to the maximum possible value of the Rayleigh limit for droplets. The effect upon deposition at this limit is likely to be high deposition of particles in the upper airways.

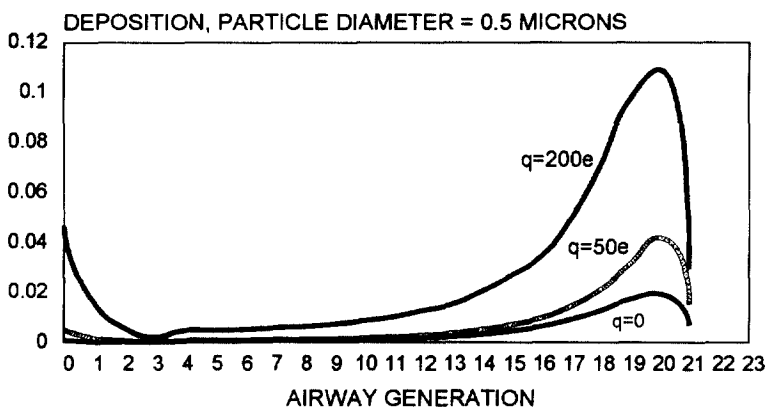

Figure 1. Deposition of inhaled 0.5μm diameter charged particles.

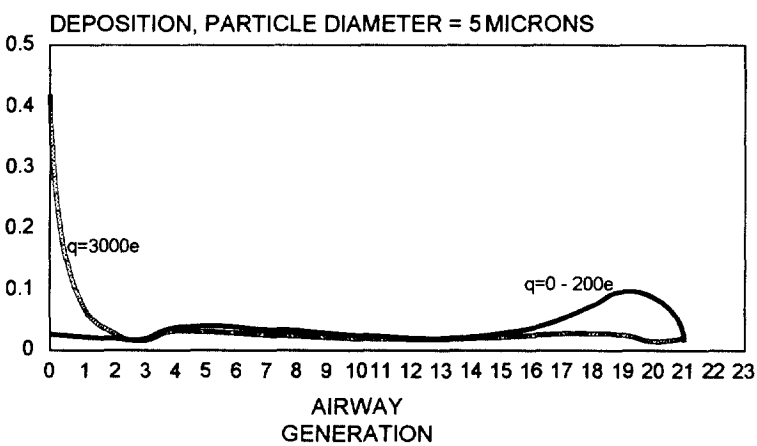

Figure 2. Deposition of inhaled 5μm particles showing higher charge required.

If breathing rate is decreased impaction of particles decreases enabling relatively large particles to penetrate further into the airway system. Experimental work proving this strategy has been carried out at the Karolinska Institute in Sweden as reported in the paper by Camner

et al[20]. Electrostatic charge on particles would have no significant effect as it was the deposition of relatively large particles that was manipulated.

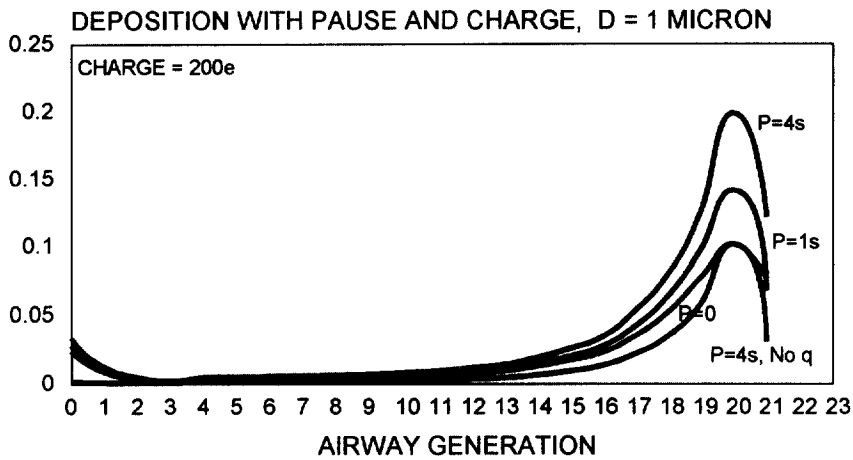

Figure 3. The effect of breath holding on charged particle deposition.

Another strategy is to pause for a few seconds at the end of the inspiration phase thus giving particles the chance to deposit out within the respiratory system. If charged particles have been inhaled the pause enables the electrostatic image force to play a significant part in the depositional processes. Fig 3 shows the effect of breath holding pauses when 1μm diameter droplets charged to 200e are inhaled.

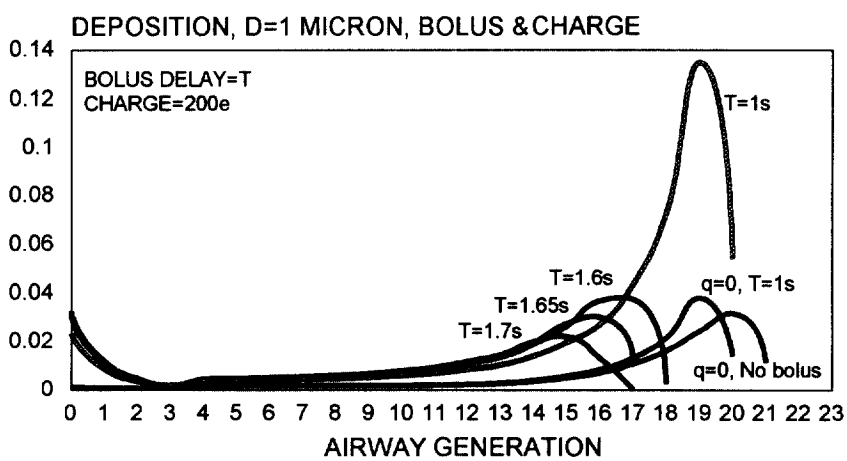

Figure 4. Controlled particle deposition using a charged bolus.

To target specific regions of the lung a strategy may be adopted in which a small amount of aerosol of predetermined volume is pulsed into the inhaled airflow. The inhaled aerosol pulse or bolus then reaches a maximum lung penetration corresponding to the desired target region. This may be followed by a respiratory pause to enhance further particle deposition and, of course, particles may be charged to even further enhance the process. By controlling the pulse duration and the delay time after the start of the inhalation cycle, the pulsed aerosol can be made to penetrate to different volumetric depths within the respiratory system as shown in Fig 4. The data shown was obtained for a 50ml pulse inhaled during a 2s inspiration at a flow rate of $500mls^{-1}$.

6. CONCLUSIONS

Aerosol and dust particles occurring naturally or in the workplace are invariably charged. Although the levels of charge do not normally have a significant effect on the deposition of inhaled particles, charge levels can be increased artificially by say corona or induction charging to levels well below the Rayleigh limit, so that significant increases in the deposition of inhaled particles then occurs. It is shown how by choosing parameters such as particle size, charge and breath-holding pause some control of particle deposition can be achieved. By using a pulse or bolus of charged aerosol during inhalation further control is possible. The charging of particles could be utilised to give better control of drug delivery or to enhance the trapping of pollutant particles in the upper airways of the lungs.

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