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Invited review paper

Formation of particles for dry powder inhalers

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ABSTRACT

Inhalation therapy is widely employed to deliver drugs to the respiratory epithelium, predominantly for the treatment of local disorders. Recently aerosol therapy has become an attractive non-invasive way for systemic administration of biologically active components, because of the unique features of the lung, namely its large surface area, high permeability and wide blood supply. Success of a therapy depends on the effectiveness of particle delivery to a targeting site of the lungs. The paper explains mechanisms of particle transport, deposition and retention in the respiratory system coupled with the efficiency of the powder aerosolization with a dry powder inhaler (DPI) leading to the definition of the required particle structure. The most promising hollow or porous nanostructured particles have tapped density below 0.4 g/cm^3 and mass medium aerodynamic diameter (MMAD) below 5 μm. Key features of the process leading to the formation of particles with the required structure are explained. Spray-drying, spray-freeze-drying and supercritical antisolvent precipitation are shown to be the most promising methods for efficient production of particles for inhalation. Examples of the production of therapeutic particles for delivery of peptides, antibiotics, anticancer drugs, and the structures of particles obtained with the above mentioned and other methods are presented. The paper concludes with brief information about a recent construction of DPIs for aerosolization of therapeutic particles.

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1. Introduction

The success of therapy using aerosolized medications depends on the ability to deliver a drug dose to appropriate sites in the respiratory system with few side effects. The advantages of aerosols compared with other forms of therapy are ease of administration, effectiveness with much smaller doses and rapidity of therapeutic response. The objective is to deposit a sufficient quantity of aerosol in the lung. This involves the generation of adequate numbers of respirable particles or droplets and the use of a delivery system that minimizes loss of particles before they reach the lung of a patient. Physical characteristics of the various formulations of therapeutic aerosols, their production properties and the medical condition of a patient coupled with their inhalation technique determine the success of aerosol treatment of lung and systemic diseases [1–4].

Therapeutic aerosols are fitted with nebulizers, pressurized metered dose inhalers (pMDI) and dry powder inhalers (DPIs). DPIs are portable, propellant-free, easy to operate, deliver a broad range of drug doses, and show improved stability of the formulation as a result of dry state [5,6]. The advantages of DPIs over nebulizers or pMDI make them particularly suited to both chronic and intensive therapy.

Dry powder aerosols direct air through an aliquot of a loose powder. Powder dispersion into respirable particles is driven by turbulent flow in the powder container or in the inhaler, which, in turn, is a function of the intensity of flow resulting from the patient's respiratory system, construction of the powder device and, primary, from the particle–particle interaction properties in the powder structure.

Efficient systemic delivery using inhalation requires aerosol particles that meet treatment needs, including effectiveness of aerosolization, transport into defined sites of deposition and resistance to clearance mechanism. All these factors determine the morphology of a particle, which will satisfy the above requirements.

2. Particle morphology influencing inhalation therapy

2.1. Particle deposition in the respiratory system

Efficient systemic delivery using inhalation requires aerosol particles to be designed with an adequate aerodynamic diameter in order to maximize deposition in the alveolar region of the respiratory system. The first step for particle designing is deposition modeling, which should provide information about the efficiency of deposition of particle of given size at particular sites of the pulmonary region.

Before reaching the alveoli, our main target, a particle should pass the extrathoratic region or the upper airways (nose, mouth and throat) and the tracheobronchial tree (from larynx to terminal bronchioles). Some aerosol particles are lost in particular regions depending on their aerodynamic properties. Particle deposition is related to its aerodynamic diameter d_a

$$d_a = d \cdot \left(\frac{\rho}{\rho_o \cdot \varphi}\right)^{1/2} \tag{1}$$

which is equivalent to the diameter of a unit density (ρ_o) sphere that has the same terminal velocity in still air.

In Eq. (1), d is the geometric diameter of the particle, ρ is the particle density and φ is the particle dynamic shape factor denoting the deviation of shape from sphericity [7]. The effectiveness of particle deposition depends on temporary and local patterns of the airflow and particle behavior resulting from its mass.

The flow structure during breathing could be derived from the solution of the Navier–Stokes equations. These equations describe the variation of pressure and velocity in a fluid. Using Cartesian index notation x_{ijk} with the summation convention, we can write the first equation, which is an expression of mass conservation, as following:

$$\frac{\partial v_i}{\partial x_i} = 0 \tag{2}$$

and the second which is an expression of the conservation of momentum, as:

$$\frac{\partial v_i}{\partial t} + \frac{\partial V_i V_j}{\partial x_j} = -\frac{1}{\rho} \cdot \frac{\partial}{\partial x_i} + v_m \frac{\partial^2 V_i}{\partial x_i^2} \tag{3}$$

In the above equation V is fluid velocity, t – time, p – pressure, v_m – molecular kinematic viscosity and ρ – fluid density.

When the geometry of an object is defined for the fluid flow, and the initial and boundary conditions for the Navier–Stokes equations are properly stated, the system of equations can be easily solved. A fluid velocity distribution, $V(x, t)$ is determined. A particle suspended in the air with the flow pattern $V(x, t)$ moves and owing to the influence of inertia, diffusion, gravity and interception finally deposits itself on the solid surface of a compartment.

There are two, Lagrangian and Eulerian, major descriptions of particle balance within the compartment they enter. The common root for both descriptions in the case of analysis of behavior of nanostructural, diffusional aerosol particle is the stochastic Langevin equation. It could be shown [8] that with a defined path of transformations we could start from the stochastic equation of the single particle motion and arrive at the deterministic equation describing diffusional particle population balance i.e. Eulerian approach of model.

This approach is more convenient to calculate particle deposition efficiency in a complex geometry, e.g. in the pulsating alveolar region of the respiratory system. The balance equation within a controlled differential space has the following form in the dimensionless coordinate system:

$$\frac{1}{Fo} \cdot \frac{\partial C}{\partial t} + Pe \cdot U \cdot \nabla^2 C + B = 0 \tag{4}$$

where t is reduced time with respect to the characteristic time of the process (for example, breathing cycle time τ_c) and the space coordinates are reduced with respect to the cross-sectional dimension of compartment, d, Fourier number $Fo = \frac{D \cdot \tau_c}{d^2}$, Peclet number $Pe = \frac{U \cdot d}{D}$, D is the diffusional coefficient of a Brownian particle, U is the particle velocity and C stands for the number of particles in the control volume at the moment t. The term B in Eq. (4) can be expressed as:

$$B = \frac{1}{r_p}\left(Pe \cdot U_n \cdot C - \frac{dC}{dn}\right) \tag{5}$$

where r_p – particle geometrical radius, V_n – velocity component of particle normal to the surface of deposition, n – direction normal to the surface of deposition.

A system of Eqs. (2)–(5) can be used to calculate particle deposition efficiency for a given region of the respiratory system. Theoretical analysis of the problem presented in [9–12] shows that inhaled particles with aerodynamic diameter d_a smaller than 0.1 μm are entirely deposited by diffusion in the alveolar region of the lungs. Inhalation therapy for systemic drug delivery should be focused on such particles.

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