Large, Porous Inhaled Particles: A Potential Approach to Pulmonary Drug Delivery

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Received on: 07-03-2009; Accepted on: 23-04-2009

ABSTRACT

Large, porous particles with a mean geometric diameter of 10 µm. An increase in the size of aerosol particles results in a reduced fractional surface area (or likelihood) of particle-particle contact in a dry powder (or liquid suspension) and thus in less tendency to aggregate. This diminished aggregation means that less energy is required to aerosolize particles or that particles are more efficiently aerosolized with a given energy of aerosolization. Large particles deposited in the pulmonary region may escape clearance by alveolar macrophages and, therefore, permit drug release for longer periods of time and more efficiently. The ability to deliver proteins and peptides to the systemic circulation by inhalation has contributed to a rise in the number of inhalation therapies under investigation. Studies performed primarily with liquid aerosols have shown that these characteristics of inhaled aerosols lead to optimal therapeutic effect, both for local and systemic therapeutic delivery. Inefficient drug delivery can still arise, owing to excessive particle aggregation in an inhaler, deposition in the mouth and throat, and overly rapid particle removal from the lungs by mucociliary or phagocytic clearance mechanisms. To address these problems, particle surface chemistry and surface roughness are traditionally manipulated. Recent data indicate that major improvements in aerosol particle performance may also be achieved by lowering particle mass density and increasing particle size, since large, porous particles display less tendency to agglomerate than (conventional) small and nonporous particles. Also, large, porous particles inhaled into the lungs can potentially release therapeutic substances for long periods of time by escaping phagocytic clearance from the lung periphery, thus enabling therapeutic action for periods ranging from hours to many days. The delivery of large, porous particles to the lungs may also permit exceptionally long-acting therapeutic delivery following inhalation, as well described in this review.

Keywords: Inhalation therapies; respiratory illness; aerosol particles

INTRODUCTION

Drug delivery to the lungs by inhalation has attracted tremendous scientific and biomedical interest in recent years. To avoid needles, noninvasive delivery strategies have been extensively explored. Among these, inhalation delivery has proven especially attractive, since the epithelium of the human lungs is highly permeable and easily accessed by an inhaled dose. The low bioavailability of slowly absorbing macromolecules can be attributed to long residence time in the alveolar fluid before absorption, during which time activity is lost by enzymatic degradation or aggregation, a controlled-release form of the drugs might again be beneficial. Presently, this is true for many biotherapeutics currently injected intravenously, like growth hormone, glucagon α -antitrypsin, each of which could possibly be delivered to humans by inhalation with greater efficiency. Lowering particle mass density and increasing particle size may achieve the major improvements in aerosol particle performance. These drug delivery systems have the potential to shorten and simplify TB therapy by direct pulmonary drug delivery. LPPs are spray dried, optimized for physical and aerosol characteristics and assessed for physical and chemical stability. The efficacy of these vectors for drug delivery will be determined by animal pharmacokinetic and pharmacodynamic studies. These dry powders are also manufactured inexpensively and at large commercial scales using processes such as spray drying. The result is a free-flowing powder that is shelf-stable and easily delivered in large doses.

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SEM micrograph of LPPs
**Liposomes:** Liposomes are a form of vesicles that consist either of many, few or just one phospholipid bilayers. The polar character of the liposomal core enables polar drug molecules to be encapsulated. Amphiphilic and lipophilic molecules are solubilized within the phospholipid bilayer according to their affinity towards the phospholipids. Participation of nonionic surfactants instead of phospholipids in the bilayer formation results in niosomes. Channel proteins can be incorporated without loss of their activity within the hydrophobic domain of vesicle membranes, acting as a size-selective filter, only allowing passive diffusion of small solutes such as ions, nutrients and antibiotics. Thus, drugs that are encapsulated in a nanocage-functionalized with channel proteins are effectively protected from premature degradation by proteolytic enzymes. The drug molecule, however, is able to diffuse through the channel, driven by the concentration difference between the interior and the exterior of the nanocage.

**Drug encapsulation in liposomes**

A polymer-stabilized nanoreactor with the encapsulated enzyme

**Aerosols:** Aerosol preparations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium. The drugs delivery by aerosols is deposited in the airways by: gravitational sedimentation, inertial impaction, and diffusion. Mostly larger drug particles are deposited by first two mechanisms in the airways, while the smaller particles get their way into the peripheral region of the lungs by following diffusion. Although there is similarity in drug absorption from the lungs and the other mucosal surfaces, but due to the complexity in aerosol-particle disposition, the aerosol administration further complicated by the hygroscopic properties of most therapeutic aerosols that allow the particle size to change drastically during the drug transport in the highly humid atmosphere of the respiratory tract. Other factors, which directly influence the aerosol deposition by above three mechanisms, are aerodynamic size distribution of the aerosol particles, and the density of the aerosol particles.

There are three commonly used clinical aerosols: jet or ultrasonic nebulizers, metered–dose inhaler (MDI), and dry-powder inhaler (DPI). The metered–dose inhalers are most frequently used aerosol delivery system. The dry-powder-inhalers are designed to deliver drug/excipient powders to the lungs. Recently, a number of add-a-device or also called as spacers are added to use with MDIs, in order to remove some non-respirable particles by impaction on their walls and valves. Almost all aerosols were using a CFC (chlorofluorocarbon) propellant but in mid-nineties efforts were made to consider an alternative to ozone depleting CFC by other classes of environmental friendly propellants such as hydrofluoralkanes (HFAs: HFA –134a and HFA–227). These HFA compounds contain no chlorine, which in fact causing the ozone depletion effect. The safety and efficacy of these new introduced propellants were investigated to meet the requirements of American and European regulatory agencies. In most cases, these two propellants met the safety conditions and found that they have safety compliance as of their predecessor CFC propellant. In recent years, many MDIs and DPIs containing CFC were replaced by HFAs.

**Aerosol Delivery:** Research in the area of pulmonary drug delivery has gathered momentum in the last several years, with increased interest in using the lung as a means of delivering drugs systemically. Advances in device technology have led to the development of more efficient delivery systems capable of delivering larger doses and finer particles into the lungs. As more efficient pulmonary delivery devices and sophisticated formulations become available, physicians and health professionals will have a choice of a wide variety of device and formulation combinations that will target specific cells or regions of the lung, avoid the lung’s clearance mechanisms and be retained within the lung for longer periods. It is now recognized that it is not enough just to have inhalation therapy available for prescribing; physicians and other healthcare providers need a basic understanding of aerosol science, inhaled formulations, delivery devices, and bioequivalence of products to prescribe these therapies optimally.

**Table: List of CFC-free inhalers available in Europe and USA**

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<thead>
<tr>
<th>Name of Product</th>
<th>Active Ingridient of Drug</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>Airomir</td>
<td>Salbutamol</td>
<td>3M Drug Delivery Systems</td>
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<tr>
<td>Asmol</td>
<td>Salbutamol</td>
<td>3M Pharmaceuticals</td>
</tr>
<tr>
<td>Epaq</td>
<td>Salbutamol</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>Ventolin</td>
<td>Albuterol Sulfate</td>
<td>Aventis Pharmaceuticals</td>
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<td>Flixotide</td>
<td>Fluticasone propionate</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>Qvar</td>
<td>Beclomethasone dipropionate</td>
<td>Aventis Pharmaceuticals</td>
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<tr>
<td>Tilade CFC-free</td>
<td>Nedocromil Sodium</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>Seretide</td>
<td>Salmeterol xinafoate</td>
<td>3M Drug Delivery Systems</td>
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Drug Delivery System: The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Among drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) passive and (ii) active targeting. An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the enhanced vascular permeability of tumor tissues compared with healthy tissue. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Since ligand–receptor interactions can be highly selective, this could allow a more precise targeting of the site of interest.

Conclusion: Advances in particle modifications are allowing the development of particles with better dispersability, entrainment, suspendability, and deposition efficiency from dry powder inhalers. As these particles can counter the natural particle clearance mechanisms to an extent and facilitating sustained drug delivery, thus enabling therapeutic action for periods ranging from hours to many days. The young scientists must explore the gold mine of delivery systems, such as large porous particles, to bridge the gap between industry and academy.

Acknowledgement: We authors would like to thank our college members like librarian, computer experts, and Principal Dr. N. P. Jivani for their unforgettable support. Our sincere thanks to some of our student who work very hard to complete this search.

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Source of support: Nil, Conflict of interest: None Declared