Inhalable Drugs for Systemic Therapy

Kevin Corkery RRT

Introduction

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Summary

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Introduction

Aerosol systems, such as metered-dose inhalers, dry powder inhalers, and liquid jet or ultrasonic nebulizers for delivery of bronchodilators and inhalable corticosteroids to treat asthma or chronic obstructive pulmonary disease have existed for many years, and have proven effective in delivering drug to the airways for pulmonary applications. More recently, however, there has been substantial interest in using the lung, and in particular the alveolar surface, as a portal to the systemic circulation for macromolecules such as proteins and peptides, which otherwise must be given by injection.

Problems in Drug Delivery of Macromolecules

Because of their size and delicacy, peptides, proteins, and other macromolecules have traditionally been systemically administered via injection. But there are problems with administering them this way. Most patients do not like the pain and inconvenience of injection, particularly when required repeatedly for the treatment of chronic disease such as diabetes or multiple sclerosis. This dislike can result in poor patient compliance and inadequate disease management.1 With the development of more long-term and frequently administered injection drugs (eg, growth factors, anti-infectives, and other chronic disease treatments) the pharmaceutical industry has increasingly sought noninvasive alternatives to needle injection.

To date, however, traditional noninvasive delivery systems have not proved effective for macromolecules. Pills, tablets, and oral solutions are unsuitable because of poor absorption or inactivation by gastric juices and digestive enzymes. Transdermal delivery systems are also inadequate because of the size constraints of macromolecules or other inherent physical properties that prevent them from crossing skin layers without the addition of irritating enhancers. Research has also shown that the nasal route has low natural bioavailability and high variability for proteins and peptides.2 The natural bioavailability of macromolecules (eg, insulin and growth hormone) when delivered nasally is generally <2%. To achieve higher system efficiency and greater bioavailability, penetration enhancers are required that can cause local irritation and long-term mucosal injury.

Suitability of the Lung Periphery for Systemic Drug Delivery

The biology of the lung makes it suitable for systemic drug delivery. Many proteins and peptides are absorbed through the alveoli into the bloodstream naturally, with high drug absorption and without the need for enhancers used for other noninvasive routes.3 This high bioavailability-
ity makes the lung a natural target for peptides and proteins. In addition, the lung is a robust organ, able to handle about 30 mg per day of inhaled nuisance dusts day after day for years without deleterious effect.  

This combination of the bioavailability of peptides and proteins when delivered via the lung and the robustness of the lung itself make the lung periphery a logical target for drug delivery.  

On inhalation, air passes through the trachea, which branches more than 22 times into successively smaller airways that constitute the bronchial network, eventually reaching the grapelike clusters of the alveoli. Each breath of air is distributed deep into the lung tissue, to the alveolar epithelium, the surface area of which measures approximately 80–100 m² in humans. This large surface has about half a billion alveoli through which oxygen passes into the bloodstream via an extensive capillary network. Large-molecule drugs such as peptides and proteins do not easily pass through the airway surface (which has a total surface area of about 3.0 m²) because it is lined with a thick, ciliated, mucus-covered cell layer, making it nearly impermeable. But these large molecules do permeate the alveoli, which have a thin, single-cellular layer, enabling absorption into the bloodstream. Because the alveoli reside beyond the terminal branches of the airway, any pulmonary approach to delivering drugs for systemic disease must target the lung periphery.  

To reach the lung periphery, a drug must be delivered in particles of 1–3 μm (optimal size ≤ 2 μm) with slow, deep inhalation. Particles > 10 μm tend to be swallowed, and 6–10 μm particles deposit in the airways (Figure 1).  

**First-Generation Aerosol Devices**  

Until recently, pulmonary drug delivery systems were capable of dispensing drug to the airway only for local application, such as in asthma. Metered-dose inhalers, breath-activated dry powder inhalers, and liquid jet and ultrasonic nebulizers are useful in the management of asthma, but such devices were not designed to deliver drugs into the lung periphery. They have been primarily designed to deliver potent drugs such as corticosteroids and bronchodilators, both of which are bioactive in the lung at 5–20 μg per dose.  

Dose reproducibility is most often inconsistent, varying per puff, which is acceptable when the therapeutic window is large, as is true with these potent drugs. However, when the therapeutic window is narrow, as is true with most protein drugs, dose reproducibility is required. These systems have not been able to deliver most macromolecules, which need to be delivered to the lung periphery at doses of 2–20 mg, because of the devices’ low system efficiency, low drug mass (also known as “payload”) per puff, poor formulation stability for macromolecules, and poor dosing reproducibility.  

To effectively deliver macromolecules to the lung periphery in therapeutic doses, 5 basic criteria must be met.  

- The system must provide efficient delivery of the drug to the lung periphery. This requires formulating the drug so that it is deliverable in a cloud containing particles of 1–3 μm (optimal size ≤ 2 μm) with slow, deep inhalation. Some aerosol systems can deliver only 10–12% of the dispensed drug in the correct particle size for lung deposition.  

- It also requires designing the delivery device so that the aerosol generated easily reaches the alveolar region with a minimum of patient effort and with minimal oropharyngeal impaction (which causes the medication to be swallowed rather than inhaled).  

- The therapeutic drug dose must be reproducible from dose to dose. Package inserts for these products will present this in terms of nominal or dispersed dose (ie, the amount of drug in the unit dose blister package or ampule) and delivered dose (ie, the amount of drug in the dose that is bioavailable).  

- The system should accommodate flexible dosing, because patients may require different doses at different times.  

- The delivery device must be portable and easy to use to optimize patient compliance and disease management.  

- The drug formulation must be stable at room temperature. This too improves portability and convenience of using the system.  

**The Delivery Device and Lung Periphery Deposition**  

Fine powder particles adhere to each other (agglomerate) and can be difficult to break apart into respirable particles that can be slowly inhaled. Breath-activated powder inhalers for asthmatics are designed to use the force generated by fast inspiration to break apart powder clumps. Unfortunately, there is not enough energy in a human inhalation to efficiently break apart very fine powder...
clumps, and the harder the inhalation, the faster the particles move, increasing dosing variability and the tendency of particles to impact in the mouth and throat.

The Innova device technology (Inhale Therapeutic Systems) separates the patient’s breathing maneuver from the generation of the aerosol by using compressed air to deagglomerate the powder particles and deliver the aerosol plume into a clear plastic holding chamber, eliminating the need for coordination of aerosol generation and inhalation. The patient inhales the cloud with the slow, deep inspiration that optimizes alveolar deposition. Because the chamber is transparent, the patient knows immediately whether a full dose of medicine has been inhaled. The device delivers the medicine early in the inspiration, followed by a much larger volume of air that pushes the drug down into the alveoli (Fig. 2). The device requires no power source, contains no batteries or chips, and is easily cleaned.

**The Inhalable Drug Industry Today**

Currently, at least 5 companies are working on the development of inhalable proteins:
- AeroGen (AeroDose inhaler system)
- Alkermes (AIR technology)
- Aradigm Corporation (AERx pulmonary drug delivery system)
- Dura Pharmaceuticals (Spiros pulmonary drug delivery system)
- Inhale Therapeutic Systems (Inhance drug delivery platform)

**AeroGen (Sunnyvale, California)**

AeroGen’s AeroDose inhaler system is designed to enable aerosolization of small or large molecules in liquid solution or suspension formulations. The technology uses the vibration of a curved metal plate that contains pre-formed holes of a predetermined size to generate the aerosol. The device’s metering valves allow flexibility in dosing. Electronic controls enable breath actuation of drug delivery and control of aerosol flow and inspiratory flow. Delivery of a single dose of drug is accomplished with single or multiple breaths.

**Alkermes (Cambridge, Massachusetts)**

Alkermes’s AIR technology employs dry powder delivery of small-molecule, protein, and peptide drug particles to the deep lung. The delivery device is breath-activated, requiring no additional power source. Particles are produced in a one-step spray-drying process that uses only small quantities of excipients while accommodating large concentrations of drug, if needed. Its dry powder technology, according to Alkermes, has the potential for prolonged drug release. To date, the company has 3 major pharmaceutical partners and 5 drugs (proteins and small molecules) in large animal or human clinical trials.

**Aradigm Corporation (Hayward, California)**

The AERx pulmonary drug delivery system uses proprietary technology to create aerosols from liquid drug formulations and to deliver these aerosols locally to the lungs or systemically via the lungs. The delivery device, which depends on the patient’s active breath control, has data capture abilities, enabling health care professionals to download and analyze data for patient compliance. The company has several drugs in preclinical or clinical trials, including morphine (phase 2), insulin, (phase 2), and dornase alfa (preclinical).
**Dura Pharmaceuticals (San Diego, California)**

Dura’s Spiros pulmonary drug delivery system aerosolizes pharmaceuticals in a powder formulation for pulmonary delivery. The system comprises a battery-operated electromechanical inhaler and a multi-dose cassette or blisterdisk powdered-drug storage unit. The company primarily focuses on developing inhalable steroids for asthma treatment but is interested in proteins and other macromolecules as well.

**Inhale Therapeutic Systems (San Carlos, California)**

Inhale Therapeutic Systems focuses on its Inhance dry powder technology platform for lung periphery aerosol delivery of drugs. The Inhance drug delivery platform combines multiple powder and device technologies for the development of inhalable drugs. Its lead product is inhalable insulin, which is in Phase III clinical trials. The company has development agreements with a number of pharmaceutical companies, including:

- Aventis Behring (formerly Centeon) for inhalable α-1 proteinase inhibitor to treat congenital emphysema (phase 1)
- Biogen for inhalable AVONEX (interferon β-1a) (phase 1) to treat multiple sclerosis
- Lilly for an undisclosed inhalable protein (preclinical)
- Pfizer, which is partnered with Aventis Pharma to co-develop and co-promote inhalable insulin

Inhale uses unique proprietary technologies to formulate drugs for dry powder aerosol delivery.

**Table 1. Macromolecule Candidates for Pulmonary Delivery**

<table>
<thead>
<tr>
<th>Insulin^{15–17}</th>
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</thead>
<tbody>
<tr>
<td>Alpha_{1}-proteinase inhibitor^{18}</td>
</tr>
<tr>
<td>Growth hormones^{19,20}</td>
</tr>
<tr>
<td>Interferons^{21,22}</td>
</tr>
<tr>
<td>Colony-stimulating factors^{23–25}</td>
</tr>
<tr>
<td>Erythropoietins</td>
</tr>
<tr>
<td>Human calcitonin^{22}</td>
</tr>
<tr>
<td>Somatostatin analogs</td>
</tr>
<tr>
<td>Luteinizing hormone releasing hormone (LHRH) analogs^{26}</td>
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<tr>
<td>Factor IX</td>
</tr>
<tr>
<td>Vaccines</td>
</tr>
<tr>
<td>Interleukins and antagonists</td>
</tr>
<tr>
<td>Anti-obesity peptides</td>
</tr>
<tr>
<td>Parathyroid hormone^{22}</td>
</tr>
<tr>
<td>Osteoporosis peptides</td>
</tr>
<tr>
<td>Diabetes peptides</td>
</tr>
<tr>
<td>Antibodies</td>
</tr>
<tr>
<td>Immune suppression peptides</td>
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<tr>
<td>Nerve growth factors</td>
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</table>

**Table 2. Medical Conditions that Could Benefit from Pulmonary Delivery**

| Pain |
| Panic and anxiety |
| Anaphylaxis |
| Cardiac arrhythmias |
| Other cardiovascular conditions |
| Diarrhea |
| Spasms |
| Insomnia |
| Nausea and vomiting |
| Nicotine withdrawal |
| Urinary incontinence |

**The Future of Inhalable Therapeutics**

The future of pulmonary drug delivery, whether for macromolecules or small molecules, appears to be broadening. Delivery of macromolecules to the lung periphery offers many advantages over injection and other noninvasive methods. As the fields of biotechnology, genome research, and protein therapeutics continue to burgeon, the opportunities for aerosol delivery of these compounds expand accordingly (Table 1).

Interest is also focused on formulating certain small-molecule pharmaceuticals for pulmonary delivery. Although many of these drugs are readily administered in oral preparations, pulmonary delivery would offer substantial advantages over oral delivery, including rapid onset of the action, in a matter of seconds, and avoidance of the problems that can accompany gastrointestinal absorption, such as low solubility and low bioavailability of the drug, possible gastrointestinal upset caused by drug irritability, unwanted metabolites resulting from gastrointestinal metabolism, and the interaction of the drug and certain foods (Table 2).

**Summary**

Although oral and injectable drug formulations still dominate the market, interest in pulmonary delivery has been rising steadily. Given patients’ desire for an alternative to injections, and recent advances in aerosol science and pulmonary medicine, the potential for improved disease management outcomes by using aerosols for systemic drug delivery should lead the way for a shift to inhalables.

**REFERENCES**