An Overview of Pulmonary Drug Delivery

Naushad M Khan Ghilzai
Formerly of **Department of Pharmaceutical Sciences, Midwestern University Chicago College of Pharmacy, Downers Grove, IL, US**

Dr Naushad M Khan Ghilzai obtained his Ph.D. from LM University, Munich, Germany. He is currently Associate Professor at LECOM School of Pharmacy where his research interests are in the field of drug delivery systems and formulation development. He has published more than 30 research articles, reviews and reports in scientific journals.

Introduction

Pharmaceutical scientists and biomedical engineers have been exploring non- or less invasive alternatives to injectables for the delivery of several drugs (including large molecular weight drugs) for many years. Recently, pulmonary drug delivery systems have been extensively and exhaustibly investigated and a number of pulmonary drug delivery technologies have been developed. The pulmonary delivery route is close to the oral delivery route in terms of pharmaceutical company R&D investment in drug delivery systems. A large number of administration unfriendly drugs have been investigated for possible local and systemic delivery via the small alveoli in the lungs. Some of the latest developments depend upon fine aerosol particles penetrating through the lung walls, while the latest technique is the development of modified dry powder inhalers to deliver insulin.

Factors Affecting Pulmonary Drug Delivery

Their large surface area make the lungs a potent systemic delivery site for most drugs, including those of high molecular weight (peptides and proteins) that are absorbed through the alveoli into the systemic circulation. They also have the advantages of low enzyme activity, they do not suffer from first pass or GI tract effects, and they have a rich vascular system. Almost 90% of the lung surface is made up of alveolar epithelium, a thin (0.1-0.2 µm), single cell layer that is mucus-free, which permits these drugs to permeate rapidly through the alveoli. This helps peptide and other drugs to absorb quickly into the blood thus producing an enhanced therapeutic effect. Recent advances in pulmonary administration of many peptide and protein drugs have generated great interest, but although these factors make pulmonary delivery an effective and safe system, certain barriers such as respiratory mucus and mucociliary clearance have to be overcome for better administration.

Drugs administered via the lungs are effective only when the drug particle size is 2-5 µm so that it can deposit in the alveoli, and produce the desired clinical effect. If the drug particle is >5 µm, the drug will deposit in the upper respiratory tract, there will no clinical effect and systemic effects could result if it is swallowed. If the drug particles are <2 µm then there will be no clinical effect as drug particles will be exhaled making the drug ineffective to patients.

Pulmonary Drug Delivery Using Auxiliary Agents

The delivery of drugs via the lungs using absorption enhancers alone or in combination with enzyme inhibitors to improve the bioavailability of drugs including calcitonin, insulin and others has been reported in several animal studies. Such studies have shown the effectiveness of enhancers such as cyclodextrins and bile salts in enhancing drug absorption (Shao *et al*., 1994; Heinemann *et al*., 2000). Furthermore, the usefulness of enzyme inhibitors (proteases and peptidases) in improving drug therapeutic activity through the lungs has also been reported (Liu *et al.*, 1993; Fukuda *et al*., 1995; Shen *et al*., 1999). In addition, some studies have concluded that a combined approach using absorption enhancers (sodium glycocholate) with bacitracin and bestatin (enzyme inhibitors) can effectively deliver insulin and salmon calcitonin via the lungs.

Pulmonary Delivery Devices

Conventional drugs, such as corticosteroids and bronchodilators, have been used to treat asthma and chronic obstructive pulmonary diseases (COPD) in the past via the pulmonary route. The use of these drugs was restricted to local application by metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulisers (portable and handheld). Metered dose inhalers work by using propellants that atomise the drug solution resulting in a more uniform spray reaching the lungs. Many MDIs using chlorofluorocarbon (CFCs) propellants have been replaced by more environmentally friendly hydrofluoroalkanes (HFA 134 and HFA 227). The DPI is an alternative choice to MDIs and it delivers drugs in a dry powder form. Nebulisers are not a good choice because most drugs are not stable in aqueous forms and can easily decompose. Several new modified inhalation devices have been developed to deliver drugs systemically including antibiotics (cancer chemotherapy), pain relieving drugs (fentanyl and morphine) and peptide/protein drugs (insulin) in large doses. These devices are capable of delivering an acceptable amount of inhaled dose into the patient's blood. Inhaled drug absorption is quick compared with the same drug formulation delivered subcutaneously (or otherwise). Some companies have developed their own delivery device to complement their own formulation composition. These modified inhalation devices facilitate the delivery of peptide and protein drugs to the lung periphery. Some of the limitations associated with these devices are the large size and additional electrical or computer controlled systems attached to the inhalation devices, the result being that they are not very patient friendly.

Therapeutic Agents Investigated for Pulmonary Delivery

Several drugs are currently being investigated for their use in pulmonary drug delivery systems. Some have reported very promising clinical trials results and are undergoing safety and tolerability studies in human subjects. Some of the large molecular weight drugs being investigated are: insulin, leuprolide, oxytocin, erythropoietins, cetrorelix, human calcitonin, interferons, interleukins and somatostatin analogs. If any of these drugs can make it to the final stages, they will be hugely beneficial to patients suffering from life threatening medical conditions.

Pulmonary Drug Delivery Companies

Several drug delivery companies have developed their own proprietary technologies to deliver drugs to the lungs effectively and safely. Most of the therapeutic agents are in clinical trials for potential use in patients. The information below was collected from various sources including company press releases, public domains and research published in peer-reviewed journals, and shows that the companies that are actively pursuing large peptide and protein drugs, along with other difficult drugs, are making good progress. These companies are sub-divided into two categories: liquid aerosol devices and dry powder formulations.

Aerosol Containing Inhalation Devices (MDI's)

Aerodose® Inhalers (**AeroGen, Inc.**) Aerodose® Ipratropium Inhaler, Aerodose® Budesonide Inhaler and Aerodose® Insulin Inhaler (under development).
AIR® (**Alkermes, Inc.**) The company is working with **Eli Lilly** to develop inhaled insulin.
AERx® (**Aradigm Corporation**) rhDNase, opioids and insulin. AERx Insulin and morphine sulfate data are compared with SC insulin and IV morphine sulfate data from patients and has provided some good results.
Aria™ Inhaler & Technology (**Chrysalis Technologies**) has the potential to enable or enhance the delivery of new drugs; feasibility studies are being carried out with insulin and small molecules.
Mystic™ Platform (**Ventaira Pharmaceuticals, Inc.**) InfaMyst™ infant and paediatric device. OncoMyst™ Device containing Resmycin® currently in clinical trials.
Respimat® Soft Mist™ Inhaler (**Boehringer Ingelheim**). Developmental phase for several Boehringer Ingelheim bronchodilators.
TouchSpray™ Technology (**ODEM**). This technology is being developed to deliver peptides, proteins and DNA liquid formulations.

In January 2004, Diabetes Care published a research finding with AERx, reporting that pre-prandial AERx insulin is as effective as SC pre-prandial insulin in type 2 diabetic patients (Hermansen *et al*., 2004).

Dry Powder Inhalers (DPI's)

Acusphere, inhale sustained-release formulation (**Acusphere, Inc.**).
Aspirair™ (**Vectura Drug Delivery**) Technology applied with Powderhale™.
Inhance™ Pulmonary Delivery Device (**Nektar Therapeutics**). Useful for macromolecules (proteins and peptides). This technology is also used to manufacture inhaleable insulin powders, which have been undergoing trials (Exubera® – Phase III).
Meridica Xcelovair™ (**Meridica**) Xcelovair™ uses a wide range of drug molecules suitable for delivery to the lungs in both adults and children.
Oriel powder device (**Oriel Therapeutics, Inc.**) Electronic signal applied to DPI-albuterol.
SkyeHaler (**SkyePharma plc**) Products being developed for non-respiratory diseases such as diabetes and chronic pain.
SoliDose (**Quadrant Healthcare plc**) A micronised formulation to improve bioavailability of insulin in animal studies.
Sonik LDI (**Evit Lab, Inc.**) Drugs under investigation are Albuterol sulfate, insulin and human serum antibody (IgG).
Spiros® (**Dura Pharmaceuticals, Inc.**) Has potential for proteins and peptides, such as insulin.
Technospheres® Medtone™ Technology (**MannKind Pharmaceuticals**)

Others

ASES – Aerosol Solvent Extraction System (**Eiffel Technologies**).
e-Flow® Nebulizer (**PARI GmbH**).
Premaire™ (**Sheffield Pharmaceuticals**) Ultrasonic nebuliser can be used for delivering drugs to treat asthma, COPD and cystic fibrosis.
BioAir™ (**BioSante Pharmaceuticals**) Technology to deliver insulin and other proteins, for example, human growth hormone to the lungs.

Most of the above technologies have advanced into clinical trials and some are close to applying for FDA approval.
In 2004, SkyePharma announced that it had entered into a strategic alliance with Vectura whereby SkyePharma acquired proprietary rights to use Vectura's Aspirair dry powder inhaler device for some large molecular weight drugs on a non-exclusive basis.

The Future of Pulmonary Drug Delivery

In recently published reports, many academic and industrial laboratories have made some progress in achieving sustained drug release by encapsulating drug particles within a polymeric matrix or coating drug particles with a polymeric material or by putting the drug in a lipid material. These novel technologies will overcome the unresolved issues that were previously a roadblock in the pulmonary delivery process. In recent work on developing a novel formulation for insulin and human growth hormone, researchers used an encapsulation technique to trap drugs inside microscopic plastic spheres for pulmonary delivery. The plastic sphere subsequently dissolves leaving the drug to act alone (Fu *et al*., 2002; Suh *et al*., 2003). Recent advances in particle engineering have allowed the use of various drugs in a more efficient way from DPI's. The future of pulmonary drug delivery can be helpful in securing better and effective delivery systems in treating diabetes, osteoporosis, cancer-related pain, cystic fibrosis, endometriosis and lung infection.

Conclusion

The latest advancement in pulmonary drug delivery was a market approval application filed with the European office for an inhaled form of insulin (Exubera™). Several other proprietary technologies are being developed that focus on the delivery of many drugs, with the emphasis on large peptides and proteins in general and insulin in particular, through the lungs.

In the past decade, it has been scientifically proven and clinically well established (in some cases) that an increase in innovative pulmonary drug delivery systems will certainly have a positive effect on the overall drug delivery market. The technology involved in pulmonary delivery systems will continue to expand in the coming years. This is the area, which is explored extensively by the scientific community, where more drugs can be delivered non-invasively causing less discomfort. This century will certainly witness some novel delivery devices that can be used to deliver drugs to the lungs in order to achieve the desired biological activity.

References

Fu J, Fiegel J, Krauland E *et al.*, 2002. *Biomaterials*, **23**:4425-4433.

Fukuda F, Tsuji T, Fujita T *et al.*, 1995. *Biol Pharm Bull*, **18**:891-894.

Heinemann L, Klappoth W, Rave K *et al.*, 2000. *Diabetes Care*, **23**:1343-1347.

Hermansen K, Roennemaa T, Petersen AH *et al.*, 2004. *Diabetes Care*, **27**:162-167.

Liu FY, Kildsig DO, Mitra AK, 1992. *Life Sci*, **51**:1683-1689.

Shao Z, Li Y, Mitra AK, 1995. *Eur J Pharm Biopharm*, **40**:283-288.

Shen Z, Zhang Q, Wei S *et al.*, 1999. *Int J Pharm*, **192**:115-121.

Suh J, Wirtz D, Hanes J, 2003. *Proc. Natl Acad Sci*, **100**:3878-3882.