Emerging Research Opportunities in Oral Inhalation Technology

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From novel formulations to advanced inhalation platforms, oral respiratory drug delivery has made steady progress and promising breakthroughs are on the horizon.

Current therapeutic targets

The use of oral respiratory drug delivery systems for local treatment of respiratory tract diseases such as asthma, respiratory distress syndrome, and chronic obstructive pulmonary disease (COPD) is well known and continues to be an active area of research. However, says Richard Dalby, professor at the University of Maryland’s School of Pharmacy, “the real growth area is its use as an alternative to giving injections,” specifically for the systemic delivery of proteins, peptides, hormones, and gene therapy vectors. “Unless the drug is going to be used in a hospital or unless it’s a life-threatening situation,” says Dalby, “formulators are going to need to find another way of getting the drug into the body.”

Several companies have recently stepped up their efforts to meet this demand. For example, Nektar (formerly Inhale Therapeutics, Hayward, CA) is currently in Phase I studies of inhalable forms of an alpha-1 proteinase inhibitor, Tobra mycin (an antibiotic), and leuprolide (a hormone blocker used to treat various diseases such as prostate cancer and endometriosis). However, the drug currently gaining the most attention for inhaled delivery is insulin.

Inhalable insulin. Projected market potential.

Aggressive efforts toward marketing an inhalable form of insulin are supported by market research. According to Frost & Sullivan market analyst Ajit Baid, potential for considerable market growth exists in this area. The report reveals that 85% of Type 1 and Type 2 diabetes patients in the United States still use needle-and-syringe injections, even though needle-free technologies are currently available. Baid fore-
casts that when the first inhalable insulin prod-
uct enters the market “approximately 4% of pa-
tients will start using the inhalable product in the
first year.” However, “if the oral form of insulin is
not introduced during that time, that value is def-
initely going to multiply so that in the third year
it will be somewhere between 12 and 14%.”

Competition with other delivery systems is not
the only challenge, says Baid. To have a real chance
for success, the inhalation product must offer a
true competitive edge over other inhalation tech-
nologies. “Everyone is trying to say that their tech-
nology is superior to other technologies,” says Baid,
“but at the end of the day, what you may find is
that all of them do not really have an edge over
most of the existing technologies.” In short, the
best will survive.

Another challenge will be in getting FDA ap-
proval. However, notes Baid, “assuming that there
are no conditions on the approval of this product,
then you’re looking at a rapid penetration of the
market for this technology, which most likely
should be the case.”

Comparison studies. Recent studies of aerosolized
insulin solutions in humans have focused on
broadening the bioavailability range, currently re-
ported between 10 to 25% as compared with sub-
cutaneous formulations. Examples include an
Aerogen (Mountain View, CA) study of Type 2 di-
babetes patients that revealed a colinear dose-
response relationship between inhaled regular in-
sulin delivered via Aerogen’s Aerodose system in
comparison with the results obtained from the
subcutaneous injection delivery of regular insulin.
Results of that study showed that the system had
relative bioavailability and bioefficacy values that
were consistent across the dose range and had a
pharmacological predictability similar to that of
subcutaneous treatment. The Aerodose system also
was used in another Aerogen study conducted in
patients with Type 2 diabetes that showed that in-
haled regular insulin had a bioavailability (0-8 h
postdosing) of 16% and a biopotency of 13% rel-
ative to subcutaneously injected regular insulin.
The coefficients of variation and glucose infusion
rates for both treatments showed “no significant
differences” during the time range. In addition,
the inhaled insulin treatment provided “compar-
rable” dosing reproducibility and shorter time-to-
peak action.

Molecular and particle engineering. The inhaled-insulin
project currently nearest completion is the Exu-
bera project, a collaboration among Pfizer, Aven-
tis, and Nektar and currently in Phase III clinical
trials. According to Joyce Strand, Nektar’s direc-
tor of corporate communications, the Exubera
project incorporated the company’s pulmonary
technology to develop a formulation that can
spray-dry particles of insulin between 1–3 μm and
to design and manufacture a proprietary inhala-
tion device. John Patton, chief scientific officer and
cofounder of Nektar, says the company is also in
the very early research stages of developing a
long-acting inhaled insulin using PEGylation tech-
nology. PEGylation involves the attachment of
polyethylene glycol (PEG) derivatives to drug mol-
cules. According to Patton, “one of the biggest de-
terminants in how drug molecules behave in the
body is their size: the bigger they are, the longer
they last. PEGylation makes a molecule bigger,
which can extend its therapeutic effect.” Moreover,
says Patton, “these PEG molecules inhibit the
immunogenicity of therapeutic proteins,” an ef-
fect that often is not discovered until after a com-
pany has invested millions of dollars in the pro-
ject. A recent study by Leach et al. appears to
support this premise. The study showed that a PEG
derivative of molecular weight 750, compared with
insulin alone, resulted in good bioavailability across
the lung, prolonged systemic insulin levels, and
prolonged glucose suppression without affecting
clearance. The company, says Patton, is getting
ready to file but has not released a date.

BioSante Pharmaceuticals (Lincolnshire, IL), in
collaboration with the University of North Car-
olina, also recently announced positive results of
the use of PEGylation and their calcium phosphate
nanoparticulate technology for formulating vac-
cines and therapeutic proteins for inhalation. The
company’s BioAir system was shown to increase
systemic residence time and bioavailability in com-
parison with the subcutaneous delivery of insulin.
Research and development in inhaler design and formulation

Oral respiratory inhalers and formulations are the subject of extensive research efforts. Just in the past two years, at least 70 patents have been granted for inhalation designs or parts of inhaler systems, and at least another 43 are in the application process (see www.uspto.gov).

**pMDIs/MDIs.** Most of the research in pressurized metered-dose inhalers (pMDIs) continues to focus on the phasing out of CFC propellants as mandated by the 1987 Montreal protocol. The two leading alternatives are the hydrofluoralkanes HFA 134a and HFA 227. Although no deadline has been set for the industry to be in full compliance, steady progress is being made into incorporating non-CFC propellants into inhalation products. AstraZeneca, for example, plans to develop a pMDI version of its Symbicort Turbohaler system to treat exercise-induced bronchospasms. Meanwhile, 3M Corp., which was the first company to offer a non-CFC-based inhaler, continues to be at the forefront of research of non-CFC-based delivery systems. The company has marketed several products for asthma and COPD and is seeking a partner for developing an inhalation system for its smoking cessation project.

Promising developments in MDI systems include the AERx system (Aradigm, Hayward, CA) and its potential use in the treatment of cystic fibrosis. Other active areas of research for MDIs include the study of electrostatic generation during aerosolization, novel designs of MDI actuator nozzles, and MDI configurations with internal surfaces coated with a fluorocarbon polymer.

**Aqueous delivery. Nebulizers.** Julie Suman, PhD, cofounder of Next Breath (Baltimore, MD) states that nebulizers are typically a good starting point during the preclinical stage when a formulation is being tested for compatibility with inhalation systems and for companies trying to get to a Phase I trial.

By evaluating various drug–device combinations, the company serves as a liaison between formulators and device manufacturers for bringing novel inhalation and nasal systems to clinical trials. “We first start with evaluating the properties of the drug—such as its solubility, pH, its compatibility with excipients, and its dosing—then figure out what type of formulation is best and use that to choose a device platform that we think would work,” says Suman. As part of its patient-focused testing, the company uses a software package that simulates inhalation breathing patterns.

“The aerosol world is very much a niche marketplace,” says Suman. By integrating the needs of the patient with the technology of the industry, the time and dollars spent taking a project through to development are well invested.

Although they are bulky and expensive to manufacture, nebulizers often are the preferred system for the delivery of specific formulations, especially new drugs, and for use in pediatric and geriatric patients.

Current research focuses on enhancing nebulizer designs and expanding the use of nebulizers for applications such as cancer therapies. A recent in vivo study compared the performance of a nebulizer (Pari LC Plus, Pari GmbH) with that of a breath-actuated inhaler (Aerodose, Aerogen) with regard to the lung deposition of tobramycin using nebulization.

**Liquid-based inhalers.** Emerging technologies in this field include the development of inhalers incorporating electrohydrodynamics (EHD) in the design, specifically the Mystic device from BattellePharma (formerly Battelle Pulmonary Therapeutics). Categorized as soft-mist or small-volume inhalers, the EHD systems use an electric field produced from a battery source to break the surface tension of the liquid formulation and produce a fine cloud mist for inhalation. Although EHD technology has been used in various industries since 1917, says Michael E. Placke, PhD, vice-president of pharmaceutical development and chief scientist at Battelle, “the key proprietary technology is a means to discharge the aerosol.” Neutralizing the electric charge makes the particles suitable for medical aerosol use. Bill Zimlich, vice-president of device product development, says that this technology produces “a discharged aerosol of a very soft mist with no velocity and is entrained instantly in the patient’s respiratory flow volume and then drawn deep into the lung.”

**Dry-powder delivery.** The University of Maryland’s Dalby estimates that there are more than 40 dry-powder inhalers (DPIs) in development. Much of the work in academia and industry has involved the study of the forces between the particles of the powder and characteristic problems associated with powder formulations (e.g., particle adhesion, cohesion, and flow).
While some companies are working toward optimizing particle characteristics, others are conducting research of sophisticated inhaler designs to accommodate a range of formulations. Oriel Therapeutics, for example, is developing an active DPI that is a formulation independent delivery system. Specifically, says Anthony Hickey, professor of drug delivery and disposition at the University of North Carolina (Chapel Hill), the device “takes the characteristics of the powder and uses those in an algorithm to input energy to disperse the powder.” Rather than taking a formulation strategy to improving powder properties, the device uses the powder’s existing properties and inputs them as part of a “smart” electronic approach to dispersion. The design also has feedback mechanism in which “the characteristic algorithm is stored on a chip that basically matches the powder,” says Hickey. The device “matches the energy of the inspiratory flow cycle of the patient. So that it maximizes the energy input at any point in time during inspiratory flow.”

**Particle-size distribution (PSD) and characterization**

Regardless of whether the drug is in an aqueous or dry-powder format, one of the most important factors for its successful delivery into the lung is achieving and maintaining a well-defined particle-size distribution. Particles must be in the 2–6 μm range for delivery into the lung (bronchi and bronchioles) and in the 1–2 μm range for deep-lung deposition into the terminal bronchioles and alveoli (necessary for insulin).

Several companies offer proprietary technologies for sizing particles to this range. For example, the AIR pulmonary drug delivery system by Alkermes is currently part of two collaborations with Eli Lilly and Company for the development of inhaled formulations of human growth hormone and short- and long-acting inhaled formulations of insulin (www.alkermes.com). In addition, Epic Therapeutics, a wholly owned subsidiary of Baxter Healthcare Corp., has developed ProMaxx, a formulation technology for producing microspheres for insulin and other drugs. Anthony Garramone, president of Epic Therapeutics, says that the program, which began two years ago, offers “very precise size control over the microspheres. The mean of the range can be adjusted, but the range itself is very narrow.” The company is using insulin as both proof of concept and a product application. The company has been able to achieve good in vitro results for the microspheres incorporated into HFA formulations for both DPIs and MDIs (mean size ~1.2 μm). In addition, the ProMaxx insulin microsphere formulations have exhibited an improved stability profile compared with native insulin studied over the same time period. The company also reported favorable results obtained from in vivo studies in rats and dogs and has begun preclinical dose-relationship studies as a first step toward human clinical trials.

Methods for experimentally determining the PSD of inhalable particles include the use of spectrometry for MDIs, laser diffraction and inertial impaction techniques for drug products formulated as solutions, and forward light scattering to evaluate the effects on particle- and droplet-size distributions of HFA-227–based formulations containing an active pharmaceutical ingredient. In one study, laser diffraction, time-of-flight, and Anderson Cascade impaction methods were used to evaluate the particle size of salmeterol xinafoate powders for DPI delivery.

**Regulatory and guidance overview**

**PSD and bioavailability/bioequivalence.** In 1999, FDA published a draft Guidance for Industry that included the agency’s recommendations for the comparison of in vitro PSDs delivered from innovator and generic nasal products. Although the draft guidance applies to nasal delivery, the agency indicated that it would seek to draft a similar guidance for oral inhalation systems. Since that time, several organizations, including the Product Quality Research Institute’s working group on particle-size distribution, the Inhalation Technology Focus Group (ITFG) of AAPS and the International Pharmaceutical Aerosol Consortium (IPAC) as well as several academic leaders have submitted comments, voicing their concern about the removal of in vivo testing to verify bioequivalence for generic products.

In May 2001, the ITFG/IPAC group submitted its response to FDA’s Draft Guidance “Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation,” which includes information about testing PSD. Also in 2001, the...
PQRI Particle Size Distribution Mass Balance Working Group was formed to examine the mass-balance–related recommendations presented in FDA’s draft guidance. The group released a document, “Considerations for the Development and Practice of Cascade Impaction Testing Including a Mass Balance Failure Investigation Tree,” in which the authors conclude that mass balance “should not be used alone as a system suitability test when assessing aerodynamic PSD.”

**USP monograph for HFA 134a.** Charles Thiel, formerly at 3M Corp., is part of the USP committee working on a USP monograph for HFA 134a, a project that has been ongoing for the past year and half. However, there have been several challenges in this effort. “USP depends on industry to help supply the analytical methods for assessing purity,” says Thiel, “but most of the information is proprietary, so companies are reluctant to reveal the information.” A draft of the proposed monograph was presented at the 2002 Respiratory Drug Delivery Conference.

**Harmonization of USP (601).** USP General Chapter (601) “Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers” has been listed as under consideration for harmonization, with recommended changes published in 2002. The publication includes changes related to delivered-dose uniformity, which stemmed from a June 2002 meeting of the Aerosol Expert Committee to discuss the IPAC-RS proposal entitled “A Parametric Tolerance Interval Test for Improved Control of Delivered Dose Uniformity of Orally Inhaled and Nasal Drug Products.”

**Future research and education**

Drug delivery by inhalation remains an active area of research not only for formulators and device manufacturers, but for scientists still desiring an understanding of the complex nature of pulmonary delivery. As Hickey points out, a need exists to “fully understand the force of interaction between particles and the complementarity of those forces in the size range of interest for inhaled particles [1–10 μm]. There is a lot of basic physical chemistry and underlying physics that must be understood.” He states that his future research goals include the application of inhaled therapies to treat very serious pulmonary diseases, including tuberculosis, which Hickey believes is one of the most serious diseases in the world.

According to Dalby, meeting these goals means not only supplying inhalation therapies to patients, but also educating patients and practitioners—“the essential step that is often overlooked.” Keeping abreast of current developments in inhalation technology requires face-to-face conversations with other experts and the thorough education and training of all personnel involved in inhalation projects. For the past 13 years, Dalby has conducted the annual Inhalation Aerosol Technology Workshop at the University of Maryland, a three-day course that provides real-world laboratory opportunities. “We try to teach people how to use equipment instead of just putting up slides and showing pictures,” he says. In addition, Dalby is involved in coordinating the Respiratory Drug Delivery conference, held every two years, which provides in-depth information about the latest topics in pulmonary delivery.

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**FYI**

**Call for research papers and presentations**

The PDA Biopharmaceutical Program Planning Committee of the 2004 PDA SciTech Summit taking place 8-12 March 2004 in Orlando, Florida invites attendees to present research papers and educational presentations. Papers and presentations for consideration must be of high quality and focused in the areas of worldwide viral trends, multi-product facilities, costs of quality, transportation validation, and related biopharmaceutical fields.

Accepted abstracts of papers must not have been previously published or presented at scientific meetings, be non-commercial in nature and contribute to the body of knowledge of biopharmaceutical science and technology.

Proposed abstracts must be received by July 18, 2003 for consideration. For more information on abstract guidelines and instructions, visit www.pda.org.