Perspective

Delivery of Biological Agents by Aerosols

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Introduction

Inhaled aerosols as vehicles for delivering biological agents have attracted broad national attention since the death of Bob Stevens on October 5, 2001 at American Media Inc. in Florida by inhaled *Bacillus anthracis*, the bacteria that cause the disease anthrax. Since then, with more inhaled anthrax cases reported, Americans have likely heard and read more about aerosol physics, and the role it plays in establishing the "weapons-grade" quality of inhaled pathogens, than they have in the past 40 years. The same aerosol physics, however, has played a profound role since the early 1960s in our daily lives, specifically in delivering drugs to the lungs for the treatment of diseases like asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD).

Most of what we know today, in terms of fabricating aerosols, rendering them physically and chemically stable, and indeed destroying them, came from this therapy effort, a principal focus of this perspective. Serving as background to this article is the question of how current understanding of inhaled aerosols can be used to both markedly improve human therapy and possibly counteract bioterrorism efforts to deliver inhaled pathogens.

The idea of inhaling drugs for medical applications grew out of the treatment of asthma in the 1950s by orally ingested asthma drugs (Jenne and Murphy, 1987). To reach deep into the lungs, the site of action of such drugs (Figure 1), patients ingested relatively large drug doses, and this tended to produce untoward systemic side effects (Williams and Seaton, 1977; Weinberger, 1982). Patients typically ingested more than a hundredfold the quantity of drug required to achieve a therapeutic response at the site of action (lung epithelia), owing to the dilution effect of systemic administration. Industrial researchers met this problem in the 1960s by designing products that permitted direct inhalation of the drugs via handheld devices, still the mainstay of asthma treatment (Figure 2). The early products used conventional perfume valve technology with some knowledge of the optimal size range of aerosol particles for entry into and deposition in the lungs following inspiration (Thiel, 1996). Asthma drugs could then be suspended in compressed volatile liquids that exited the device and entered the lungs through the coordination of an inhaled breath and the opening of a valve to release a small quantity of compressed liquid—as one sprayed perfume—into the mouth. Inevitably, some small fraction of the aerosol particles generated by this process fell into the optimal size range of 1 to 5 μm and then usually entered the lungs to have a therapeutic effect (Goodman et al., 1994).

Inhalation therapy, at least as practiced commercially, appears much the same today as it did 30 years ago. In clinical trials in the U.S. and around the world, however, new advances in inhalation technology promise to radically change the way we treat respiratory and even systematic diseases, like asthma, diabetes, and growth deficiency (Edwards and Dunbar, 2002). One of the primary goals of this new technology is to magnify the efficiency of existing delivery systems for a growing range of drugs without sacrificing the patient friendliness of currently marketed products. This is the technological driving force behind the "large porous particle" (LPP) idea (Edwards et al., 1997), among other novel particle design ideas (Dellamary et al., 2000; Tong et al., 2001; Bot et al., 2000) generally aimed at permitting portable devices to deliver more drug to the lungs in a single inhalation, extend drug duration up to a day or more, and achieve greater efficiencies of delivery than possible with classical technologies. These kinds of developments are changing the way we think about making inhaled aerosols for therapy and, at the same time, may help inform us increasingly as to how aerosols might be stopped from spreading disease.

Key Aerosol Properties for Delivery

Modern methods for creating aerosol particles include spray drying, supercritical fluids, and sophisticated liquid droplet production technologies (Masters, 1985; DeYoung, 1998; Schuster et al., 1997; Tong et al., 2001). These manufacturing (and delivery) technologies provide advantages over classical milling and nebulization operations (Hinds, 1998) in that they provide greater control over aerosol particle chemical composition and physical characteristics. This is key as many new therapies require the ability to use combinations of pharmaceutical excipients (e.g., amino acids, sugars, lipids, and polymers) to provide control over, for example, the rate at which the drug particle dissolves in the lungs, particle physical characteristics, and shelf-life stability (Ansel et al., 1999). Practically, one might imagine that there would be relatively few limits (aside from time and effort) to the control that we might exert on inhaled drug aerosols apart from that imposed by practicality itself. That is, inhaled therapies must be user-friendly. There are practical limits to the sophistication and cost that can be invested in the manufacture and delivery of commercially viable therapeutic aerosols (Dunbar et al., 1998). For this reason, particle design provides a popular current approach to developing highly efficient, "user-friendly" aerosol systems. This generally involves manipulation of particle physical characteristics, bearing in mind those characteristics sought in an inhaled aerosol particle for entry into and deposition in the lungs.

Briefly, particles enter the lungs by convection, and deposit primarily by inertial impaction, diffusion, and sedimentation (Heyder et al., 1986). Deposition in the lungs, particularly for particles subject to gravitational and inertial forces—the primary class of particles for drug delivery—is conveniently characterized in terms of aerodynamic diameter, which can be understood by considering a spherical particle of geometric diameter d_g and mass density ρ. Under gravity, the particle settles with a velocity that is proportional to ρd_g^2, or equivalently to d_a^2, where d_a is the aerodynamic diameter

$$d_a=(\rho/\chi)^{0.5}d_g \qquad (1)$$

where χ is a shape factor denoting deviation of shape from sphericity. Aerodynamic diameter determines how well particles enter and how far they go in the lungs. Filtering of particles occurs in the upper airways by inertial impaction, with large particles (d_a>5 μm) depositing in the mouth and the first few generation of airways (trachea, main bronchi) (Heyder et al., 1986; Heyder and Rudolf, 1994). Smaller particles (1<d_a<5 μm) are deposited in the central and peripheral airways, and in the alveolar lung region by a combination of inertial impaction and sedimentation. Very small particles (d_a<1 μm) are animated by diffusion, and a large fraction of these particles remain suspended in the air flow and are exhaled.

Aerosol particle design therefore involves two basic strategies. Either particles are made of standard density with a geometric size in the 1 to 5 μm range, or they are created with nonstandard density, and therefore with geometric sizes outside the standard range. (Nonspherically isotropic particles are generally avoided owing to issues related to processing and aerosolization, as well as potentially to local toxic effects). All currently marketed inhaled products employ the first strategy. LPP aerosols provide an example of the second strategy. Characterized by large size (10–20 μm), particles of these aerosols possess small mass density, such that the aerodynamic particle size remains small (1–5 μm) (Edwards et al., 1997). LPP aerosols disperse from a packed dry powder more easily than small particles, all other things equal (Dunbar et al., 1998) (see Figure 3), and effectively escape inertial and gravity deposition prior to penetrating deep into the lungs (Scheuch et al., 1999). This strategy aims to provide the convenience of the conventional systems (Figure 2) with the effectiveness of new clinical therapies. Also, since particle uptake by scavenging macrophages diminishes with increasing particle size, the LPP strategy may make it possible to deliver drugs for a more sustained duration by avoiding drug particle clearance, as, e.g., can be useful in reducing the frequency of dosing for asthma (Ben Jebria et al., 1999).

Figure 1. Cast of the human lungs.
Courtesy of Dr. J. Heyder, GSF Institute, Munich. The twin lobes of human lungs branch off from the trachea, starting with the main bronchi and reaching through multiple bifurcations past the terminal bronchioles (e.g., Weibel, 1963, 1973). Beyond conducting airways is the respiratory zone, where primary gas exchange occurs with circulatory blood. Insoluble particles are rapidly cleared from conducting airways by cilia within the mucous layer lining the epithelia, which carries particles toward the pharynx, where they are swallowed. This clearance typically takes 12–24 h following deposition. In the respiratory zone, beginning with the terminal bronchioles and ending with millions of alveolar sacs, deposited particles can reside for many months, though typically within alveolar macrophages, which phagocytically ingest deposited particles quickly after deposition. The alveolar region of lungs is highly vascularized to permit effective gas exchange, providing about 75 m^2 of contact surface with blood capillaries, or nearly 40 times more surface area than external body surface area. The epithelial cell membrane of the alveolar lung region is also thin, with an average thickness of 0.2 μm, permitting relatively rapid equilibration of blood and alveolar fluid proteins.

How Efficient Can Aerosol Therapy Be?

Currently marketed inhalation therapies, based on commercially-available dry powder and metered-dose inhaler (MDI) devices, deliver around 10–20% of a drug load into the lungs following an effective inhalation (Clark, 1995). Animals breathing standing cloud aerosols in inhalation chambers inhale perhaps 1–2% of loaded drug (Walton and McGovern, 1977). To achieve success with new inhaled therapies, for instance, in the case of diabetes, inhaler systems need to achieve efficiencies of delivery that range above about 50%, which is the target for the newest generation of inhalation technologies.

Several of these technologies now propel inhaled insulin clinical programs currently underway with the backing of the world's principal insulin suppliers. The first, introduced in the mid-1990s, involves a dry powder

insulin formulation delivered from an inhaler that releases the aerosol into a holding chamber, the Inhale system (Dunbar, 2000), now in Phase III human clinical trials through the joint efforts of Inhale Therapeutics, Pfizer, and Aventis (Skyler et al., 2001). The Inhale system achieves relatively high aerosol delivery efficiency by producing insulin particles combined with pharmaceutical excipients (e.g., sugars) through spray drying. The dry insulin particles are placed in individual blisters loaded into an inhaler whose energy source resembles an air gun (Dunbar, 2000). The patient pumps the inhaler, "shoots" the powder into a standing cloud in a transparent chamber, and then inhales the standing insulin-particle cloud through one or more slow deep breaths. The second system, now in Phase II clinical trials in a partnership with Novo-Nordisk (Brunner et al., 2001), is the Aradigm—or AerX—system, a vast improvement on the kinds of therapeutic aerosols generated by traditional nebulizer (Schuster et al., 1997) and metered-dose inhaler (MDI) (Farr et al., 2000) systems. AerX involves the delivery of a liquid drug solution through small plates into which laser-etched holds have been drilled (Schuster et al., 1997). The plates can be discarded after each use, permitting AerX to maintain solution sterility, a principal concern for liquid-based protein solutions (Adjei, 2000). Both systems produce insulin bioavailabilities in early human studies ranging from 10–13% (Brunner et al., 2001; Skyler et al., 2001), with bioavailability defined here as the percent area-under-the-curve (AUC) of exogenous systemic insulin by inhalation (as plotted vs. time) relative to the equivalent AUC obtained by subcutaneous insulin injection, with the dose adjusted. These bioavailabilities contrast with the 7.6% insulin biopotency (with biopotency defined here based on systemic glucose concentration, rather than exogenous insulin concentrations) human study with a Turbuhaler device (Heinneman et al., 1997), one of the more efficient of the currently marketed "simple" inhalers. The LPP idea led to net lung deposition efficiency (of the nominal dose) of approximately 59% (Scheuch et al., 1999), and insulin delivery efficiency at least comparable to the AerX and Inhale systems, yet with a less sophisticated inhaler device (Osborn et al., 2001). This technology underlies the AIR program, now in Phase I clinical trials in a joint collaboration between Alkermes and Eli Lilly & Co. Table 1 summarizes the status of these three inhaled insulin clinical programs.

Figure 2. Commercially available dry powder and metered-dose inhalers.
Courtesy of Alkermes, Inc., Cambridge, MA. These inhalers represent portable, handheld, single- or multiple-use inhaler devices for delivering drugs for respiratory disease. New inhalation technology currently in the clinic may employ devices of greater technical sophistication.

Table 1. Inhaled Insulin Programs with Major Insulin Suppliers

Company	Collaboration	Clinical Phase	Aerosol Form	Device Type
Inhale	Pfizer/Aventis	Post-Phase III	Dry powder	Hand-actuated
Aradigm	Novo Nordisk	Phase II	Liquid	Electronic
Alkermes	Eli Lilly	Phase I	Dry powder	Breath-actuated

Inhaled Pathogen Threat

In the same way that inhaled aerosols can be used to effectively administer a drug for human therapy, they can serve as frighteningly effective carriers of human disease. Inhaled aerosols can transmit, e.g. (NRC Committee, 1999), the pathogens for anthrax, pneumonic plague, tularemia, Q fever, smallpox, viral encephalitides, viral hemorrhagic fevers, botulism, and staphylococcal enterotoxin B (SEB), among others. Inhalation is often the most effective route these pathogens can follow to enter the body (NRC Committee, 1999).

Given the plethora of potential threats, identification of specific bacterial or viral pathogen may be more problematic than identification of a particle capable of entering the lungs, whether the particle contains a pathogen or not. Counteracting efforts to achieve terrorist ends through inhaled pathogens might therefore be thought of, in a sense, as the reverse engineering of an effective inhaled drug delivery system. Lessons learned and drawn from the development of inhaled drug delivery systems then prove useful to increasing our understanding as to what might hamper attempts to deliver pathogens through inhalation in the future.

Pathogen-laced aerosols might be rendered inactive, even if the pathogen itself remains viable, by altering the physical state of the aerosol in various ways. First, moisture and heat, the twin nemeses of dry-powder shelf-life storage, can each lead to aggregation of dry particles, particularly if the particles are presented in a powder form prior to aerosolization. Most therapeutic aerosols when exposed in the absence of protective packing to an environment of 40°C and 75% relative humidity (standard "stress" conditions for pharmaceutical-product shelf-life stability testing) will show serious signs of aggregation within a matter of hours. Aggregation occurs through capillary forces (in the case of moisture exposure) or physical fusion (in the case of heat, sufficient to cause melting of the particles). A lifting force such as provided by an air current will then tend to aerosolize the particles in aggregate form, if at all, such that they fail to penetrate the nose or mouth with a sufficiently small aerodynamic diameter to enter the lungs. Once aerosolized, particles—whether in liquid or in dry form—can be captured and removed from the air. We remove small particles in the same way from the air for

other industrial applications. Thus, electrical fields, filters, high humidity, and air currents can each be used to sweep aerosols away from human-use facilities and prevent human exposure (Davies, 1973; Strauss, 1975). These and other technologies will likely be adopted in high security, as well as civilian, settings to aid our protection against the use of inhaled aerosols to spread disease.

At the same time, new inhalation aerosol technology might also lead to new therapies for treating symptoms of biological terror. Current asthma inhalers deliver less than a milligram of drug per inspiration, typically far too small a mass to be useful for (e.g., antibiotic) drug delivery following exposure to an inhaled pathogen. For this reason, intravenous or intramuscular injection is often the delivery route of choice. Thus, emergency postexposure treatment for pneumatic plague, tularemia, smallpox, and viral hemorrhagic fevers all involve needle injection (NRC Committee, 1999).

New antibacterial, antiviral, and antitoxin drugs in development often also require injection for delivery. However, the new inhalation technologies can often deliver much more than a single milligram of drug per inhalation—say 10 to 20 mg. In some cases, it may then be possible to use inhalation technology to deliver such drugs systemically, in the same way that insulin is now being delivered systemically via inhalation in clinical trials. The key advantage, apart from convenience, would be that the public could self-administer medications in the event of a biological attack, and therefore inhalation-administered medication could potentially provide mass civilian protection.

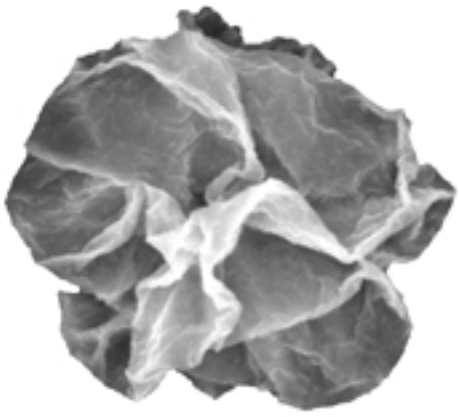

Figure 3. Large (8-μm-dia.) porous drug particle.
Courtesy of Dr. Michael Lipp, Alkermes, Inc., Cambridge, MA.

Future

Inhalation of biological agents, as a delivery paradigm for human therapy—and possibly as a vehicle for the spread of disease—is poised to acquire increasing attention. The potential launch of new inhalation products in the next several years for the treatment of diseases like diabetes, pain, and growth deficiency promises to change the way we think of inhaler devices—currently associated almost exclusively with the treatment of respiratory disease. Scientific and technological questions will continue to require attention, both in the realm of new technology, and in the area of inhalation biology and disease. What we have learned in recent years about delivering aerosols to the lungs, efficiently, will hopefully be as useful in the future to treating disease, as it is to preventing its spread.

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