invited review

Recent advances in pulmonary drug delivery using large, porous inhaled particles

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Edwards, David A., Abdelaziz Ben-Jebria, and Robert Langer. Recent advances in pulmonary drug delivery using large, porous inhaled particles. *J. Appl. Physiol.* 84(2): 379–385, 1998.—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. For most of these therapies, aerosols are designed to comprise small spherical droplets or particles of mass density near 1 g/cm^3 and mean geometric diameter between ~1 and 3 μm, suitable for particle penetration into the airways or lung periphery. 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 mucocilliary 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.

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DRUG DELIVERY TO THE LUNGS by inhalation has attracted tremendous scientific and biomedical interest in recent years. This trend accompanies a rise in respiratory illnesses, dramatized by an increase in asthma population in the United States of 46% between 1982 and 1993 (Centers for Disease Control and Prevention, Atlanta, GA). Of at least equal impact has been the development of many new biotherapeutics (primarily peptide and protein drugs) that in most cases can be delivered to humans only by intravenous injection, often with low patient compliance. 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 (7, 15, 23, 24, 26, 30).

While promising, inhalation therapy is not yet optimized (22). In many cases, the loss of efficiency or reproducibility that this lack of optimization entails can preclude inhalation as a practical noninvasive human therapy. Presently, this is true for many biotherapeutics currently injected intravenously, like growth hormone, glucagon, or α_1-antitrypsin, each of which could possibly be delivered to humans by inhalation were the efficiency of inhalation therapy greater. Losses of inhaled therapeutic can be attributed to a variety of factors; for example, inhaled aerosol particles must possess a very narrow range of "aerodynamic diameters" (related to a particle's geometric diameter and mass density) to pass through the filter of the mouth and throat. Even if properly designed and produced, aerosol particles may be propelled with too high a velocity and consequently deposited in the mouth and throat by inertia. Once in the lungs, particles must release the therapeutic substance at a desired rate and, in some cases, escape the lungs' natural clearance mechanisms until their therapeutic payload has been delivered.

To meet these challenges, new inhaler devices have been, and continue to be, developed. These fall in the

categories of metered-dose inhalers, dry-powder inhalers, and nebulizers (14, 21, 32). When combined with optimized aerosol formulations, these new inhalers promise to significantly expand the use of inhalation therapy in humans (20).

Among the factors that can be adjusted to optimize the efficiency of aerosol formulations, particle chemistry and surface morphology (manipulated to reduce particle-particle aggregation or hygroscopicity) and particle solubility (altered to influence the rate of therapeutic release) are rather well documented (10, 11). Less well documented is the potential for major improvements in aerosolization efficiency by diminishing aerosol particle mass density and increasing particle size, as done in recent studies for select formulations (6, 35). The delivery of large, porous particles to the lungs may also permit exceptionally long-acting therapeutic delivery following inhalation, as further described in this review.

THE AERODYNAMIC DIAMETER WINDOW

To understand the rationale behind therapeutic aerosol particle design, it is helpful to briefly review the concept of aerodynamic diameter and its relation to the pattern of particle deposition in the lungs. Aerodynamic diameter is the geometric diameter a particle appears to possess on the basis of its in-flight speed, were it assumed to be spherical and to possess a mass density of 1 g/cm^3; stated differently, the geometric diameter of a spherical particle possessing unit mass density (1 g/cm^3) is equivalent to its aerodynamic diameter. Because many naturally occurring particles possess a mass density near this value and because sphericity is a tendency of nature based on surface energetic considerations, such a "base-case" particle has proven useful for discussing the sites and extent of aerosol particle deposition in the lungs as a function of particle size.

A more quantitative idea of aerodynamic diameter can be gathered by imagining a spherical particle falling under gravity through air; so long as the characteristic particle size is substantially larger than the mean free path of the surrounding air molecules, it can be shown that the particle will settle with a velocity (v)

$$v = \frac{mg}{3\pi\mu d}$$

where m is the particle mass, g is the gravitational constant, μ is the viscosity of air, and d is the particle diameter. Expressed in terms of particle mass density (ρ), this gives

$$v = \left(\frac{g}{18\mu}\right)\rho d^2 \qquad (1)$$

Equation 1 shows that spherical particles will fall under gravity with a velocity that is proportional to their mass density ρ and the square of their geometric diameter (d^2). If we consider the heuristic definition of aerodynamic diameter provided above, it is possible to rewrite *Eq. 1* in terms of the particle's aerodynamic diameter, as

$$v = \left(\frac{\rho_a g}{18\mu}\right) d_a^2 \qquad (2)$$

where $\rho_a = 1$ g/cm^3, and where we have defined the aerodynamic diameter (d_a) by the relationship

$$\rho_a d_a^2 = \rho d^2 \qquad (3a)$$

or

$$d_a = \sqrt{\frac{\rho}{\rho_a}}\, d \qquad (3b)$$

Equation 2 shows that a spherical particle of any mass density ρ will settle with a velocity that depends only on its aerodynamic diameter d_a, i.e., is dependent on size and mass density through the specific relation of *Eq. 3*. Modifications to *Eq. 3* arise for nonspherical particles (10); these modifications can include more than a single aerodynamic coefficient, particularly in the case of nonisotropic particles (e.g., cylinders), wherein the particles translate with a preferred orientation.

Because gravitational settling constitutes one of the principal mechanisms of aerosol particle deposition in the lungs, the concept of aerodynamic diameter becomes a useful intrinsic particle property with which to discuss a particle's expected lung deposition performance following inhalation. Moreover, as shown by Landahl (17) in his landmark study of aerosol particle deposition in the lungs, the second principal mechanism of particle deposition in the lungs, inertial impaction, also depends uniquely on d_a (see Fig. 1, reproduced from Ref. 9). Aerodynamic diameter has thus been used for several decades to quantify an aerosol particle's inherent propensity to deposit in the lungs, essentially independently of its shape, mass density, and (in principle) geometric size.

Numerous experimental (2, 5, 12, 19) and theoretical (3, 9, 13) studies have demonstrated that particles of mean aerodynamic diameter of 1–3 μm deposit minimally in the mouth and throat and maximally in the lung's parenchymal (i.e., alveolar or "deep-lung") region. Tracheobronchial deposition, generally not desired for an inhalation therapy, is maximized for aerodynamic diameter between ~8 and 10 μm. Particles possessing an aerodynamic diameter smaller than ~1 μm (although greater than several hundred nanometers) are mostly exhaled, and particles larger than ~10 μm have little chance of making it beyond the mouth.

The aerodynamic diameter window of 1–3 μm has also proven optimal for inhalation drug delivery. By using liquid aerosols (whence aerodynamic and geometric diameters coincide) Clay et al. (4) found that optimal bronchodilation in human asthmatics occurred after inhalation of 1.8-μm-diameter (terbutaline) droplets, relative to droplets of 4.6 or 10.3 μm in diameter (all other factors held constant). Johnson et al. (16) and

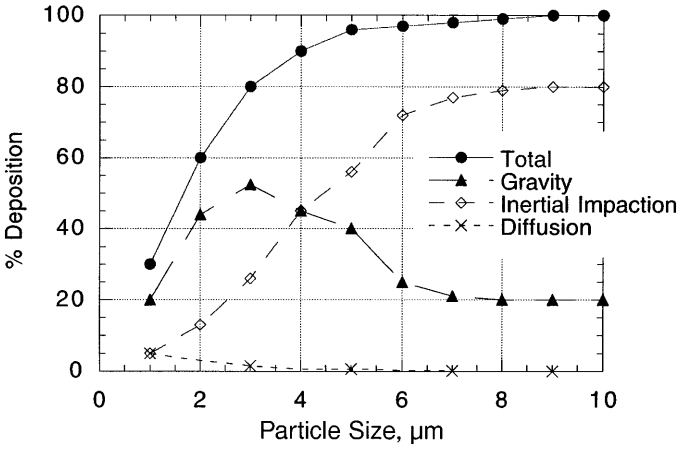

Fig. 1. Relative deposition in a human lung model after inhalation of a monodisperse aerosol as a function of aerosol particle aerodynamic diameter, for particles with a mean aerodynamic diameter of 1–10 μm. Contributions from the 3 predominant mechanisms of deposition are listed; these include gravitational sedimentation, inertial impaction, and Brownian diffusion. The latter mechanism of deposition becomes predominant for particles of mean aerodynamic diameter less than ~0.5 mm (9), hence it does not substantially contribute to therapeutic particle-deposition patterns in lungs. Other deposition mechanisms, including electrostatic precipitation (e.g., in an inhaler) or interception, are not considered and may be assumed either to be minor contributors to overall particle deposition or to play an important role in limited circumstances, such as those involving particles with significant surface charge. [From Gerrity et al. (9).]

Ruffin et al. (28), respectively, showed that liquid aerosols comprising 3.3-μm (salbutamol) and 1.5-μm (isoproterenol) droplets also produced greater bronchodilation in human asthma patients than did droplets substantially larger than 3 μm. Also, Zanen et al. (37, 38) in two separate studies found that 2.8-μm aerosols of salbutamol and ipratropium bromide produce greater bronchodilation than droplets of larger or smaller size (although little difference was seen between the 1.5- and 2.8-μm ipratropium bromide aerosols). The aerodynamic diameter window of 1–3 μm has also been shown to be optimal for systemic delivery in dogs after inhalation of leuprolide acetate (liquid) aerosols (1).

Given that most published studies of particle size effect on therapeutic efficacy have used approximately spherical aerosol particles of mass density near unity (1 g/cm^3) and considering that manipulation of aerodynamic diameter by particle mass density has tended to be viewed as hard to achieve (10, 11), the aerodynamic diameter window of 1–3 μm has become associated in many published research articles with an intrinsic geometric diameter window in the same range (1–3 μm) (1, 30). This partly explains why therapeutic aerosol particles are primarily designed today with geometric diameters in the range of 1–3 μm, even though aerosol particles of much larger size (and lower mass density) can be encountered in the environment and often enter into the lungs. This latter point is reflected in the following list of airborne particles (note that increasing particle size generally coincides with diminishing mass density, in accordance with the relationship indicated by *Eq. 3*) (25, 33): pollen (10–100 μm), natural fog (2–80 μm), coal dust (3–30 μm), and metal fumes (0.01–100 μm).

THE BIOAVAILABILITY QUESTION

To further clarify the optimal characteristics sought in an "ideal" therapeutic aerosol formulation, we review one of the major driving forces for the expanding use of inhaled therapies; namely, to replace injectables with an easy-to-use, affordable, noninvasive delivery technology.

Intravenous (iv) injection, the primary route of protein therapeutic administration, is painful, and patient compliance is often low as a consequence; several excellent reviews have documented the case for pulmonary administration as a practically viable alternative (22, 30, 34). Relative to oral administration, pulmonary delivery exposes the administered drug to a less harsh environment, and the permeability of the alveolar epithelium is high. Compared with the sites of transdermal, nasal, vaginal, buccal, or ocular delivery, the exposed surface area of the lungs is extremely large, estimated to approximate the area of a tennis court (22).

The efficiency of drug delivery by a noninvasive route can be expressed in terms of bioavailability (B) defined as

$$B = \left(\frac{AUC}{AUC_{iv}}\right) \times \left(\frac{dose_{iv}}{dose}\right) \times 100 \qquad (4)$$

where AUC represents the integrated area under the curve of systemic plasma concentrations of administered drug vs. time, given a particular dose (dose); and AUC_{iv} is the comparable area obtained after iv injection of the same drug with dose ($dose_{iv}$). Because inhalation of drugs involves losses of drug in the inhaler as well as in the mouth and throat, researchers define bioavailability either in terms of the actual dose administered or the dose delivered to the pulmonary system, the latter being a kind of optimal intrinsic value and the former having more direct relevance to an actual therapy. Depending on the dosage form, a relative bioavailability may also be defined in terms of subcutaneous (rather than iv) injection, i.e.

$$B_{sc} = \left(\frac{AUC}{AUC_{sc}}\right) \times \left(\frac{dose_{sc}}{dose}\right) \times 100 \qquad (5)$$

where sc denotes subcutaneous administration. As measures of bioavailability, values of B_{sc} overestimate the "absolute" value of B. Table 1 lists the bioavailabilities of several different proteins following inhalation, with absolute definitions of B.

Together with the question of appropriate pharmacokinetics, the question of bioavailability is central to the viability of a systemic inhalation therapy. Given a required dose to be administered to the systemic circulation, as well as the acceptable dose variability and upper limit on the amount of mass that can be inhaled into the lungs at any one time without unwanted side-effects such as coughing (e.g., ~20 mg), a practical lower limit is placed on B, below which inhalation is an unacceptable alternative to iv injection. This value may be, for example, 1, 10, or 30%, depending on the drug

Table 1. *Bioavailabilities and absorption times of peptides and proteins after administration to the lung*

Compound (mol wt)	Species	Bioavailability	Absorption Time	Reference
Leuprolide (1,209)	Human	17%	t_{max} ~1–2 h	17
Calcitonin (3,416)	Rat	17%	t_{max} ~15 min	32
Glucagon (3,481)	Rat	<1%	Undetermined	33
PTH-34 (4,278)	Rat	40%	t_{max} ~15 min	33
Insulin (5,786)	Human	7–16%	t_{max} ~15 min	34
Growth hormone (22,000)	Rat	9–10%	t_{max} ~1–4 h	35
AIA (52,000)	Sheep	<5%	48-h study	36
IgG (150,000)	Rat	1.5–1.8%	192-h study	37

PTH, phenylthiohydantoin; AIA, α_1-antitrypsin; t_{max}, maximal time of absorption.

and therapy, with the understanding that an increase in B value above this theoretical minimum will always tend to benefit the therapy by decreasing cost and likely increasing reproducibility. In the case of insulin, widely studied for its role in the chronic treatment of diabetes, reproducibility must be especially high to avoid hypoglycemic shock. Sufficient bioavailability and reproducibility have, however, been observed in human insulin trials (29) to justify hopes that an inhalation insulin therapy may soon reach the commercial US market. Calcitonin, interferons, parathyroid hormone, and leuprolide are also in human clinical trials for systemic action after inhalation. On the other hand, proteins such as glucagon (used to treat hypoglycemic coma), α_1-antitrypsin (used for the treatment of emphysema), or growth hormone (used for the treatment of growth deficiency), while attractive molecules for inhalation, have not yet reached the human trial stage.

A second key element to inhalation therapy concerns pharmacokinetic profile following administration. Lacking control over delivery by a long-lived, controlled-release particle, the systemic delivery rate of drugs from the lungs depends strongly on molecular size and structure, as indicated by the varied plasma absorption times listed in Table 1. A drug's intrinsic absorption profile may, however, not perfectly suit the required therapy, as is the case for sustained release of insulin for diabetic patients (29). A sustained-release inhaled therapeutic particle might serve to change the pharmacokinetic plasma profile, making it more suitable to the particular therapy. Sustained release from an inhaled therapeutic particle may also help to improve the bioavailability of very large proteins, such as IgG (Table 1), that absorb extremely slowly into the systemic circulation from the lungs. To the extent that 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. By controlling the release of a drug from an inhaled particle such that it approximates the rate of absorption into the bloodstream, the overall bioavailability of the drug might be increased without necessarily its purpose is to control the pharmacokinetic profile or to protect a protein over the time period of its absorption, controlled release from an aerosolized particle into the lungs over periods ranging from minutes to, perhaps, many days may be desirable.

Barriers that must be surmounted to achieve high bioavailability and proper pharmacokinetic profile naturally differ with drug but generally include *1*) loss of drug owing to filtration of aerosolized dose in the inhaler, mouth, or throat; and *2*) clearance of drug from the lungs before drug action. The fact that particles of mean diameter of 1–3 μm are both prone to aggregation and can be rapidly phagocytosed in the deep lungs by alveolar macrophages makes these barriers intrinsically problematic for conventional aerosol particles. For example, by using conventional aerosol particles of 1- to 3-μm size, current inhalers deliver ~10–20% of inhaled drug to the lungs (32). Clearance of drug from the lungs after deposition can include enzymatic degradation, mucocilliary clearance, and phagocytosis. The first of these can be important for molecules like vasoactive intestinal polypeptide (34). Mucocilliary clearance is especially important in the upper and central airways (22), but phagocytosis of slowly soluble particles may be the most significant mechanism of clearance from the deep lungs (6); Gehr et al. (8), for example, report that approximately one-third of polystyrene particles are immediately phagocytosed after inhalation into the lungs of hamsters. This rapid clearance acts against the potential benefits of an inhaled particle with controlled-release features, rendering sustained release of drugs into or from the lungs hard to achieve with current inhalation aerosol particles.

ADVANTAGE OF LARGE AND POROUS AEROSOL PARTICLES

A new type of inhalation aerosol has recently been identified that may help to address limitations of the current inhalation therapies (6). This aerosol is formed by particles possessing low mass density and, consequently, large size, such that the particles' mean aerodynamic diameter fits into the window of 1–3 μm. The advantage of large size and low mass density is twofold: first, increased particle size results in decreased tendency to aggregate; hence, in combination with low mass density, this leads to more efficient aerosolization in a given air field; second, since phagocytosis of particles by macrophages diminishes with increasing particle size beyond ~2–3 μm (27, 31), very 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.

To clarify the potential for large and porous aerosols to increase systemic bioavailability as well as to provide sustained-release capability in the lungs, Edwards et al. (6) encapsulated insulin into a biodegradable copolymer commonly used in biodegradable sutures and in controlled-release, implantable or injectable depot systems (18). Poly(lactic-co-glycolic) acid polymer particles were prepared with encapsulated insulin in two forms: a small, nonporous (conventional) aerosol

similar d_a (2.15 μm). Relative bioavailability of the conventional aerosol particle after aerosolization as a dry powder into the lungs of rats was 12%, and the release time was ~4 h. Figure 2 shows that insulin release into the systemic circulation from the large and porous aerosol particle lasted ~96 h, with similar inhalation and subcutaneous release profiles. The relative bioavailability (cf. *Eq. 5*) of the large and porous insulin particle was 87.5%, about seven times greater than that of the small and nonporous insulin particle.

One reason for the relatively high bioavailability of the inhaled large-particle insulin is more efficient delivery of drug to the lung as a consequence of less powder aggregation (6). 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.

However, perhaps the predominant cause of the sustained insulin delivery is the role of large particle size in discouraging phagocytosis. In a parallel study (6), the lungs of rats were lavaged both immediately after inhalation and 48 h after inhalation, with an aim to determine the location of the two types of insulin particles in the alveolar fluid. Similar numbers of porous and nonporous particles were inspired into the rat lungs by administering identical masses of porous and nonporous particles into the trachea.[1] Immediately after inhalation, 30 ± 3% of macrophages contained insulin particles in the case of rat lungs into which small and nonporous particles had been inspired, compared with 8 ± 2% of macrophages containing large and porous particles. After 48 h, 17.5 ± 1.5% of macrophages contained three or more small and nonporous particles compared with 4 ± 1% of macrophages containing three or more large and porous particles. Figure 3*B* shows two alveolar macrophages 48 h after inhalation of the small and nonporous insulin particles. Each macrophage contains numerous particles. Figure 3*C* shows several alveolar macrophages 48 h after inhalation of the large and porous insulin particles. The macrophages surround a large, porous particle without, however, engulfing it; other particles can be seen along the periphery of the macrophages. The lower extent of particle phagocytosis in the case of the large and porous therapeutic particles accompanies a relatively low inflammatory response as well. These results support the findings of in vitro experimental studies, cited above (27, 31), that show a trend of diminished particle phagocytosis with increasing particle size beyond ~3 mm.

The potential of large, porous particles for inhalation of a variety of drugs is presently being explored. In addition to insulin and testosterone (6), promising results in animals have recently been obtained with long-lasting formulations of estradiol (35), for hormone therapy, and albuterol (35), for asthma. In the estradiol study, particles were produced by spray drying, comprising estradiol and combinations of lung surfactant (dipalmitoylphosphatidylcholine), human albumin, and lactose. Large, porous particles with a mean geometric diameter of 10 μm and bulk (tapped) density 0.09 g/cm^3

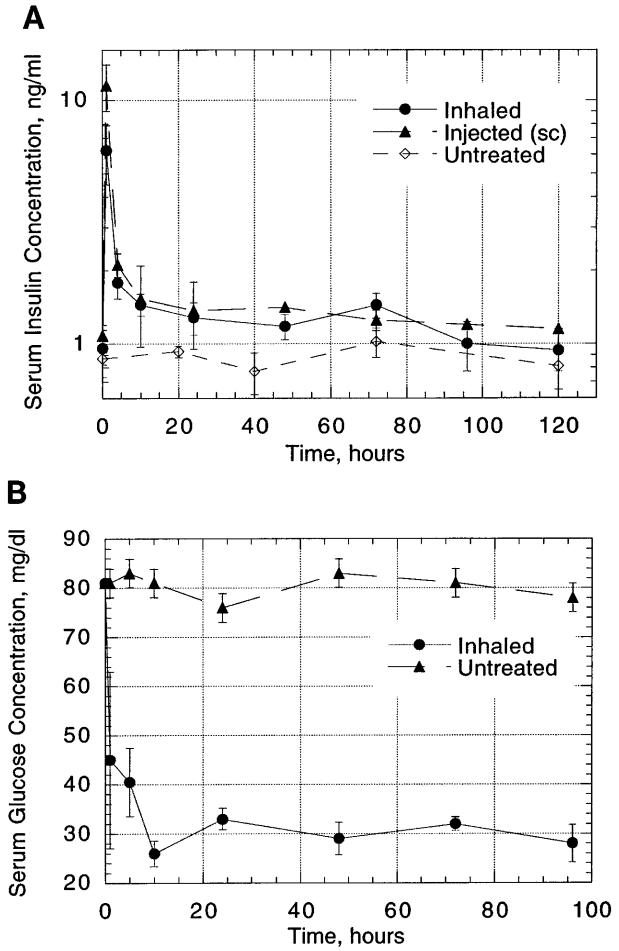

Fig. 2. Systemic concentrations after administration of porous therapeutic particles. *A*: serum insulin concentration after inhalation and subcutaneous injection of 9 mg of large, porous insulin particles. No insulin particles were administered to nontreated controls. Porous particles contained insulin (20.0 wt%) and 50:50 poly(lactic-co-glycolic) acid (80.0 wt%). Their mean geometric and mean aerodynamic diameters were, respectively, 6.8 and 2.15 μm. Mean and SE values are based on $n = 3$ subjects. *B*: serum glucose concentrations after inhalation of 9-mg large, porous insulin particles. No insulin particles were administered to nontreated controls. Mean and SE values are based on $n = 3$ subjects. [Reprinted with permission from D. A. Edwards, J. Hanes, G. Caponnetti, J. Hrkach, A. Ben-Jebria, M.-L. Eskew, J. Mintzes, D. Deaver, N. Lotan, and R. Langer. Large porous particles for pulmonary drug delivery. *Science* 276: 1868–1871, 1997. Copyright 1997 American Association for the Advance

[1] Due to the relatively inefficient aerosolization properties of the nonporous particles, based on in vitro and in vivo measurements using particles of similar size and porosity (6), approximately twice the porous powder mass is estimated to have entered the lungs relative to nonporous powder mass. At the same time, the larger size of the porous particles resulted in fewer particles per powder mass; this can be seen as follows: if 1 and 2 denote porous and nonporous particles, respectively; N is the number of particles; d is the particle diameter; and ρ is the particle mass density, the porous powder mass can be represented as $N_1(1/6)\pi\rho_1 d_1^3$ and the nonporous powder mass as $N_2(1/6)\pi\rho_2 d_2^3$. Accounting for the lesser amount of aerosolized nonporous mass entering the lungs, and noting *Eq. 3a*, gives the relation $N_1/N_2 \sim 2d_2/d_1$. Using $d_1 = 6.8$ μm, and $d_2 = 4.4$ μm (6), the ratio of porous to nonporous particle numbers entering the lungs is

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