Deposition of Inhaled Particles in the Human Respiratory Tract and Consequences for Regional Targeting in Respiratory Drug Delivery

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Particle behavior in the human respiratory tract is well understood and can be used to (*1*) estimate particle deposition in all regions of the respiratory tract for any aerosol respired at any pattern, and (*2*) optimize targeting of all regions of the respiratory tract in respiratory drug delivery. Extrathoracic and alveolar regions can effectively be targeted with mono- and polydisperse aerosols respired steadily. Effective targeting of the bronchial region can only be achieved with bolus inhalations. When particles are suspended in a gas heavier than air, targeting the alveolar region can be enhanced.

Keywords: inhaled particles; lung regions; deposition mechanisms; targeting; drug delivery

Every day billions of particles are inhaled with the ambient air by every human being. Many of these particles are deposited in the respiratory tract depending on the size, density, shape, charge, and surface properties of the particles and the breathing pattern of the individual. From the toxicologic point of view, all particles smaller than 10 μm in diameter have the potential of being biologically active in susceptible individuals.

Patients inhale medicinal particles for the treatment of respiratory diseases generated from formulations especially designed for this purpose. In contrast to ambient particles, medicinal particles are distributed over a limited size range, their shape and composition are known, and their deposition in the respiratory tract can thus be predicted rather precisely.

Inhaled particles are carried with the tidal air through the respiratory system. However, because of forces acting upon the particles, their trajectories are different from air stream lines. The most important mechanical forces are gravity, inertia, and impulse transfer from collisions with gas molecules. Particles are therefore displaced off stream lines and transported toward the surfaces of the respiratory tract by sedimentation, impaction, and diffusion. Whenever particles cover more than 30 μm/second by one of these transport mechanisms, particle deposition is influenced by them (1).

PARTICLE DEPOSITION

Deposition of Particles Composed of Hydrophobic Substances

Total deposition is the mean probability that an inhaled particle is deposited in the respiratory tract. Particles smaller than 0.1 μm in diameter are solely deposited due to diffusion (Figure 1). The distance a particle travels by diffusional transport increases with decreasing particle size and increasing respiratory cycle period (decreasing respiratory rate). Total diffusional deposition therefore decreases with increasing particle size up to about 1 μm and becomes negligible for larger particles. However, particles larger than 0.1 μm in diameter are also deposited due to sedimentation, and deposition increases with particle size, particle density, and respiratory cycle period. Consequently, in the size range of 0.1–1 μm, particles are simultaneously deposited by gravitational and diffusional transport (Figure 1). For larger particles, inertial transport becomes an effective transport mechanism, and deposition due to impaction increases with particle size, particle density, and airflow rate. Thus, in the size range above 1 μm particles are deposited due to impaction and sedimentation. Deposition in the extrathoracic and upper bronchial airways through which the inhaled air passes at high speed is governed by impaction. Sedimentation governs deposition in the lower bronchial airways and the gas exchange region where the residence time of the inhaled air is large.

As a result of numerous human deposition studies with monodisperse particles of varying size and density inhaled through the mouth or nose at varying breathing patterns total deposition could be partitioned into deposition in four regions of the respiratory tract (extrathoracic, upper bronchial, lower bronchial, and alveolar region) and a semiempirical deposition model was developed predicting regional deposition for particles larger than 0.08 μm for any particle density, respiratory cycle period, and flow rate (2). This model was extended to smaller particles by the International Commission on Radiological Protection (ICRP) (3). The mathematical formulae describing diffusional, gravitational, and inertial deposition in the regions were also slightly modified by taking mean deposition values from other studies into account and thus better account for the intersubject variability of particle deposition. Figure 2 summarizes the results for uncharged, unit-density spheres orally inhaled at the mean breathing pattern of an adult white male in the sitting position (5-second respiratory cycle period and 300 cm^3/second flow rate) (4).

Deposition of Particles Composed of Hydrophilic Substances

Due to water vapor uptake from the moist air in the respiratory tract, inhaled compact, hydrophilic particles grow in size and diminish their density. The experimentally determined intrapulmonary growth of 0.7 μm sodium chloride particles inhaled orally with aerosol boluses of 0.5 relative humidity at a flow rate of 250 cm^3/second are shown in Figure 3 as a function of the volumetric depth to which the boluses were inhaled (5). Because the growth of sodium chloride particles with increasing relative humidity is well known, the longitudinal profile of relative humidity in the respiratory tract can be calculated. The relative humidity increases from 0.5 in the upper airway to 0.995 at 80 cm^3 lung depth and remains at this level beyond this depth. By incorporating this profile into a Findeisen-type mathematical deposition model (6), the intrapulmonary growth of hydrophilic particles can be simulated (Figure 3).

Total and alveolar depositions of polydisperse, log-normally distributed particles generated from a hydrophilic powder, a

(*Received in original form and accepted in final form September 28, 2004*)

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Proc Am Thorac Soc Vol 1. pp 315–320, 2004
DOI: 10.1513/pats.200409-046TA
Internet address: www.atsjournals.org

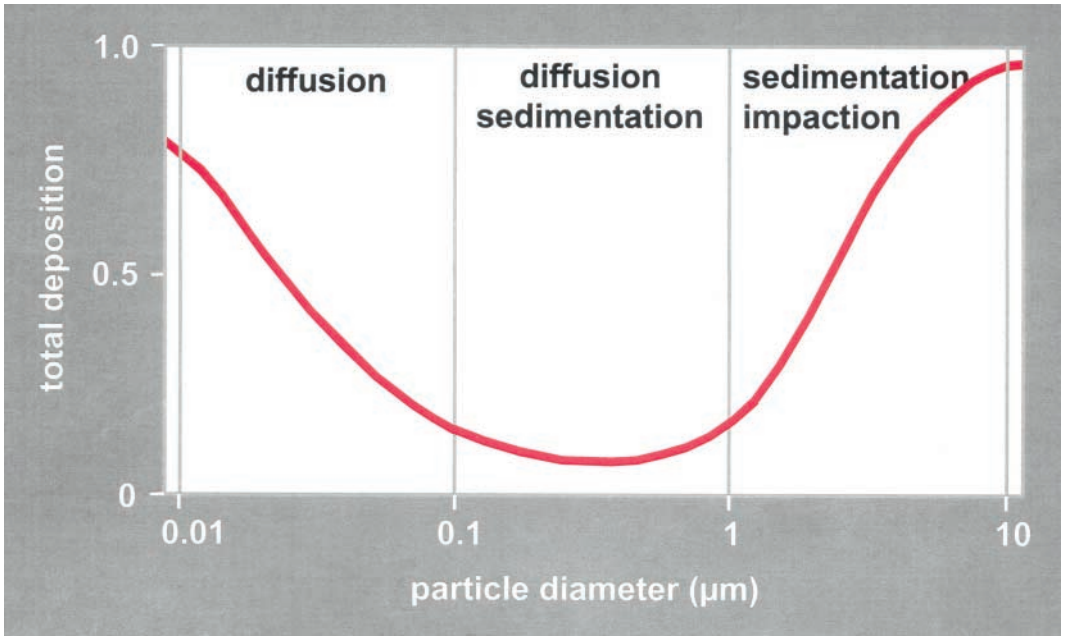

Figure 1. Total deposition of unit-density spheres in the human respiratory tract inhaled orally at rest.

hydrophilic liquid and a ficticious hydrophobic formulation of terbutaline sulfate simulated with Ferron's deposition model (6) for oral resting breathing of an adult white male, are shown in Figures 4 and 5. Deposition of the hydrophilic particles larger than about 0.3 μm in median diameter is larger and that of smaller particles smaller than that of the corresponding hydrophobic particles. For instance, alveolar deposition of hydrophilic 1 μm powder particles is 0.40 and that of droplets 0.48. In contrast, deposition of 1μm hydrophobic particles is 0.22. Thus, deposition can considerably be enhanced when medicinal particles larger than 0.3 μm in diameter are generated from hydrophilic formulations.

TARGETING LUNG REGIONS

A region is effectively targeted with a drug if more than 50% of the drug deposited in the entire respiratory tract occurs in that region. Targeting lung regions requires manipulation of particle

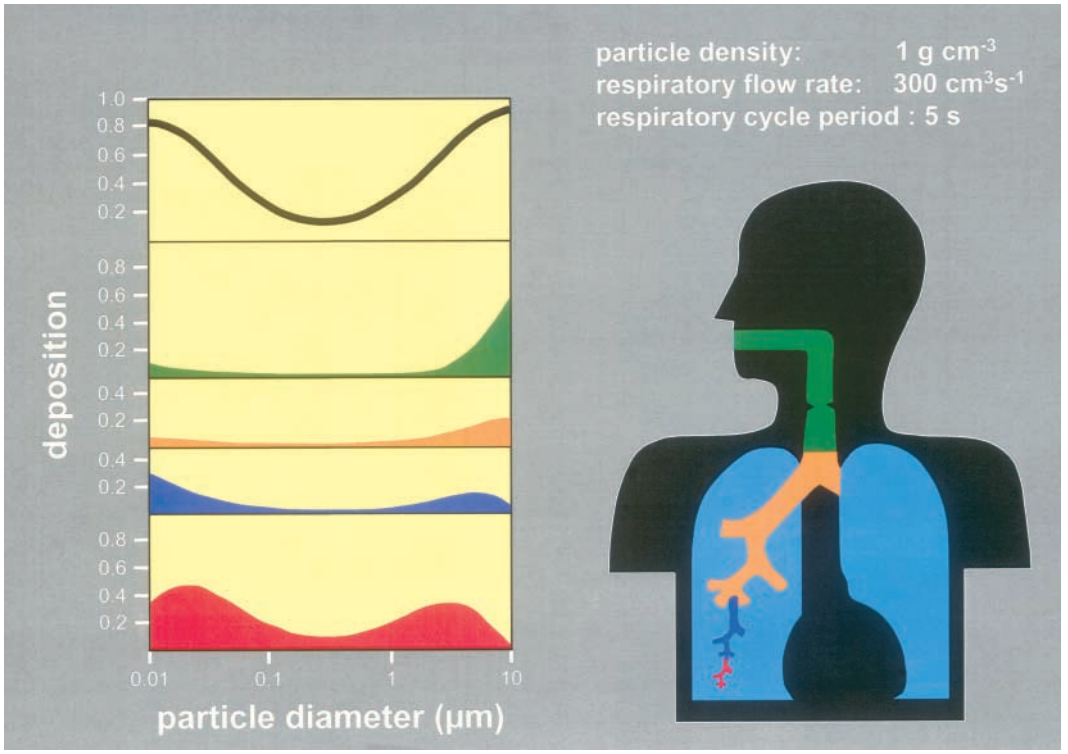

Figure 2. Total and regional deposition of unit-density spheres in the human respiratory tract predicted by the ICRP deposition model for oral inhalation at rest.

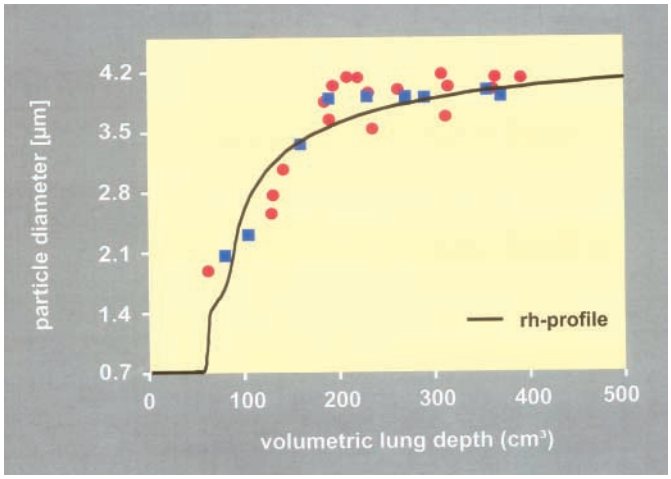

Figure 3. Experimentally determined intrapulmonary growth of solid 0.7 µm sodium chloride particles inhaled with aerosol boluses to different volumetric lung depth into the human respiratory tract.

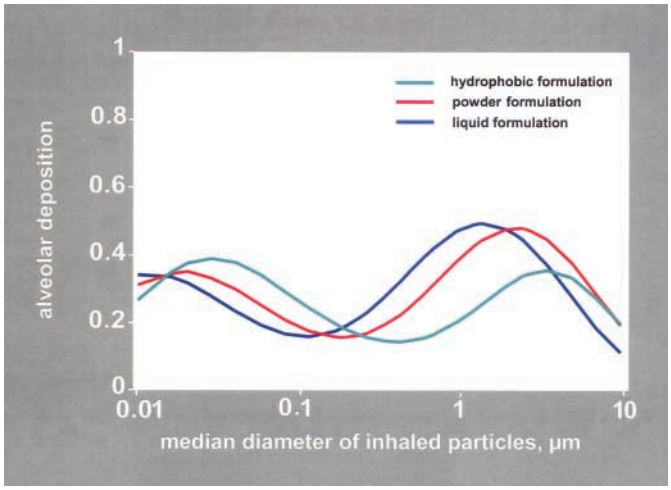

Figure 5. Predicted alveolar deposition in the human respiratory tract for oral breathing at rest of terbutaline sulfate particles generated from two hydrophilic formulations and a fictitious hydrophobic formulation.

and breathing parameters, the mode of inhalation (steady state, single breath, and bolus inhalation), and the composition of the gas in which particles are inhaled.

Optimization Particle and Breathing Parameters

The ICRP deposition model can be used to determine those particle and breathing parameters that allow targeting extrathoracic, upper bronchial, lower bronchial, and alveolar region for steady state breathing of aerosols (Figure 6). Deposition in the extrathoracic and upper bronchial regions is due to inertial particle transport; that in the lower bronchial and alveolar regions is due to gravitational particle transport. Targeting the extrathoracic airways requires 6-µm particles of unit density, fast breathing (500 cm^3/second flow rate), and a 150 cm^3 tidal volume. However, optimum targeting can only be achieved with 65% efficiency. Targeting the upper bronchial region is not possible. A targeting efficiency of 25% is the maximum efficiency achievable for that region. Targeting the lower bronchial region is also rather ineffective; it also requires 6-µm particles of unit density and a tidal volume of 1,000 cm^3 respired at a very low flow rate (50 cm^3/second). In contrast, targeting the lung periphery can be performed with an efficiency of 75% with particles with a unit density of 1 µm inhaled at a flow rate of 100 cm^3/second within a 1,000 cm^3 volume.

When particle sizes that are not monodisperse but log-normally distributed with a geometric standard deviation of 2 (and a median size equal to that of the monodisperse particles) are inhaled with the same breathing patterns as the monodisperse aerosols, targeting the lower bronchial region is no longer possible, but that of the lung periphery is still rather effective (71% efficiency) (Figure 7). The targeting efficiency can be increased for mono- as well as polydisperse aerosols to more than 90% by combining extrathoracic and upper bronchial regions and lower bronchial and alveolar regions. The combined upper region can effectively be targeted with 8-µm particles of unit density inhaled rapidly within a 180 cm^3 volume; the combined lower region can be targeted with 1 µm particles inhaled slowly within a 1,000 cm^3 volume (Figure 8).

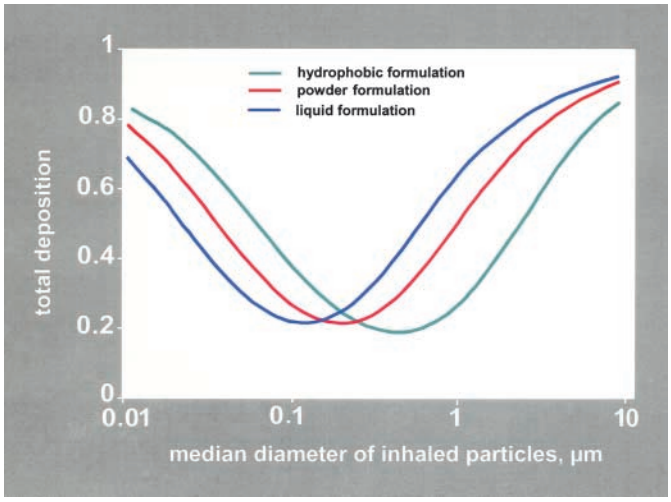

Figure 4. Predicted total deposition in the human respiratory tract for oral breathing at rest of terbutaline sulfate particles generated from two hydrophilic formulations and a fictitious hydrophobic formulation.

Bolus Inhalation

Many commercially available devices for respiratory drug delivery produce aerosol boluses. Boluses are very suitable for targeting as long as the above discussed particle sizes and breathing patterns are used.

The respiratory tract can be considered as a series of particle-collecting regions of equal volume. Measuring particle deposition from inhaled boluses penetrating to these regions allows one to determine the particle collection efficiency of and deposition in each region through which the boluses pass during inspiration and expiration (7). Deposition of 1 µm particles from 100 cm^3 boluses inhaled at 250 cm^3/second flow rate to regions of 100 cm^3 volume and exhaled from these regions show that no targeting is achieved in any of the volumetric regions.

However, at the end of inhalation all airborne particles are confined in the most distal region to which the bolus penetrated to. These particles can be completely deposited by gravitational transport during breath-holding of about 12 seconds. This enhances deposition for instance in the region between 900 and 1,000 cm^3 from 3 to 87% and decreases deposition in proximal regions by about a factor of 2 (Figure 9). The targeting efficiency

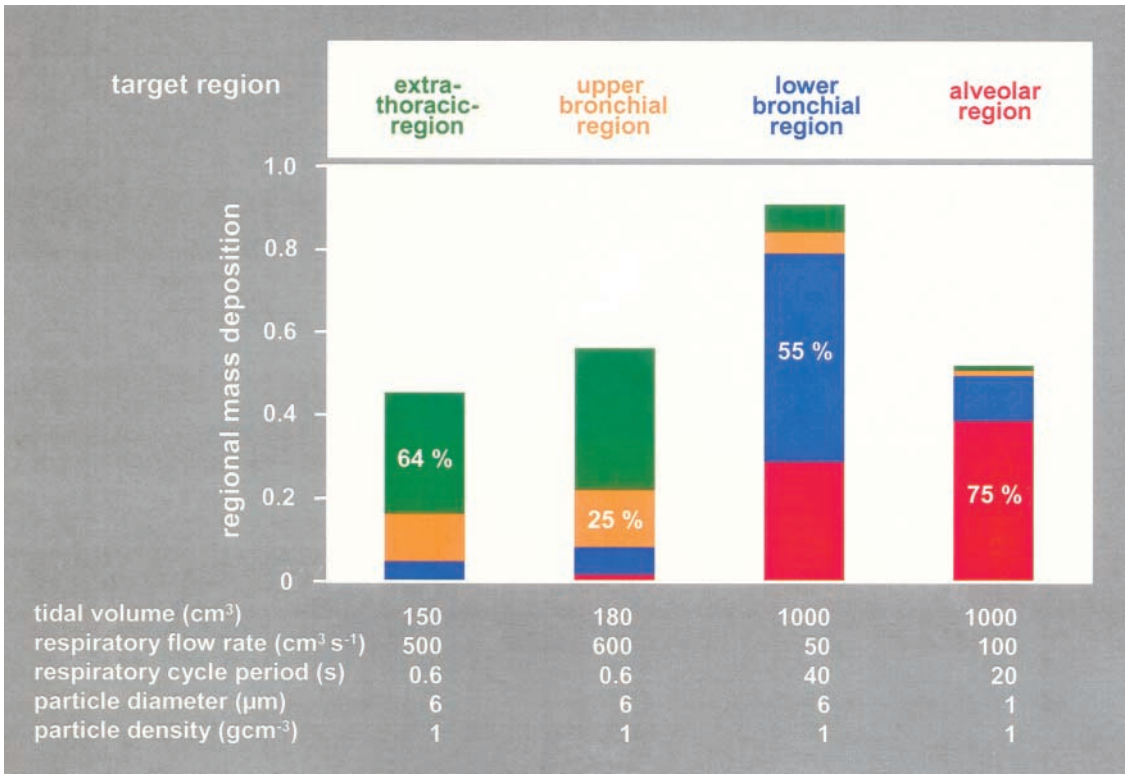

Figure 6. Characteristics of monodisperse particles and breathing patterns for optimum targeting extrathoracic, upper bronchial, lower bronchial, and alveolar region of the human respiratory tract during steady-state breathing (1).

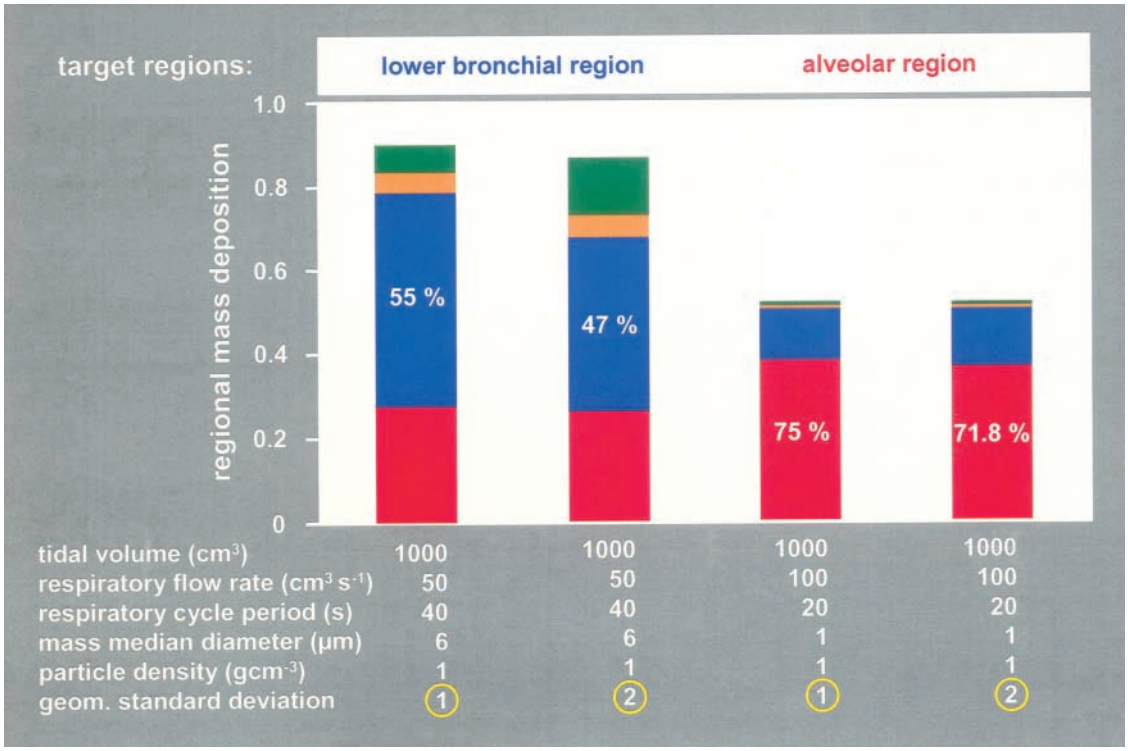

Figure 7. Targeting lower bronchial and alveolar region of the human respiratory tract with mono- and polydisperse (log-normally distributed) particles during steady-state breathing (1).

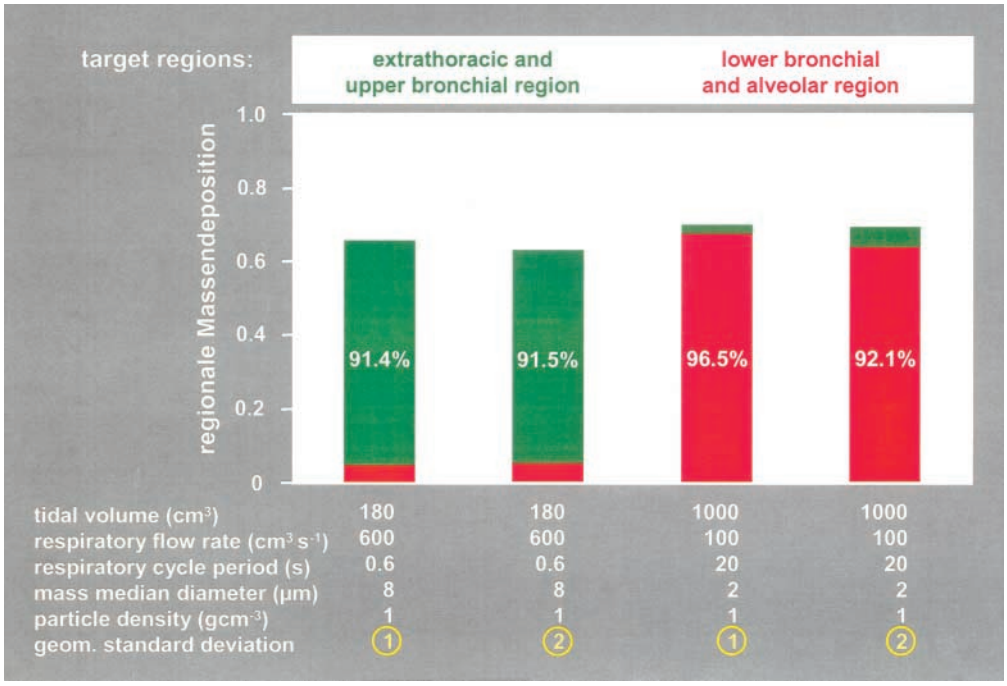

Figure 8. Targeting combined regions of the human respiratory tract (1).

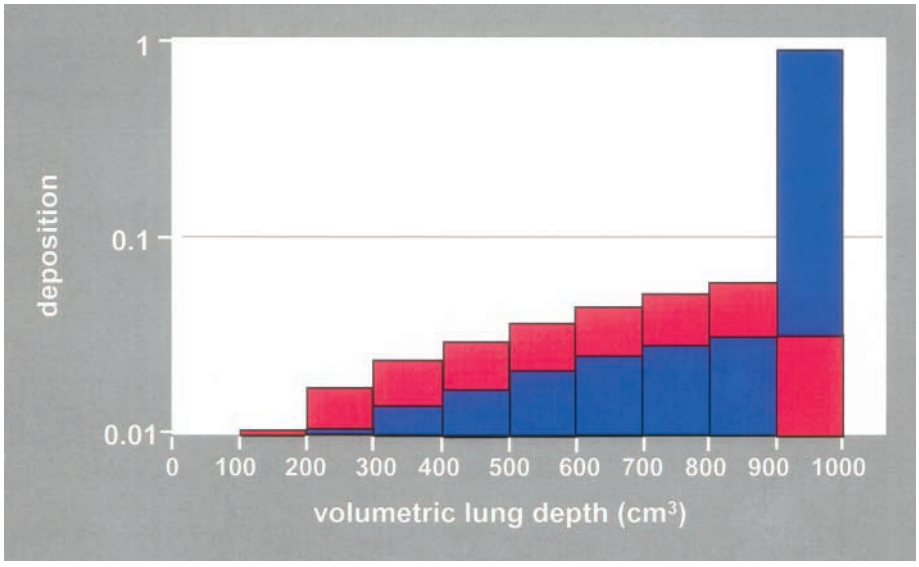

Figure 9. Deposition of hydrophobic 1 µm particles in ten longitudinal 100 cm³ regions in the human respiratory tract inhaled within a 100 cm³ bolus at 250 cm³/second flow rate into the region between 900 and 1,000 cm³ lung depth without breath-holding (*red values*) and with a 10-second breath-hold (*blue values*).

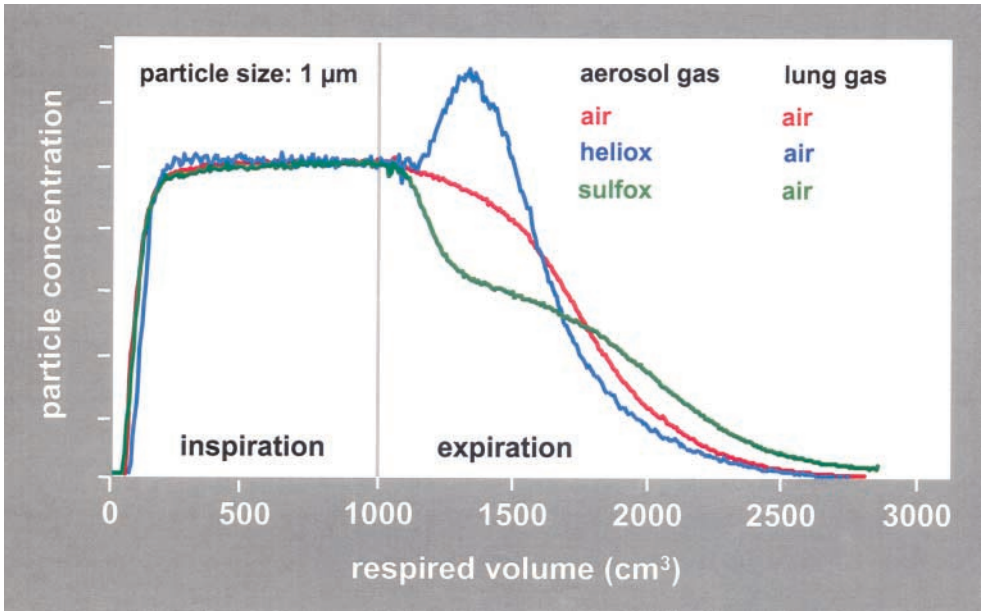

Figure 10. Influence of gas composition on particle transport in the human respiratory tract.

is therefore as large as 0.87. Only 2% of the inhaled particles are deposited in the first 100 cm^3 of the respiratory tract (extrathoracic region) and 6% in the second 100 cm^3 (bronchial region). Volumetric regions 3 to 10 comprise the ventilated part of the alveolar region. In case this entire region is the target region, a targeting efficiency of 0.96 can be achieved without breath-holding. Breath-holding, however, has two advantages. It allows targeting of subregions of the alveolar region and, at the same time, increases the dose delivered to the alveolar subregion under consideration.

Slow inhalation of aerosol boli with medicinal monodisperse 1 μm particles in conjunction with breath-holding is a very effective technique to achieve targeting of lung regions, especially the lung periphery for the topical treatment of peripheral respiratory diseases or drug delivery to the systemic circulation. Particles 1 μm in size are ideal for this purpose because of their very low deposition on their way to the targeted region and their large deposition in the small peripheral lung structures during breath-holding. For the treatment of airway diseases drugs should be directed to the second region. Particles 6 μm in size can be used to achieve complete deposition in small airways during 10 seconds of breath-holding. An alternative is the inhalation of boli with hydrophilic 1 μm particles. They are too small to be deposited in the oropharynx and larynx, but can grow to sizes large enough for complete deposition in small airways during breath-holding.

Gas Composition

Particle transport across the interface between tidal and lung air is due to convective mixing and intrinsic particle motion. Neither process is affected by changes in gas composition as long as the tidal and the lung gas are identical in composition. However, this transport is altered if the composition of the gas in which the particles are inhaled is different from that of the lung gas. When the particle-loaded inhaled gas is heavier (lighter) than air, particles penetrate deeper (less deep) into the lungs than in case that the particles are inhaled in air.

In the gas exhaled first, particles are concentrated when inhaled in heliox (80% helium and 20% oxygen) and diluted when inhaled in sulphox (80% sulfur hexafluoride) (8). This is due to phoretic forces acting upon the particles at the tidal/lung gas interface as a result of molecular diffusion. This phenomenon is called diffusiophoresis and results in particle transport toward the lighter gas which alters the particle concentration in the exhaled gas and thus deposition. Deposition occurs deeper in the lungs when particle-loaded sulphox rather than particle-loaded heliox is inhaled (Figure 10). Deposition in the peripheral airspaces can further be enhanced by breath-holding.

Conflict of Interest Statement: J.H. received $2,000 in 2002 and 2003 for serving on an advisory board for Alkermes, Inc., and €1,500 in 2002, 2003, and 2004 for serving on an advisory board for Intelligent Aerosol Medicine GmbH.

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