Optimal Parameters for Pulmonary Particle Deposition as Function of Age

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Abstract

Background: As a result of dissimilarity in lung morphometry and physiological conditions, therapeutic aerosol particles deposit differently in humans of various ages and body weights. Recently, clinical findings observed low inter- and intra- patient reliability in dosing, suggesting that a single aerosol device and particle size distribution is ineffective. Methods: This work conducts a formal optimization study to determine the optimal particle size distribution for maximum drug delivery for a 2, 9 and 21 year old individual over a range of breath rates. The work also explores the optimal particle size distribution for the therapeutic aerosol to provide the same dose volume regardless of breath rate. This study utilizes classical, static statistical, probabilistic models in conjunction with lung cast data to calculate deposition and imparts population variation within normal distributions. Results: This study finds that both optimal particle size for maximum volume weighted deposition efficiencies are age/weight dependent as well as breath rate dependent. A monodisperse particle size is obtained even when a polydisperse spray is allowed for optimization when investigating a single condition (i.e., age or flow rate). The optimal particle size increases from 2 to 5 μm for toddler to adults, while the optimal size decreases from 5 to 3 μm for a 21 year old adult with a flow rate increasing from 13 to 60 L/min. Optimizing the particle size distribution for reliable dosing of a 21 year old adult was dependent on the minimum dose volume constraint applied. As the dose volume constraint increased from 0.1% to 5% a single peak at 0.5 micron was replace by a bimodal distribution and the mean size grew.

Introduction

The benefits of drug delivery via the lung, the efficiency and efficacy of medication deposition utilizing this method are dependent upon, and critically affected by, numerous parameters. These parameters include particles properties, physiological factors, and the morphometry of the respiratory system [1-5]. In addition, a high deposition percentage of therapeutic particles in the appropriate generations of the lung is imperative when treating a particular disease, and as a result maximizing the particle deposition is essential when optimizing pulmonary drug delivery. When comparing the parameters that deposition is dependent upon, it is apparent that the primary factors that are capable of being manipulated to optimize drug delivery are the particle properties. One of the most convenient particle properties to influence, which plays a critical role in particle deposition, is aerodynamic particle diameter, which can be easily adjusted to determine optimal deposition.

As previously mentioned, physiological factors and respiratory system morphometry also affect particle deposition [6]. These factors are essentially fixed; additionally, they are not consistent from infants to adults. As infants grow and their body mass increases, their respiratory system also continues to increase in size and develop. As a result, the morphometry of the lung is continually changing until growth stabilizes. Studies have shown that the terminal bronchioles are already developed at birth, but that the respiratory airways (respiratory bronchioles, alveolar ducts, alveoli) continue to develop. Not only does the respiratory system increase in size as body mass increases, but the number of alveoli and respiratory airways continue to increase as well. Studies have shown that infants and young children have a different number of lung generations than adults as a result of this [7, 8]. Also, the lung growth in children is not linear and the largest growth rate occurs in the first two years after birth. Since lung morphometry, an important factor in particle deposition, changes substantially from infancy to adulthood, there is also a high likelihood that particle deposition varies in infants, children, and adults [2-4]. In addition, physiological factors such as breathing frequency, tidal volume, and respiratory rate also vary as a function of age [2, 9]. All of these parameters contribute to particle deposition and, as a result, it is necessary to determine the optimum particle diameter for deposition in infants and children as well as in adults.

Previously, our work in this area utilizing monodisperse aerosols demonstrated that both optimal particle size and maximum dose delivered based on volume weighted deposition efficiencies are age and weight dependent; as age/weight increase, optimal particle size and deposition increase. Optimal particle size varies from ~2.5 μm for infants to 5-6 μm for adults. Also, for all ages, breathing rates that are lower than normal enhance the delivered dose and shift optimal particle size. A sensitivity analysis of breathing rate and particle diameter on deposition shows that for young children, sensitivity to breathing rate is greater than sensitivity to particle diameter at normal breathing rates; however, sensitivities to both become similar as age/body weight increase. This trend is greatest in young children and lessens with age, likely because the optimal and normal breathing rates converge.

This work seeks to find the optimal polydisperse droplet size distribution for maximum drug volume delivered as well as hypothesizes that a distribution exists that is not the maximum which provides reliable dosing over a range of operating conditions.

Materials and Methods

Airway lengths and diameters as a function of lung generation are needed to perform particle deposition calculations. There are many adult lung models with complete airway dimensions available to utilize in particle deposition calculations; however, complete lung models for infants and children are considerably more scarce. Many of the available deterministic models were considered in this study when choosing appropriate lung models to use for infants, children, and adults.

The symmetrical lung model (Model "A") provided by Weibel (1963) is one of the most well known and frequently used models available for the adult. Although this model is commonly used, it is known for under predicting the diameters of conducting airways as well as diameters and lengths of the alveolar airways[2]. An additional work revised the small airway dimensions in the alveolar region and modified the generation where the respiratory bronchioles begin, but the issue with the undersized conducting airway diameters has not been addressed. The lung dimensions in this model are at a volume of 4800 ml (or ¾ TLC), and thus the model considers the volume of the lung at maximum inflation, or total lung capacity (TLC), of the adult to be 6400 ml (Weibel 1963). Often times lung dimensions are scaled to functional residual capacity (FRC), which is the volume still present in the lung after each breath has been exhaled. The Weibel model is commonly scaled because FRC in an adult male is approximately 3100 ml and a lung volume of ¾ TLC is not especially useful in calculations. In addition to the Weibel model, several other complete morphometric lung models are also available for the adult.

As previously mentioned, there are significantly fewer models with complete lung morphometry for infants and children. Several of the studies that do include infants or children have only scaled the airway geometries provided by one or more adult models (such as Weibel "A") instead of determining infant and children morphometry based on casting and extrapolation [7]. In addition, many of the studies that provide airway data based upon casting often include only morphometry for conducting airways and the airways distal to the terminal bronchiole have not been incorporated.

It is difficult to reasonably compare many of the adult models available to the models of children because they are nearly all constructed using different methods. Since a variety of different ages will be taken into consideration in this study, lung models provided by Ménache, et al. (2008) will be utilized in all calculations. The lung geometries in these models are provided in Appendix A. The models provided by Ménache, et al. are all constructed using the same method for consistency and include both males and females of various ages, which are summarized in Table 1.

Age (yr)	Gender	Weight (kg)	Height (cm)	BMI
0.25	F	5.9	66.0	13.5
1.75	M	9.0	71.1	17.8
1.92	M	9.1	94.0	10.3
2.33	F	12.2	94.5	13.7
3.00	F	13.6	109.0	11.4
8.67	M	26.0	118.0	18.7
9.42	M	40.9	143.0	20.0
14.00	F	51.0	175.2	16.6
14.08	F	56.0	147.0	25.9
18.00	M	52.0	135.0	28.5
21.00	M	67.0	177.8	21.2

Table 1: Information regarding human lung casts (Ménache, et al. 2008)

Using these lung models will allow for a wide range of ages to be evaluated and will contribute to a more reasonable comparison between deposition results. However, all of the airway dimensions in these models assume that the lung is at TLC. This is not an acceptable assumption when analyzing particle deposition because the lung is never actually at TLC. Therefore, these models must be scaled so that the airway dimensions more accurately represent the volume of the lung when breathing. In this study the lung models have been scaled to FRC + TV/2, where TV is the tidal volume (average volume inhaled or exhaled when breathing). This scaled volume is the average volume in the lung halfway through one breath. Only diameters are assumed to constrict as a function of the decrease in volume that occurs when scaling the lungs down from TLC. Consequently, the diameters have been scaled down proportionally; the airway lengths are assumed to remain constant. It is important to mention that in this study, the airways in each generation are considered to be cylinders and the presence of alveoli and their effect on fluid flow is neglected.

Since particle deposition is not only dependent upon morphometry, but is also dependent upon physiological factors such as respiratory conditions and lung volumes, these must also be determined. The physiological parameters that are required include breathing frequency (BF), TV, FRC, and TLC. BF and TV are dependent upon age and are used to determine minute volume (MV), or respiratory rate. They are calculated using the following analytical expressions presented in Hofmann (1982), where t is age in years.

$$TV\ (ml) = 21.7 + 35.13t - 0.64t^2$$

$$BF(\mathrm{min}^{-1}) = \frac{15.17}{0.25t + 0.5} + 11.75$$

FRC and TLC are determined by utilizing numerous analytical expressions that are a function of age, body mass, height, or a combination of the three and averaging the results. Averaging a multitude of correlations provided by numerous sources should assist in removing variation caused by small sample numbers bias by health state and provide consistent values that lie within a clinically acceptable range. The analytical expressions that are averaged are provided by Taussig, et al. (1997), Quanjer, et al. (1993), Stocks and Quanjer (1995), Cook and Hamman (1961), Gaultier, et al. (1979), Zeltner, et al. 1987, and Quanjer, et al. (1989). The values for BF, TV, MV, FRC, and TLC that are used in calculations are summarized in Table 2.

Age (yr)	Gender	BF (min^{-1})	TV (ml)	MV (L/min)	FRC (ml)	TLC (ml)
0.25	F	39	30	2.36	178	328
1.75	M	28	81	4.54	232	465
1.92	M	27	87	4.73	329	589
2.33	F	26	100	5.16	371	699
3.00	F	24	121	5.80	458	822
8.67	M	17	278	9.70	908	1990
9.42	M	17	296	10.09	1573	3243
14.00	F	16	388	12.06	2578	5362
14.08	F	16	389	12.09	1650	3533
18.00	M	15	447	13.20	1348	2871
21.00	M	14	477	13.73	3281	6656

Table 1: Summary of human respiratory conditions and lung volumes

This study will evaluate deposition of particles with a geometric particle diameter d from 1.0 µm to 7.0 µm in .5 µm increments. A number of assumptions relating to the fluid (air) and the particles are made before beginning particle deposition calculations. First, it is assumed that the particles are spherical. In addition, it is assumed that the particles are homogeneously distributed throughout the inhaled volume. All of the particles are not forced to deposit or see each airway generation. Instead, this study models the inhalation more realistically, where a particular volume is inhaled and the initial section of the volume passes through more generations than the final segment of that volume. It is assumed that the aerosol cloud is charge-neutral and electrostatic effects are negligible. This is a reasonable assumption because the high humidity in the lung neutralizes the charge of the particles. This study also assumes that the particle growth by hygroscopic effect is negligible. It is assumed the flow is incompressible, which is considered a reasonable approximation in most cases of aerosol inhalation. Finally, buccal and nasal depositions are not taken into consideration as this study only evaluates deposition that occurs from the trachea to the deep lung.

Various fluid and particles properties are required for deposition calculations. The air temperature is assumed to be 37ºC (310.15K), which is the temperature of the human body. The particle density ρ_p used in this study is 1.0×10^3 kg/m^3. For air, the following properties are assumed: the density ρ_f is 1.2 kg/m^3, the dynamic viscosity µ is 1.90x10-5 kg/m-s, and the mean free path λ is 0.072 µm at 37ºC and 1 atm. In addition, the branching angle of the airways in each generation is assumed to be 38.24º.

Particle deposition, particle motion, and fluid dynamics calculations utilized in this study are described by Finlay, 2001. Particle deposition is determined using a statistical mathematical model. Particle motion and fluids dynamics calculations are required to evaluate particle deposition. For particle motion, it is assumed that there is a single particle with a density much larger than the fluid density; this particle is assumed to be isolated, so all interactions between particles are neglected. This is generally true except for some dry powder inhalers.

First, it is essential to know the fluid velocity in a particular lung generation. The fluid velocity U_0 (in m/s) is

$$U_0 = \frac{MV}{A_c \cdot N}$$

where MV is in m^3/s, Ac is the cross-sectional area of an airway in that generation in m^2, and N is the number of airways in that generation. Once the fluid velocity is known, the Reynolds numbers for the particle and the fluid can be determined. The Reynolds numbers display the importance of inertial forces to viscous forces and are non-dimensional. The particle Reynolds number Rep is necessary to ascertain the validity of numerous equations and is

$$Re_p = \frac{U_0 d}{\nu}$$

where d is in m and ν is the kinematic viscosity of air in m^2/s, which is defined as

$$\nu = \frac{\mu}{\rho_f}$$

The fluid Reynolds number Ref is necessary to evaluate the fluid flow regime for a particular generation and is

$$Re_f = \frac{U_0 D}{\nu}$$

where D is the diameter of the airway in that generation in m. The fluid flow regime is laminar when $Re_f < 2300$. Under normal breathing conditions, the flow is laminar in all generations of the lung.

Aerodynamic diameter is often used instead of geometric diameter to describe a particle in an aerosol. Aerodynamic diameter d_{ae} is given as

$$d_{ae} = d\sqrt{SG}$$

where SG is the specific gravity the particle. This equation is only valid when the Rep is much less than 1 and d is much less than λ. Both of these conditions are satisfied in this study. Since the particle density that is chosen is about the same as the density of water, the aerodynamic diameters are determined and are very nearly the same as the geometric diameters, thus there is no effect on the results.

Particle deposition occurs in the respiratory tract by three primary mechanisms: sedimentation, inertial impaction, and diffusion. Sedimentation is when the particles deposit in an airway because of gravitational settling. For sedimentation calculations, the fluid velocity profile is assumed to be laminar plug flow. In plug flow, the fluid velocity is the same across any cross-sectional area of the tube. When determining the probability of sedimentation, the terminal settling velocity (velocity at which the particle settles due to gravity) for each particle must be determined. The settling velocity $\nu_{settling}$ (in m/s) is

$$\nu_{settling} = \frac{C_c \rho_p g d^2}{18\mu}$$

where g is acceleration due to gravity in m/s2, d is in m, and Cc is the Cunningham slip correction factor. This equation is also only valid when the Rep is much less than 1 and d is much less than λ. The Cunningham slip correction factor is necessary when the particle diameter gets smaller and the mean free path is not much smaller than particle radii. The Cunningham slip correction factor is non-dimensional and is

$$C_c = 1 + 2.25\frac{\lambda}{d}$$

The distance in which the particle will settle in a particular generation x_s (in m) is given by

$$x_s = \nu_{settling}\, t$$

where t is the residence time of a particle in that generation in s. It is also necessary to compute κ to determine sedimentation probability. The value of κ is

$$\kappa = \frac{3\nu_{settling} L}{4U_0 D}\cos\theta$$

where L is the length of an airway in a particular generation in m and θ is the branching angle. The probability of sedimentation for laminar plug flow is

$$P_s = 1 - \frac{2}{\pi}\left[cos^{-1}\left(\tfrac{4}{3}\kappa\right) - \tfrac{4}{3}\kappa\sqrt{1-\left(\tfrac{4}{3}\kappa\right)^2}\right]$$

When using this equation, it is important to note that κ is only a real number when it is less than ¾. Due to this, Ps is frequently set to 1 when $\kappa \geq ¾$ because this indicates that it takes a particle longer to travel through the length of the tube than it does for it to travel the diameter of the tube perpendicular to the flow and therefore sedimentation will occur.

Particle deposition also occurs by means of inertial impaction. Deposition occurs via inertial impaction when there is curvature in an airway and the inertia of the particle is too great, resulting in a particle trajectory that no longer follows the fluid flow streamline causing the particle to deposit on the airway wall. The Stokes number determines whether or not inertial impaction will occur and therefore is necessary when evaluating the probability of deposition via impaction. The Stokes number Stk is non-dimensional and is

$$Stk = \frac{U_0 \rho_p d^2 C_c}{18\mu D}$$

The probability of inertial impaction is given by Chan and Lippmann (1980) and is

$$P_i = 1.606Stk + 0.0023$$

Other than sedimentation and impaction, particle deposition also takes place as a result of Brownian diffusion. Very small particles have Brownian motion due to interactions with the molecules of the gas they are carried by. Brownian motion is when a particle collides with the molecules and random walk occurs. This is considered to be diffusion when this takes place with many particles. The root mean square displacement x_d (in m) describes the distance the particle travels due to Brownian motion and is

$$x_d = \sqrt[2]{2D_d t}$$

where D_d is the particle diffusion coefficient in m2/s. The particle diffusion coefficient Dd is

$$D_d = \frac{kTC_c}{3\pi\mu d}$$

where k is Boltzmann's constant (1.38x10-23 J•K-1) and T is the temperature in K (37 ºC=310.15K). To determine the probability of Brownian diffusion, Δ is

$$\Delta = \frac{kTC_cL}{3\pi\mu d U_0 R^2}$$

where k is Boltzmann's constant and R is the radius of the airway in a generation in m. The probability of deposition due to Brownian diffusion is given by Ingham (1975) and is

$$P_d = 1 - 0.819e^{-14.63\Delta} - 0.0967e^{-89.22\Delta} - 0.0325e^{-228\Delta} - 0.0509e^{-125.9\Delta^{2/3}}$$

So far, the equations provided determine the probability of each of these deposition mechanisms occurring alone, which is unrealistic; in reality, these deposition mechanisms occur simultaneously in the lung. Consequently, an empirical relation that calculates the total probability of deposition by taking into consideration all three types of deposition is used. The total probability P is determined using

$$P = (P_i^{\,p} + P_s^{\,p} + P_d^{\,p})^{1/p}$$

where the value of p (in the exponents) is assumed to be 2 in this study.

The ratio of x_d/x_s is useful for assessing how important diffusion is when compared with sedimentation. If $x_d/x_s < 0.1$, then diffusion becomes negligible and no longer needs to be taken into consideration. When diffusion is not taken into consideration, the total probability becomes

$$P = P_i + P_s - P_i P_s$$

Once the total probability of deposition is determined in each lung generation for each particle size, it is necessary to quantify the results in a way that is more applicable to dosing. Most studies assume that the particles move through the lung at the same time at an infinite particle density. This is both physically unrealistic and violates several of the assumptions used to develop the statistical models. It was instead chosen in this study to have each model inhale a normal tidal volume where the particles are homogenously distributed throughout the entire volume. This has the consequence of needing to tag particles to a particular segment of the tidal volume as the last segment of the tidal volume inhaled never reaches the deep lung. This is achieved using the following equation

$$F_{V_i} = 1 - \frac{\sum V_{i-1}}{V_{Total}}$$

where F_{Vi} is the fraction of the adjusted cumulative volume still available, V_{Total} is the total adjusted cumulative volume, and $\sum V_i$-1 is the sum of the adjusted volumes above that generation.

Numerical optimization techniques are designed to minimize an objective function subject to constraints, with many algorithms developed over the past several decades [10]. In general, the algorithms require a starting point, x_0, and then iterate or step until there is no more progression, or the approximate solution falls within a user-defined tolerance. Typically, algorithms follow one of two types of strategies, line search or trust region. This study implemented an active-set algorithm because the design space is assumed to be rather monatomic in nature; however, the end point might be dependent on the initial starting point thus this needs to be investigated.

The optimization algorithm was scripted into Matlab®, however numerous optimization algorithms are readily available and easily implement into the flow of this design tool. The percent of the initial 100,000 particles in a given size of the distribution is variable constrained by an upper and lower bound or 1 and 0 respectively. Finally, the objective function was minimized by the optimization routine. For maximizing the deposited volume of drug, the inverse of the drug volume was the objective function minimized. For maximizing reliability, the standard deviation from a mean deposition volume was minimized.

Results and Discussion

Based on the optimization calculations to determine the maximum volume of delivered drug volume to a 2, 9 and 21 year old male, clear differences in the particle size distribution were observed. For all cases a monodisperse or single valued optimal size was obtained. Figure 1. Notice that as the age or weight of the individual increases the mean particle size increases.

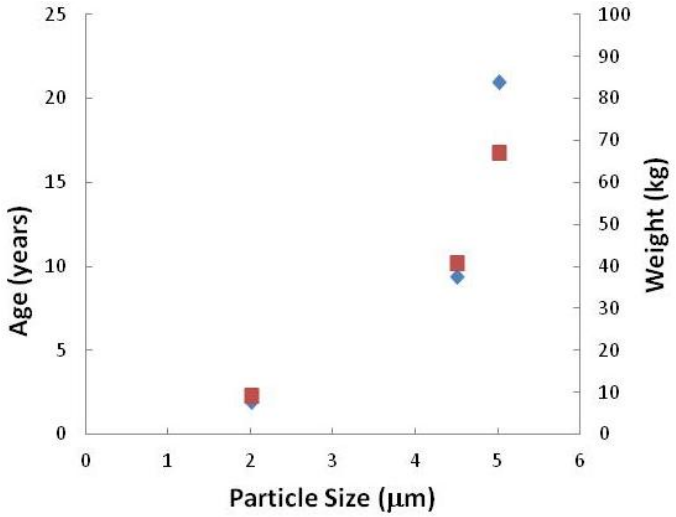

Figure 1. Optimal particle size for maximum delivered dose to a (a) 2 year, (b) 9 year and (c) 21 year old person at normal breath rate.

Optimal Size Distribution as a Function of Flow Rate

Based on the optimization calculations for maximum deposited drug volume to a 21 year old male at 13, 25 and 60 L/min, clear differences in particle size is observed, Figure 2. Notice that as the flow rate increase, the single valued optimal particle size decreases monotonically.

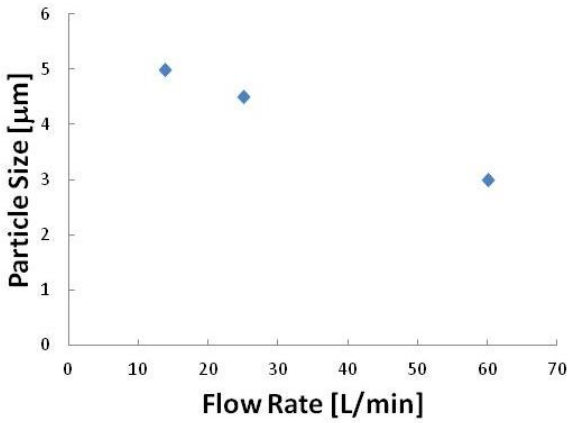

Figure 2. Optimal particle size distributions for maximum delivered dose to a 21 year old person at (a) 13-normal, (b) 25-asthmatic and (c) 60-meter dose velocity L/min.

Optimal Size Distribution for Reliable Doing

The optimization for reliable drug delivery represents a difficult calculation as the process can seek multiple local minima. One extreme is on either boundary where almost no deposition occurs thus no variation exists. This, however, is not the desired outcome. A constraint must set on the minimum amount of drug deposited. Additionally, the starting point for the distribution has to be carefully selected to be far from a zero volume deposition or the optimization code converged to that local minimum. Figure3 shows that as the constraint on the minimum drug volume deposited in the low airways increases, the optimal distribution changes. At a low dose constraint, a relatively monodisperse small particle size distribution is obtained which, subsequently, becomes a bimodal distribution with a small increase in required dosing requirement. Finally, a shift in the entire biomodal distribution towards larger particle sizes is observed when the minimum dose requirement becomes more clinically relevant. Figure 4 demonstrates that the reliability or standard deviation between dose volumes is still rather poor, suggesting that an approach that forces a particle distribution about a mean with a variable span may provide better outcomes.

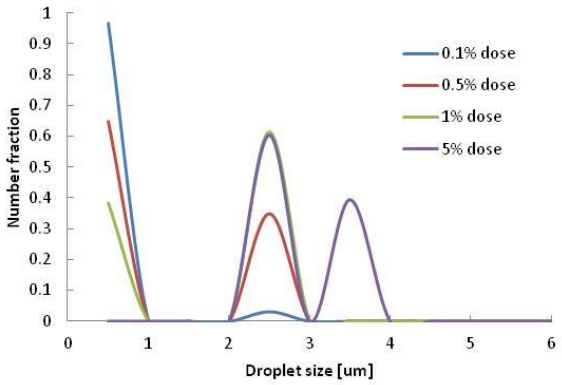

Figure 3. Optimal particle size distributions for reliable dosing of a 21 year old person at over 10 to 30 L/min.

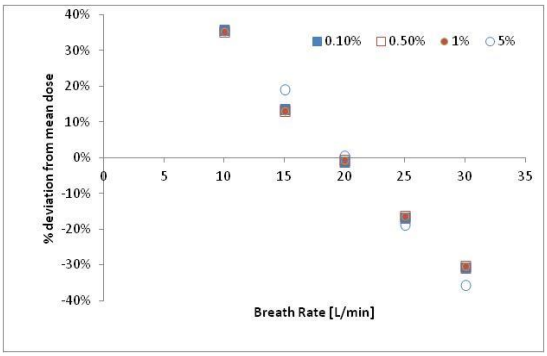

Figure 4. Variation in dose volume standard deviation as a function of flow rate and dose volume constraint

Conclusions

This study represents the first known effort to specify an optimal particle size distribution from a medical device intended for therapeutic drug delivery to the lung. The results provide particle size distribution for maximum drug delivery over a range of ages/weights and inhalation flow rates. Optimized particle size distribution for reliable dosing is a function of the minimum deposited dose. Raising this constraint volume not only shifts the distribution to higher sizes, but also exhibits a bimodal distribution.

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