

DOES SIZE REALLY MATTER?

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The age-old question, "Does size really matter?" can be applied to medicinal aerosol particles about as readily as it can be applied to many other things in life. And the answer, not surprisingly, is, "It all depends." Haven't we all heard that before?

The respiratory tract is exquisitely designed to keep things out! We generally breathe through our nose, and the nares are relatively small. The nasal passages have a small diameter, they are lined with a sticky mucosa and they are somewhat tortuous. Aside from their humidification function, they are designed to keep things out. Even when we breathe mostly through our mouths we encounter the same situation in the lower portion of the upper airways: relatively small diameter, sticky mucosa and a narrowing pathway that is really good at keeping things out. It would seem that dust, dirt, lint, bugs, and other assorted debris don't stand a chance of being inhaled. Thankfully! But what about all the nebulized aerosol drugs that are administered to patients by the tens of millions of doses per day all across our country? What chance do those particles have?

We have all seen the "classic" diagrams showing aerosol deposition fractions in different areas of the tracheobronchial tract as a function of particle size. Every respiratory care textbook ever published probably has at least one variation of Dautreband's original diagram. At the end of the semester it seems that the only thing anyone ever remembers is "3-5 microns." But many contemporary aerosol scientists are not in agreement. Maybe 3-5 μ m (micrometers or "microns" for short) doesn't cut it anymore.

My first major issue is with the veracity of the early work concerning aerosol particle sizing, which is still commonly taught in school. It is as old as the hills and its relevancy is questionable. Some of the original work concerning the optimum particle size for intrapulmonary deposition and retention was conducted by industrial/environmental engineers and scientists working for the government who were trying to predict the detrimental health effects of nuclear warfare. Some of this work actually predates the Cold War and anticipates a possible nuclear attack by the Soviet Union. The particles in question were mostly of inorganic substances in the form of powder, dust and debris created by a nuclear explosion, not medicinal aerosols. These particles were likely to be highly irregular in shape across an extensive size range. The burning questions (no pun intended) were how many radioactive particles from an atomic bomb will penetrate into the lung when inhaled, what is their size and how deep will they go? So our first problem with this classical size data is that it does not necessarily apply to contemporary nebulizer-generated liquid aerosol particles. We expect most of the particles of aqueous inhaled medications, such as albuterol, to be generally spherical. When describing the size of something that is uniformly round, or spherical, the diameter of the particle is about as good a measurement of its size as you're going to get. How do you measure the "diameter" of an irregularly shaped particle? Or a population of many irregularly shaped particles in which each one is different? The point is that the mass of drug deposited in the lung can be much more accurately predicted when the size range distribution is known and the particles are regular, especially spherical, in shape. So, upon reflection, perhaps the classic data concerning optimum particle size does not apply to spherical liquid medication particles created by today's nebulizers.

The second issue is that some of these early particle sizes were purely estimates rather than measurements. And when actual measurements were made, the instrumentation that was used was quite crude compared to what is available today. We really do not know whether the particle sizes reported from instrumentation 50 years ago was right on the money or had a bias in one direction or the other. Further, even today there is an enormous amount of disagreement and controversy surrounding the techniques and instrumentation for measurement of airborne particles. This is not surprising when you consider that the challenge is to characterize the size of hundreds of thousands of microscopic particles in an aerosol stream. You and I can not see an individual aerosol particle created by a nebulizer. What we see when we observe the mist emanating from a nebulizer is not a stream of individual particles so much as it is an optical phenomenon affecting the way the light passing through the cloud of particles is scattered. The denser the aerosol, the greater the scattering. This phenomenon allows us to generalize about the density of the aerosol stream (i.e., the number of particles in the stream) from our visual observation, but we certainly can not see the particle size. It is known however that the particles created by contemporary nebulizers span a large range of sizes, giving rise

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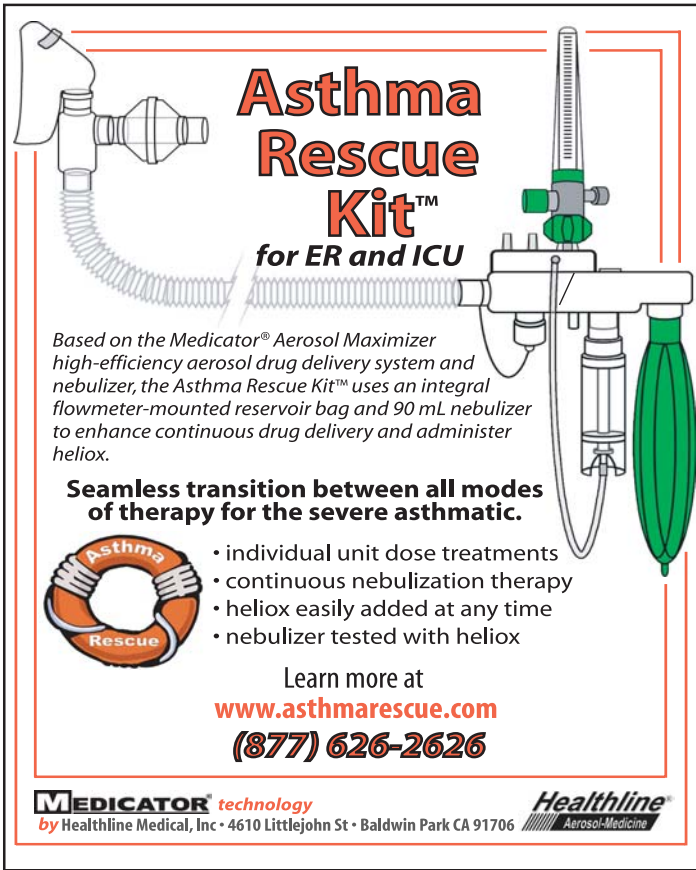
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to the descriptive term polydisperse distribution. By contrast, a monodisperse particle distribution would be one in which all the particles are nearly identical in size. This, in turn, leads to the terminology we have adopted when we state the size of a population of aerosol particles. We are really stating the statistical probability that the particles exist within a range of sizes described by the statistical median, hence the terms Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD). We'll cover the various methods of particle size measurement and terminology in depth in a future installment.

The object of aerosol drug therapy is to deposit a relatively predictable and consistent mass of medication in the lung. Thus, the mass of drug becomes an important determinant of effectiveness. Unfortunately, rather than learning about delivered drug mass, we are taught almost exclusively about particle size as it pertains to distribution and deposition. Smaller particles, in general, tend to penetrate more deeply into the lung and therefore deposit more peripherally. So it would seem, on that basis, that smaller particles are better. But what happens to deposition and distribution of drug mass? There is another factor that is not often considered by clinicians. It is hygroscopic growth, the tendency of aqueous particles to enlarge as a consequence of absorbing water from the vapor phase inside the hot, humid respiratory tract. One of the respiratory care textbooks refers to this phenomenon as "aging." For example, let's assume that we generate a particle that is 3.5 μm in diameter when it leaves the nebulizer. Assuming the particle does not change size before it is inhaled (not always a safe assumption), it enters the tracheobronchial tract where it quickly doubles in size by hygroscopic growth. Now it is 7 μm in diame-

ter, twice as large as it was when it was created and theoretically outside the optimum range. Although it is larger, it still contains only the original drug mass imparted to it when it was created and emitted from the nebulizer. However, now that it has enlarged hygroscopically, it is probably more likely to deposit in the upper respiratory tract than the lower and the majority of the drug mass may not be delivered to where it is required. Perhaps the concept of "optimum particle size range" should be modified to refer to particles once they have already been inhaled and experienced hygroscopic growth.

It may seem by now that we are leaning toward endorsing particles smaller than the traditional 3 – 5 μm range. We are, but it is not quite that simple. Because the mass of drug carried by a spherical particle is related to the 3rd power of the particle radius (r^3), a doubling or halving of the particle diameter has the effect of an 8-fold increase, or 8-fold decrease, respectively, on the mass of drug the particle can carry. For example, if a nebulizer creates a 4 μm diameter particle, it has a radius of 2 μm and r^3 is 8 ($2 \times 2 \times 2$), thus the drug mass carried is 8 units. If the nebulizer creates an 8 μm diameter particle from the same solution, it has a radius of 4 and r^3 is 64 ($4 \times 4 \times 4$), thus the drug mass carried is 64 units, or 8 times as great. Conversely, if the nebulizer creates a 2 μm diameter particle, it has a radius of 1 μm and r^3 is 1 ($1 \times 1 \times 1$), thus the drug mass carried is 1 unit, which represents an 8-fold decrease in drug carrying capacity. Applying the concept of hygroscopic growth to this situation suggests that even the 4 micron particle, which is right in the middle of the so-called 3-5 μm optimum particle size range, will likely grow too large for effective endobronchial deposition shortly after it is inhaled. A smaller particle, for example 1 μm , could double or even triple in size by hygroscopic growth and still remain small enough for optimum deposition. However, because smaller particles carry significantly less drug mass than larger particles, the delivery system for small particles will have to be especially efficient to make sure that the greatest number of particles is delivered and deposited in the endobronchial regions.

So, size really does matter. Bigger is not better. But smaller is not necessarily better unless aerosol particles are delivered with a highly efficient delivery system to compensate for the smaller drug mass carried by each small particle.

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