Nebulizer Efficiency: Modeling Versus In Vitro Testing

In this issue of RESPIRATORY CARE, Chatburn and McPeck present a "New System for Understanding Nebulizer Performance,"[1] which aims to identify the primary component variables involved in the generation and delivery of nebulized aerosol, and to use those variables to derive performance indices for a given nebulizer, and ultimately a measure of the efficiency of nebulizer treatment. Chatburn and McPeck make clear their interest in furthering cost-effective and time-effective aerosol treatment in the clinical setting, and they pursue the goal of identifying the ultimate nebulizer from their modeling process.

SEE THE SPECIAL ARTICLE ON PAGE 1037

Though not entirely a new concept, the authors present a well constructed conceptual model that could yield an overall measure of nebulizer performance. If this were true, then the clinical, pharmacologic, and aerosol community could breathe a collective sigh of relief. However, there are problems with their specific modeling process, and, more generally, in any model of jet nebulizer performance.

Further, the range of nebulizer designs differs greatly. While the traditional jet nebulizer introduced in the 1950s has progressively evolved, with new plastics, electronics, and valve technology, the same cannot be said of the more regulatory-encumbered technology of pressurized metered-dose inhalers (pMDIs). Though pMDIs dominate the market, their fundamental design and overall low efficiency has changed little since they were introduced in the 1950s.

Traditional jet nebulizers come in many different forms: constant-output, breath-enhanced, and dosimetric. Ultrasonic designs may do as well, but without (necessarily) incorporating a compressed airflow. New-generation vibrating-mesh nebulizers, such as eFlow, Omron U22, and AeroNeb, promise to diversify nebulizer designs even further, and promise major design advantages over pMDIs in versatility, portability, and efficiency of delivery.[2] Exciting times, but whether nebulizers can shake the established market dominance of pMDIs remains to be seen. As with the VHS versus Betamax formats of the "old-fashioned" DVD-precursor tapes, or Apple versus MSDOS, the best technology may not necessarily win over commercial interests or effective marketing.

Diverse nebulizer designs will create major obstacles for any conceptual model that seeks to establish a universal system to predict nebulizer efficiency. Ignoring the variables introduced by patients for the moment, consider just the variables introduced by the clinical treatment environment, both in the home and clinical settings across the world. Temperatures ranging from cool to hot, combined with humidity ranging from dry to wet, make for complex interactions and a wide range of physical environments. Even at the same location, the environment can radically change from day to night, and day to day. The impact humidity and temperature have on nebulized aerosol continues to be poorly understood, but remains a critical subject to address to effectively model nebulizer performance and efficiency. This is primarily due to the confounding effects of evaporation, which is primarily dictated by temperature and humidity. A conceptual model to understand how 3 different types of evaporation affect nebulized aerosol is presented in the 2nd section of this editorial, and the 3rd section relates to the complexity of predicting aerosol deposition.

Evaporation Concepts Related to Jet Nebulizers

It is misleading to believe that evaporation is a straightforward concept where it concerns nebulized aerosol. This editorial presents an introduction to 3 different "types" of evaporation related to nebulizers, nebulized aerosol, and droplet size measurement of nebulized aerosol. These 3 types can be usefully defined and described as follows.

Type 1: Evaporation Inside the Jet Nebulizer

Compressed air (which is invariably dry, and on re-expansion to atmosphere is always dry) draws up and mixes with nebulizer reservoir solution being sprayed around inside the nebulizer. The residence time of the decompressed air (flow, for example, 6 L/min, or 100 mL/s) within the nebulizer (internal volume < 100 mL) is short (< 1 s). Even so, the wet surface area from airborne and impacted spray in the nebulizer interior is huge. Rapid evaporation of water solvent to the decompressed air ensures that the air leaving the nebulizer is saturated with water vapor (approximately 100% relative humidity). Further, because of the latent heat lost to evaporation, the nebulizer reservoir cools, and the initial ambient temperature (eg, 20°C),

would normally drop to around 10°C. The aerosol-laden air also leaves the nebulizer in a cooled state, relative to ambient. In this cooled saturated air shroud, the nebulized aerosol is stable until it either mixes with ambient air (see type 2 below) or increases in temperature (see type 3 below). One of the more interesting and little-recognized results of type 1 evaporation, besides cooling of the nebulizer reservoir, is that as the nebulization treatment progresses, the concentration of solute (eg, drug, excipient, saline) in the drug formulation progressively increases, so by the time nebulization is complete, the final solute concentration may be as high as twice that of the initial charge.[3] That is an interesting point for pharmacists to consider, as they may reconsider the reasons for careful formulation of isotonic salt concentrations.

Type 2: Evaporation of Nebulized Aerosol Solvent When Mixed With Ambient Air

Nebulized aerosol leaving a jet or ultrasonic nebulizer exists in a shroud of 100% relative humidity air. The aerosol is relatively stable with regard to evaporation, up until the point when it mixes with ambient air. This is a reality of constant-output nebulizers, where the nebulized aerosol is emitted into a T-piece and the patient's inhalation flow causes make-up air (ambient percent relative humidity) to be drawn into the T-piece. The ambient make-up air mixes with the nebulized-aerosol-laden air and temporarily reduces the relative humidity. The relative humidity is quickly reinstated to 100% by evaporation of water solvent from the nebulized aerosol. This evaporation occurs in a couple of milliseconds, or, using another reference, this evaporation happens by the time any given aerosol exits from the nebulizer mouthpiece (or very shortly thereafter). Of course, this volume loss implies that the size distribution of the nebulized aerosol has shifted downwards. Further, this shift may not be constant, as smaller droplets have propensity to evaporate more readily than larger, so the distribution shift is not homogenous. In any case, after the nebulized aerosol gives up solvent to resaturate the air, the nebulized aerosol is again stable. It is important to note that this form of evaporation is more a feature of constant-output nebulizers and less a feature of air-entrainment or breath-enhanced nebulizers, whose design causes entrained ambient air to draw solvent vapor from the nebulizer reservoir (eg, Pari LC series, Sidestream, or AeroEclipse).

Particularly for constant-output nebulizers, the drier the ambient air, the greater the impact of evaporation on the size of the nebulized aerosol. Further, the smaller the rate of aerosol output relative to the flow of ambient air, the greater the effect of this evaporation on the nebulized aerosol. Consider that saturated air at ambient condition holds some 20 g/m^3 of water vapor; that is 20 μL water vapor per L of air. If the ambient air is, say, 50% humidified, the air then requires some 10 μL of water vapor per L of airflow. If the total inhalation draw is 15 L/min, and the nebulized airflow rate is 7 L/min, then ambient airflow is 8 L/min, and the solvent vapor requirement to saturate is 80 μL/min. This volume loss is significant compared with cheap and cheerful jet nebulizers (approximately 100–200 μl/min). Further, the effect is, of course, more startling in dry ambient conditions.[4] Further discussion of this evaporation is discussed in detail elsewhere.[5]

Type 3: Evaporation of Nebulized Aerosol Solvent Due to Thermal Transfer From a Cascade Impactor

This type of evaporation was first described by Finlay and Stapleton for the Anderson cascade impactor.[6] The phenomenon has since been confirmed in the Next Generation Pharmaceutical Impactor.[7] Nebulized aerosol, after mixing with ambient air, equilibrates to 100% relative humidity and is relatively stable. However, it is cool because of the latent heat of evaporation (eg, 10°C). The cool stable nebulized aerosol passes through tubing into a cascade impactor. The cascade impactor is at ambient temperature (eg, 20°C). The cooled air is in contact with the cascade, which can act like a kind of radiator, warming up the nebulized-aerosol-laden air. As the air warms up while traveling through the cascade, the capacity of the warmer air to hold moisture increases. In order to maintain 100% relative humidity, further evaporation occurs from the nebulized aerosol during its flight through the cascade. Where and when this happens during the flight is probably complex. As with type 2 evaporation, the smaller the amount of nebulized aerosol, the more significant the losses and the greater the size change.

This discussion serves to introduce the reader to the 3 different kinds of evaporation that influence the efficiency of nebulizers. In doing so, this editorial seeks to provide names by which researchers can refer to these 3 types of evaporation: type 1, type 2, and type 3. This might allow more efficient discussion of how evaporation can impact nebulized aerosol output and size.

Modeling Respiratory-Tract Deposition: The Finlay-Martin Factor

Recently, Finlay and Martin, working at the University of Alberta, published a seminal concept; they outlined a general algebraic equation for predicting total human respiratory-tract deposition of inhaled particles.[8] Though the mathematical concepts they presented consolidate and build upon many previously published works, the resulting universal equation may well prove a defining concept. Figure 1 depicts this new composite index. The Y axis represents respiratory tract deposition. The X axis represents the composite indices derived from 3 dimensionless vari-

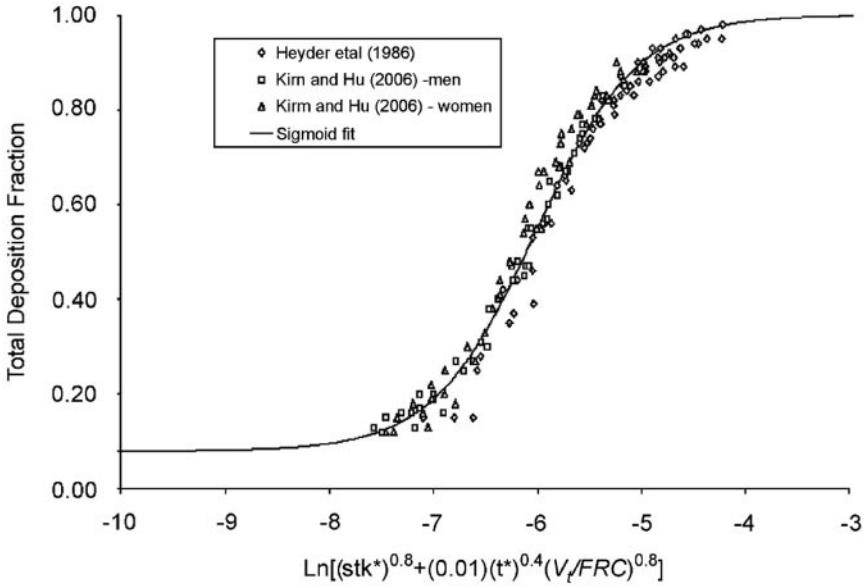

Fig. 1. Finlay and Martin's composite index for predicting respiratory tract deposition of inhaled particles. (From Reference 8, with permission.)

ables: a Stokes number (Stk) that encompasses the variables that influence inertial impaction; a gravitational sedimentation variable, related to particle settling velocity; and a dimensionless variable related to patient breathing pattern (the ratio of tidal volume to functional residual capacity). The resulting sigmoidal curve fit convincingly correlates with respiratory tract deposition determined by in vivo research work.[9,10]

The resulting algebraic equation may captivate the interest of aerosol modelers, but confounds discussion of the concept by respiratory therapists, nurses, physicians, and other interested clinicians also working in this field. To help progress discussion, perhaps a new term can be coined for this concept: the Finlay-Martin factor. This label acknowledges the researchers who adapted and developed the equations, and its use could simplify discussions around the concept. To this end, a new graph is plotted in Figure 2, in which the rather cumbersome algebraic equation of the Figure 1 X axis is replaced by this new label.

Having recognized the state-of-the-art model that relates aerosol size to total respiratory-tract deposition through the Finlay-Martin factor, it is critical to note that this model relies on aerosols with a stable particle size, including aerosols from powder inhalers, pMDIs (after propellant evaporation), and many ambient, environmental aerosols. As discussed in the 2nd section of this editorial, nebulized aerosol droplets are not stable, and particularly type 2 evaporation of solvent from released droplets invariably contributes (to a greater or lesser degree) to the dynamic aerosol characteristics of nebulized aerosol. This is not to say that the Finlay-Martin factor does not apply to nebulized aerosol, but that there are restrictions in how we can apply it (particularly when evaporation is expected to persist through the first few generations of the respiratory tract), and it cannot be as universal for nebulized aerosol as it appears to be for stable dry aerosols.

Summary

The paper by Chatburn and McPeck in this issue of RESPIRATORY CARE[1] highlights the usefulness of models that can define the performance efficiency of a given nebulizer, or a series of nebulizers. It forms a useful contribution to the literature in this field. However, it should not be used as a definitive source for estimating performance of nebulized aerosol. No account is made of evaporation of water solvent from the nebulizer reservoir (type 1 evaporation), which will progressively concentrate the drug formulation. No account has been made of dynamic instability of nebulized aerosol after potential mixing with ambient air and release to the patient (type 2 evaporation). This is not to say that the model cannot help health care workers gauge nebulizer efficiency, as such models may well help gauge some measure of nebulizer efficiency.

Some would argue (Warren Finlay, University of Alberta, Edmonton, Alberta, personal communication, 2007) that our understanding of nebulized aerosols is sufficiently advanced to model performance. The coupled equations that describe the behavior of droplet evaporation in fluid flow are well known (eg, more than a decade ago these equations were used to examine the effect of different ambient humidity on nebulizer aerosol behavior in the lung,[11] and to compare different nebulizers[12]). The prob-

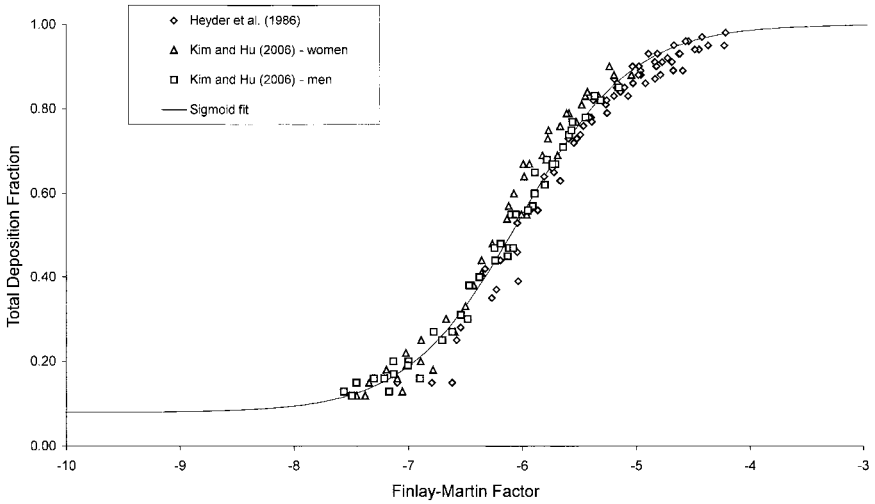

Fig. 2. The complex algebraic equation in Figure 1 is here called the Finlay-Martin factor. (Adapted from Reference 8, with permission.)

lem is that solving these equations takes more effort than can normally be brought to bear, and the complexity of the equations also results in highly complex behavior (and the need for very careful measurements in order to have meaningful characterization of particle size). Perhaps it is a matter of semantics, but there is the view that we have the capability to understand nebulized aerosols, it is just that most of the time we don't want to solve the rather nasty equations that describe their behavior or take the necessary steps to make meaningful measurements of particle sizes that are dynamic, and so their behavior seems mysterious (Warren Finlay, University of Alberta, Edmonton, Alberta, personal communication, 2007).

So, while it may be possible to model a given nebulizer design under carefully controlled environmental conditions, universal application has yet to be achieved. The challenges in producing a universal model are substantial, and include the wide range of nebulizer designs, the subtle interaction and complexity of factors that affect nebulizer performance, and uncontrolled variables introduced by patient and physical environmental conditions. While modeling research continues for holistic understanding of nebulized aerosol, we are forced to conclude that, for the time being, there is no substitute for in vitro testing of nebulizer efficiency. Standardization of meaningful in vitro testing methodology has been much slower in North America.

Europeans have long defined and applied a clinically meaningful battery of in vitro tests[13,14] for device type testing, which has allowed the development of strategies for "ranking" nebulizer efficiency for various clinical applications.[15,16] The North American equivalent does not exist, but this may shortly change with the development of a new International Standards Organization standard and adoption of appropriate in vitro nebulizer testing methods in upcoming revisions of the Pharmacopeias. I argue that, for the time-being, in vitro testing of nebulized aerosol, using clinically meaningful and well recognized and validated test methods, will provide a more useful measure of nebulizer efficiency than current models can predict.

For more than 50 years nebulizers have offered ever more sophisticated routes for generation of drug aerosols. Imagine what we, as a clinical community, might accomplish if we truly understood all aspects of nebulized aerosol. The field of nebulized aerosol continues to retain unexploited potential. Our full understanding of nebulizers remains a work in progress, and though we are well traveled down the path in developing and applying this most versatile of drug aerosol delivery tool, we have not yet realized their full potential.

Perhaps the answer posed by the title of this editorial is that for the time being we must rely primarily on in vitro test results to gauge the efficiency of a particular nebulizer or group of nebulizers. Modeling of nebulized aerosol output and size is a more challenging route to follow, and, though much progress is being made, models are either too limited in their scope or so complex that they prohibit application.

Ultimately, the efficiency of a nebulizer is best determined by clinical outcomes, which will depend as much on factors such as patient adherence to recommended treatment and usability as it does on the technical performance of the nebulizer unit. In this respect, the humble jet nebulizer remains a

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marriage between art and science, evolving within the harsh commercial world of clinical aerosol therapy.

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