Use of Analytically Defined Estimates of Aerosol Respirable Fraction to Predict Lung Deposition Patterns[1]

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Analytical estimates of the respirable fractions on inhaled pharmaceutical aerosols are obtained by inertial sampling techniques. The respirable fraction may be defined as that portion of the particle size distribution less than a designated diameter. The diameter size below which particles were considered respirable in these studies was 6.4 μm. In clinical practice, a variety of particle size distributions may be related to a single respirable fraction. Herein, three respirable fractions were each defined by six particle size distributions. The deposition patterns of aerosols exhibiting these particle size characteristics were examined in a mathematical model. The analytically defined respirable fractions were compared with predicted lung deposition values. Under clearly defined breathing conditions, there is a correlation between the nominal respirable fraction and deposition. However, it was concluded that the variations which occur in breathing parameters within patient populations may not allow a single analytically derived respirable fraction to be appropriate for all individual subjects.

KEY WORDS: compendial standards; pharmaceutical aerosols; lung deposition.

INTRODUCTION

The British Pharmacopoeia has two inertial sampling techniques listed for assessment of the respirable fraction of inhaled pharmaceutical aerosols (1). Similar methods have been suggested for inclusion in the United States Pharmacopoeia (2). To augment these procedures multistage cascade impactors capable of higher resolution classification of particle size distributions can be employed (3).

Particle size distributions of aerosols produced by pressurized metered-dose inhalers (MDIs), breath-actuated dry powder inhalers (DPIs), and nebulizers may frequently be fitted to log-normal functions (4). In the aerosol therapy literature it is recognized that well-defined mathematical probabilities may be ascribed to the deposition of particles of specific sizes, shapes, and densities in different regions of the human lung and surrogate airways (5,6). The designation of that fraction of an aerosol size distribution which is below a single size as being respirable is, therefore, an oversimplification of actual deposition processes. Nevertheless, this is the common approach taken for the purposes of quality control of pharmaceutical products.

In this focused study, the effects of individual particle characteristics and nominal aerosol respirable fraction on lung deposition patterns are investigated using analytical techniques (7,8). The model is validated by comparisons of calculations with data from human subject exposures.

MATERIALS AND METHODS

A mathematical model describing the particle size distributions of inhaled aerosols and their equivalent respirable fractions was used to investigate the respective influences of these factors upon lung deposition. The respirable fraction values assumed for this study have been based upon experimental data obtained from previous aerosol classification studies (9,10). To begin, we address the characteristics of instrumentation from which estimates of particle sizes and related respirable fractions may be obtained.

Particle Size Measurement Techniques

A number of compendial techniques employ inertial effects as the preferred method of collecting aerosols of pharmaceutical interest (1,2).

For the purpose of this study, particles below 6.4 μm in aerodynamic diameters (D_{ae}) are considered "respirable." This value was selected from the nominal value employed in the British Pharmacopoeial Apparatus A (1). A diagram of this device is shown in Fig. 1. The apparatus consists of an inlet (designated the throat), a primary chamber which collects particles >6.4 μm and a secondary chamber which collects particles <6.4 μm. To allow the distribution of an aerosol to be established, the composite particles must be segregated by size. Multistage impaction is a methodology employing the same principle of inertial classification as the compendial techniques and offers the advantage of allowing increased resolution of the particle size distribution of the sampled aerosol (3,8). Compendial techniques have been designed to sample aerosols at 60 L min^{-1} (1,2), while the common inertial impactor techniques employ much lower airflow rates, in the range of 12.5 to 28.3 L min^{-1} (9–11).

Aerosol Size Distributions

Aerosols produced by pressurized MDIs, breath-activated DPIs, and the various forms of nebulizers are polydisperse. In practice, such particle size distributions may be similar to mathematical functions described as "log-normal." Properties of log-normal functions, characterized by mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) values, have been extensively documented by Raabe (12).

In Fig. 2 six particle size distributions are depicted, all of which have a 30% respirable fraction. The plot is of pro-

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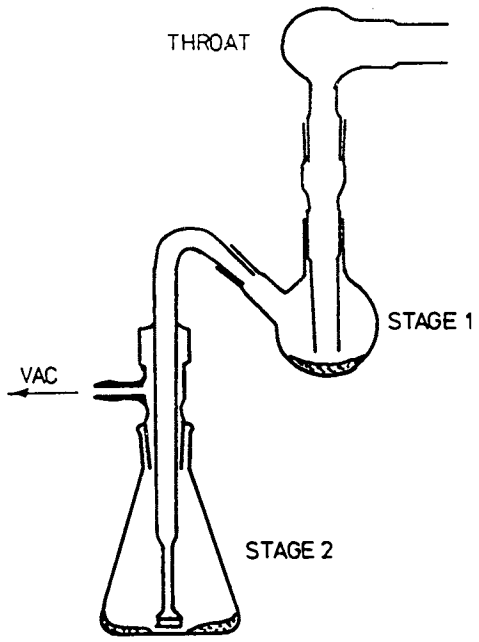

Fig. 1. Diagram of a twin impinger, Apparatus A, British Pharmacopoeia. See Ref. 1.

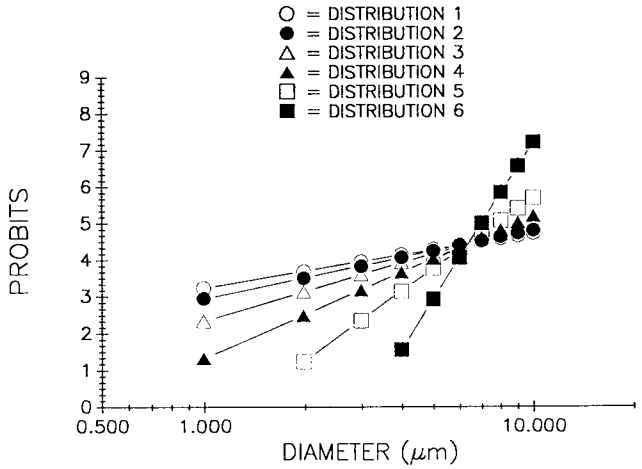

Fig. 2. Logarithmic-probability plot of probits (linearized frequency scale based on variance) versus particle size.

bits (a linear function of variance) versus particle size on a logarithmic scale (13). Table I lists six particle size (MMAD) and geometric standard deviation (GSD) combinations, which define respirable fractions of 30, 40, and 50%, respectively.

Each of the data sets in Table I has been employed in the lung deposition model in subsequent computations. In Fig. 3, examples are given for the log-normal distributions related to three representative aerosols defined in columns 6 and 7 in Table I for RF = 50%.

Respiratory Parameters

In aerosol therapy regimens a range of tidal volumes and breathing frequencies must be addressed to target the delivery of drugs (6) and elicit optimum effects. Herein, a range of breathing parameters was selected for their relevance to (i) adult human subjects at various degrees of respiratory intensity (7) and (ii) methods of inertial classification of pharmaceutical aerosols. Accordingly, the inspiratory flow rates which have been employed in these deposition calculations are 12, 14, 40 and 60 L min^{-1}. They are given in Table II. The ventilatory parameters selected to characterize sedentary, light, and moderate activity levels have been defined previously (7). The Test 1, 2, and 3 values in Table II are used below to determine effects of breathing conditions upon deposition patterns of inhaled aerosols.

Particle Deposition Model

It is necessary to know the deposition sites of inhaled particulate matter within the respiratory tract for pharmacologic applications. The development of a mathematical deposition model requires definition of the following for human subjects: lung morphology, respiratory parameters, airflow dynamics, aerosol size distributions, and particle deposition processes.

Since inhaled particles will be entrained in an airstream, their trajectories are naturally influenced by its magnitude and velocity profile, which are, in turn, determined by airway geometry and ventilation. Hence, deposition probability formulas must be sensitive to local conditions in the lung which produce the sites of enhancement detected in experimental deposition studies (14–16). Such "hot spots" of deposition will have significance in aerosol therapy protocols, as exposed airway cells will receive massive doses of pharmacologic drugs (6).

In this work, aerosol deposition patterns will be calculated using a mathematical model (7) validated via comparisons of theoretical values with clinical data from human subject exposures (17,18). The model is based upon the sys-

Table I. Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) Defining Particle Size Distributions Related to Respirable Fractions (RF) of Particles <6.4 μm

Aerosol identification	RF = 30%		RF = 40%		RF = 50%	
	MMAD	GSD	MMAD	GSD	MMAD	GSD
1	14.1	4.5	8.8	3.6	6.4	3.1
2	12.1	3.4	8.3	2.8	6.4	2.5
3	10.1	2.4	7.7	2.1	6.4	1.9
4	8.7	1.8	7.3	1.6	6.4	1.6
5	7.7	1.4	6.9	1.4	6.4	1.3
6	7.0	1.2	6.6	1.2	6.4	1.1

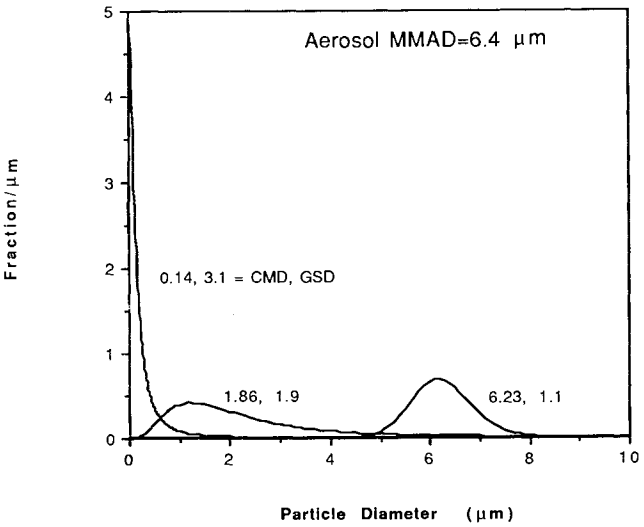

Fig. 3. Definition of the log-normal particle size distributions of representative polydisperse aerosols considered in this study: mass median aerodynamic diameter (MMAD) = 6.4 μm, count median diameter (CMD) = 6.2 μm, geometric standard deviation (GSD) = 1.1; MMAD = 6.4 μm, CMD = 1.9 μm, GSD = 1.9; and MMAD = 6.4 μm, CMD = 0.14 μm, GSD = 3.1.

tem of deposition efficiency equations defined by Martonen (19,20). Herein, the model assumes a Weibel (21) morphology for the adult human lung, and aerosol size distributions and ventilatory parameters defined in Tables I and II, respectively. Deposition is calculated on an airway-by-airway basis and can be partitioned into different compartments. Generations 17–23 inclusive, the alveolated airways, have been designated the pulmonary region for these studies.

RESULTS AND DISCUSSION

To demonstrate the mathematical model presented herein, we have performed a series of computer simulations of actual human inhalation exposure experiments. In Table III calculated aerosol deposition efficiencies are compared to the laboratory results of Heyder *et al.* (22). The tabulated values are total deposition for healthy volunteers who inhaled radiolabeled particles. The deposition data were determined via measurements of particle clearance using gamma camera techniques and related lung scans. Therefore, the reported experimental values were inherently normalized to the aerosol quantity entering the lung (i.e., the trachea). Our computations were done likewise to facilitate a comparison of theory and experiment. The three respiratory protocols defined in Table III were precisely controlled by Heyder *et al.* (22) during the tests. By design, the instrumentation monitoring ventilatory parameters permitted the real-time breathing profiles to be superimposed upon a CRT screen, and the subjects were trained to mimic any imprinted (i.e., displayed) respiratory conditions. In each test, the subjects inspired at a prescribed constant flow rate up to a predetermined tidal volume, then exhaled at an identical flow rate. There were no intermittent pauses between the inspiratory and the expiratory phases of a breath.

The theoretical predictions in Table III are in agreement with measurements over the broad spectrum of experimental conditions considered (i.e., particle sizes and ventilatory parameters). This is consistent with previous examinations (17,18) and indicates that the inhaled particle physics has been accurately formulated.

In the remainder of the text we use the validated model to calculate aerosol deposition patterns for selected aerosol characteristics (MMAD, GSD, and RF) and ventilatory parameters (TV, f, and Q); see Tables I and II, respectively. The breathing profiles to be examined that are associated with ventilatory parameters are displayed in Fig. 4. The Test 1 and moderate activity curves have been omitted for clarity. These profiles are qualitatively similar to those used in the human subject experiments, having constant inspiratory flow rates, no pauses, and equal (i.e., to inspiratory values) expiratory flow rates (22).

The results are depicted in the form of the series of Figs. 5–7 showing calculated lower lung deposition plotted as a function of the nominal respirable fraction. Each point indicates the mean value and the error bars represent the standard deviation for the six particle size distributions corresponding to each nominal respirable fraction defined in Table I.

Figure 5 demonstrates that increasing the inspiratory flow rate greatly reduces the aerosol quantity deposited in the peripheral airways of the lung. For example, when the respirable fraction is 40% the mean pulmonary deposition value is approximately 18% at 12 L min^{-1} and 7% at 60 L min^{-1} (see Table II). The effect of particle size, which is indicated by the error bars for each RF value, is reduced considerably as the magnitude of the inspiratory flow rate is increased from 12 to 60 L min^{-1}. It may be noted, however, that there is a trend toward increased lower lung deposition with increasing nominal respirable fraction.

In Fig. 6 the influence of tidal volume is examined. Two deposition curves are shown, each equivalent to an inspiratory flow rate of 14 L min^{-1} (see Table II); but in one instance the tidal volume is 500 ml and in the other it is 1291 ml. Increasing the tidal volume significantly influences deposition in the lower lung, raising values by a factor of 2. The large error bars, attributable to the effects of the particle size distributions, overlap. This indicates the inability of the lung

Table II. Definition of Breathing Conditions Corresponding to Different Levels of Respiratory Intensity in Adult Human Subjects

	Physical states					
Ventilatory parameters	Test 1	Sedentary	Test 2	Light activity	Test 3	Moderate activity
TV = tidal volume (ml)	500	500	500	1291	1291	1622
f = breathing frequency (min^{-1})	12	14	40	15.5	5.5	18.5
Q = inspiratory flow rate (L min^{-1})	12	14	40	40	14	60

Table III. Comparison of Calculated Aerosol Deposition Patterns with Experimental Human Subject Data from Heyder *et al.* (22): Respiratory Conditions Were Defined by Tidal Volume (TV) and Breathing Cycle (τ)

Particle size D_{ae} (μm)	Ventilatory parameters					
	TV = 1000 cm^3, τ = 8 sec		TV = 500 cm^3, τ = 4 sec		TV = 1500 cm^3, τ = 4 sec	
	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.
0.005	0.92	0.82	0.86	0.67	0.94	0.87
0.007	0.92	0.81	0.84	0.65	0.93	0.86
0.010	0.90	0.80	0.81	0.62	0.91	0.84
0.020	0.85	0.74	0.70	0.52	0.82	0.72
0.030	0.78	0.67	0.59	0.44	0.71	0.61
0.050	0.64	0.52	0.43	0.33	0.52	0.45
0.070	0.53	0.43	0.34	0.27	0.41	0.36
0.100	0.41	0.34	0.25	0.21	0.30	0.25
0.200	0.25	0.21	0.14	0.13	0.17	0.14
0.400	0.16	0.18	0.09	0.11	0.11	0.12
0.700	0.16	0.19	0.08	0.12	0.11	0.12
1	0.20	0.25	0.10	0.15	0.13	0.15
2	0.48	0.53	0.24	0.27	0.32	0.38
3	0.66	0.66	0.41	0.39	0.54	0.59
4	0.77	0.74	0.56	0.47	0.72	0.71
5	0.83	0.77	0.66	0.53	0.82	0.76
6	0.86	0.80	0.73	0.58	0.88	0.80
7	0.89	0.82	0.77	0.62	0.91	0.82
8	0.90	0.82	0.80	0.63	0.94	0.84
9	0.91	0.81	0.82	0.60	0.95	0.83
10	0.92	0.80	0.85	0.60	0.96	0.84

(i.e., as simulated by the model) to distinguish among the variations for each nominal respirable fraction under the conditions tested.

In Fig. 7 two deposition plots are given for an inspiratory flow rate of 40 L min^{-1} (see Table II). The tidal volumes are 500 and 1291 ml. A twofold increase in mean lower lung deposition results from the prescribed increase in tidal volume. These estimates of deposition are much lower than the results for 14 L min^{-1}. Also, the deviations which may be ascribed to particle size are smaller and do not overlap.

It should be emphasized that the lung deposition model employed is based upon passive inhalation and is therefore applicable to certain pharmaceutical aerosols. For example, dry solid powders are generated (i.e., actuated) by the breath of the patient, suggesting simulation by a passive inhalation model to be appropriate. Nebulized droplets are also inhaled passively. Metered-dose, pressurized aerosols are noteworthy for not being subject, directly, to description by passive inhalation. The droplets generated by these devices are propelled and travel at much higher linear velocities, potentially in excess of 30 m sec^{-1}, than achieved by inspiration (24). The linear velocity of inspiration based on a flow rate of 60

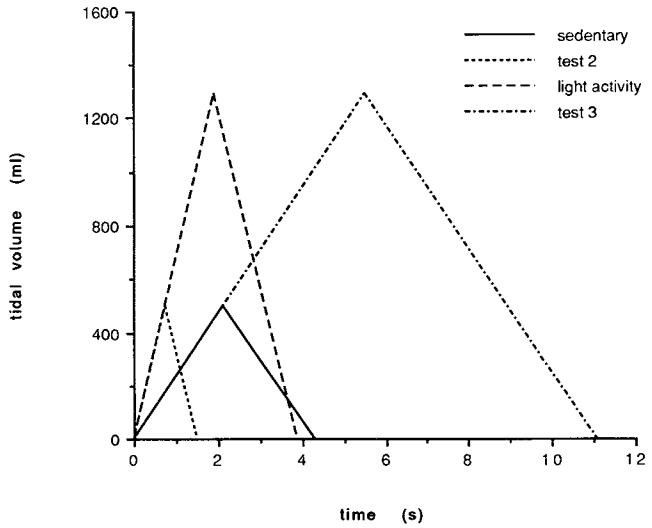

Fig. 4. Respiratory protocols used with the mathematical model to calculate aerosol deposition patterns in the human lung. The curves represent sedentary and light activity levels, and Test 2 and 3 conditions, as defined in Table II.

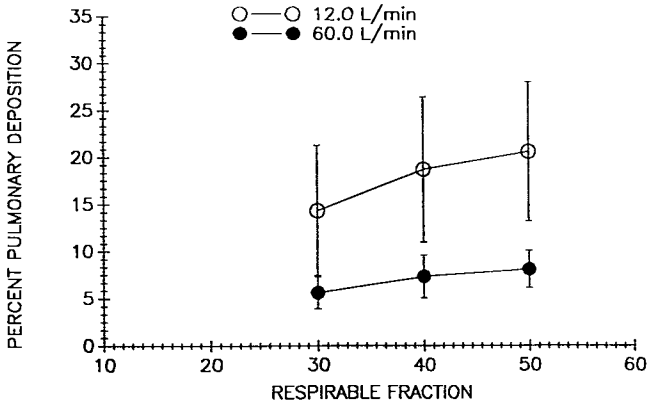

Fig. 5. Predicted pulmonary deposition as a function of nominal respirable fraction (<6.4 μm) at selected inspiratory flow rates.

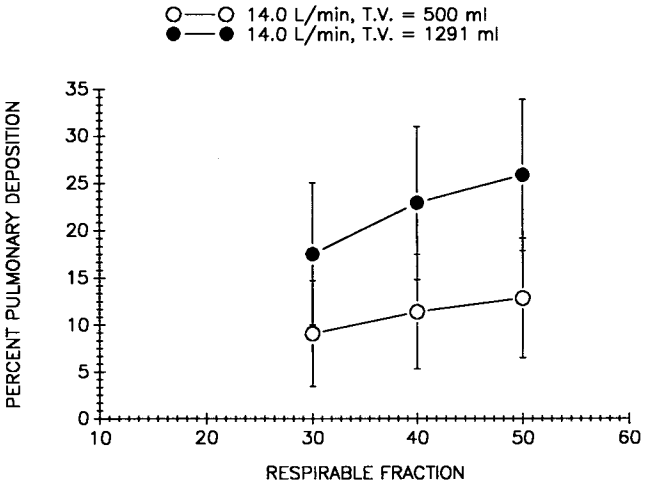

Fig. 6. Predicted pulmonary deposition as a function of nominal respirable fraction (<6.4 μm) at a prescribed inspiratory flow rate for different tidal volumes.

L min^{-1} and an oropharyngeal cross-sectional area of 10 cm^2 is 1 m sec^{-1}. A range of inspiratory flow rates and anatomical dimensions is possible, all of which will give rise to different linear velocities, but passive inhalation is certainly an order of magnitude slower than propelled aerosol delivery. A spacer device may render an aerosol virtually stationary for subsequent passive inhalation. Therefore, the model presented herein does simulate the administration of MDIs when they are used in conjunction with spacer devices, which is often the case in clinical practice.

Both droplets and dry particles may undergo dynamic, physicochemical changes in transit through the airways which may result in errors in their predicted deposition pattern. These hygroscopic effects have not been addressed in these studies as the effects differ for each drug but have been examined elsewhere (23). The model can, however, be modified to address these behavioral characteristics.

CONCLUSION

A mathematical model describing the behavior of inhaled aerosols has been presented and validated by data from human subject exposures. The model has been used to study factors affecting the deposition of airborne pharmacologic drugs in the lung. There is a correlation between nominal respirable fraction and estimated lower lung deposition at specific inspiratory flow rates and tidal volumes. The effects of particle size distributions are more pronounced at the higher inspiratory flow rates and greater tidal volumes examined.

From a quality control standpoint the findings suggest the model to be a valid method of estimating the fraction which will deposit in the pulmonary compartment under well-defined conditions. In clinical practice, variations in deposition may be anticipated due to differences in ventilatory parameters and morphologies naturally occurring among individuals (i.e., intersubject differences) and as a function of gender and disease state.

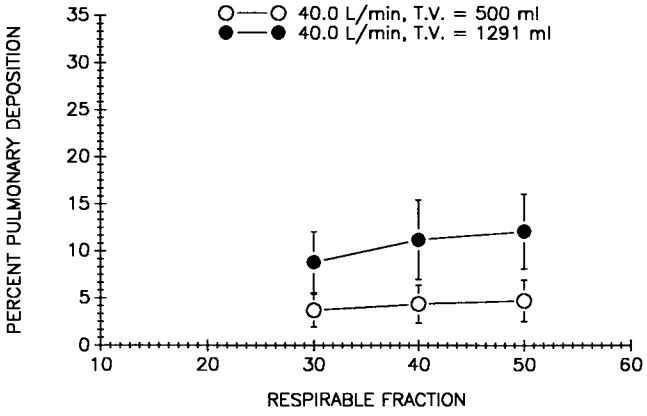

Fig. 7. Predicted pulmonary deposition as a function of nominal respirable fraction (<6.4 μm) at a prescribed inspiratory flow rate for different tidal volumes.

REFERENCES

1. *British Pharmacopoeia, Vol. II,* Appendix XVIIB, HMSO, London, pp. A204–A207.
2. USP Advisory Panel on Aerosols (1985–1990). Report and Recommendations of the USP Advisory Panel on Aerosols on the USP General Chapter ⟨601⟩ on Aerosols. *Pharm. Forum* 17:1703–1713 (1991).
3. A. J. Hickey. Factors influencing aerosol deposition in inertial impactors and their effect on particle size characterization. *Pharm. Tech.* 14:118–130 (1990).
4. O. G. Raabe. A general method for fitting size distributions to multicomponent aerosol data using weighted least-squares. *Env. Sci. Tech* 12:1162–1167 (1978).
5. W. Stahlhofen, G. Rudolf, and A. C. James. Intercomparison of experimental regional aerosol deposition data. *J. Aerosol Med.* 2:285–308 (1989).
6. T. B. Martonen. Aerosol therapy implications of particle deposition patterns in simulated human airways. *J. Aerosol Med.* 4:25–40 (1991).
7. T. B. Martonen, R. C. Graham, and W. Hofmann. Human subject age and activity level: Factors addressed in biomathematical deposition program for extrapolation modeling. *Health Phys.* 57:49–59 (1989).
8. K. Fults and A. J. Hickey. Correlation of estimated respirable fraction of an aerosol with theoretical lung deposition. *Pharm. Res.* 8:S6 (1991).
9. E. M. Phillips, P. R. Byron, K. Fults, and A. J. Hickey. Optimized inhalation aerosols. II. Inertial testing methods for aerosol particle size analysis. *Pharm. Res.* 7:1228–1233 (1990).
10. K. Fults, T. D. Cyr, and A. J. Hickey. The influence of sampling port geometry upon particle size measurement using an inertial impactor. *J. Pharm. Pharmacol.* 43:726–728 (1991).
11. A. J. Hickey. An investigation of size deposition upon individual stages of cascade impactor. *Drug Dev. Ind. Pharm.* 16:1911–1929 (1990).
12. O. G. Raabe. Particle size analysis utilizing grouped data and the log-normal distribution. *J. Aerosol Sci.* 2:289–303 (1971).
13. T. Allen. In *Particle Size Measurement,* Chapman and Hall, London, 1990, pp. 156–170.
14. T. B. Martonen. Measurement of particle dose distribution in a model of a human larynx and tracheobronchial tree. *J. Aerosol Sci.* 14:11–22 (1983).
15. T. B. Martonen. Development of surrogate lung systems with controlled thermodynamic environments to study hygroscopic particles: Air pollutants and pharmacologic drugs. *Particle Sci. Tech.* 8:1–20 (1990).
16. T. B. Martonen and J. Lowe. In V. A. Marple and B. Y. H. Liu (eds.), *Aerosols in the Mining and Industrial Work Environments,* Ann Arbor Science, Ann Arbor, MI, 1983, pp. 151–164.
17. T. B. Martonen. On the fate of inhaled particles in the human: A comparison of experimental data with theoretical computa-

tions based on a symmetric and asymmetric lung. *Bull. Math. Biol.* 45:409–424 (1983).

18. T. B. Martonen, W. Hofmann, A. D. Eisner, and M. G. Menache. In J. D. Crapo, E. D. Smolko, F. J. Miller, J. A. Graham, and A. W. Wallace (eds.), *Extrapolation of Dosimetric Relationships for Inhaled Particles and Gases,* Academic Press, San Diego, 1989, pp. 303–316.
19. T. B. Martonen. Analytical model of hygroscopic particle behavior in human airways. *Bull. Math. Biol.* 44:425–442 (1982).
20. T. Martonen. Deposition of inhaled particulate matter in the upper respiratory tract, larynx, and bronchial airways: A mathematical description. *J. Toxicol. Environ. Health* 12:787–800 (1983).
21. E. R. Weibel. *Morphometry of the Human Lung,* Academic Press, New York, 1963.
22. J. Heyder, J. Gebhart, G. Rudolf, C. F. Schiller, and W. Stahlhofen. Deposition of particles in the human respiratory tract in the size range 0.005–15 μm. *J. Aerosol Sci.* 17:811–825 (1986).
23. A. J. Hickey and T. B. Martonen. Behavior of hygroscopic pharmaceutical aerosols and the influence of hydrophobic additives. *Pharm. Res.*, 10(1): in press (1993).
24. R. W. Rance. Studies of the factors controlling hair sprays. III. The influence of particle velocity and diameter on the capture of particles by arrays of hair fibers. *J. Soc. Cosmet. Chem.* 25:545–561 (1974).