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

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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 probability 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 (Dₐₑ) 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-
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         | MMAD  | GSD   | MMAD  | GSD   | MMAD  | GSD   |
| identification  |       |       |       |       |       |       |
| 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   |