Review

Behavior of Hygroscopic Pharmaceutical Aerosols and the Influence of Hydrophobic Additives

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The high temperature and relative humidity in the lung can result in the hygroscopic growth of susceptible aerosol particles or droplets. The term hygroscopic growth describes the increase in particle diameter which occurs as the result of association with water vapor. The influence of hygroscopicity upon lung deposition of aerosols has been a productive area of research in industrial hygiene, environmental sciences, and inhalation toxicology. Many pharmaceutical inhalation aerosols display hygroscopic behavior in their passage through the airways; however, the effect has been neglected. Controlling the phenomenon of hygroscopic growth and, thus, the related lung deposition of aerosols might result in the therapeutic advantage of targeting the site of action. Such an approach might also allow identification of the location of pharmacologic receptor sites in the lung. This Review discusses an approach to achieving control of hygroscopic growth of aerosol particles. Theoretical and experimental studies have indicated that inhaled particle diameters increased significantly for drugs commonly administered to the lung. The presence of certain additives, notably glycerol, cetly alcohol, and lauric and capric acids, has been demonstrated to reduce the growth of particles under conditions approaching those in the lung. Very few quantitative studies of the nature discussed herein have appeared in the literature. It is conceivable that an aerosol particle could be fabricated of known initial size and density, and by implication, deposition characteristics, and this might be induced to follow specific growth kinetics to enhance deposition in a particular region of the lung. Thus, physical targeting of regions within the lung might be achieved.

KEY WORDS: aerosol; hygroscopic growth; lung deposition; inhalation.

INTRODUCTION

The deposition pattern of an inhaled aerosol, for a prescribed breathing protocol, is related to the physical characteristics of its constituent particles; specifically, the mass median aerodynamic diameter (MMAD) and geometric standard deviation (σg) of the particle size distribution. Such laboratory experiments performed with human test subjects, as reviewed by Stahlhofen et al. (1), have intentionally utilized nonaqueous particles to avoid effects of hygroscopicity upon deposition processes. Hygroscopic substances absorb the ubiquitous water vapor present within the warm and humid environment of the respiratory tract. Consequently, the sizes and densities of hygroscopic aerosols change following inhalation, and therefore, the deposition sites of hygroscopic particles will differ from those of nonhygroscopic particles of identical preinspired physical features.

The hygroscopic behavior of aerosols and its influence upon airborne particle kinetics have been well established. Initially, atmospheric physicists and industrial hygienists recognized the influence of hygroscopicity in conjunction with nuclei of specific atmospheric pollutants in producing clouds and rain (2–10). The high incidence of respiratory disease in urban areas following decades of industrialization led researchers to investigate the behavior of atmospheric pollutants upon entry into the respiratory tract (11–16).

Many pharmaceuticals take up water vapor, which suggests that hygroscopic growth may take place upon inhalation (17). Other drugs, although relatively nonhygroscopic per se, are commonly administered in clinical practice as saline solutions. Those nebulized drug formulations, therefore, will behave as sodium chloride particles, which are very hygroscopic (18,19). If the hygroscopic growth characteristics of such medicines were known (i.e., either alone or as saline droplets), aerosol hygroscopicity could be an important factor in the administration of drugs. Further, accounting for hygroscopicity may permit the selective deliv-

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ery of drugs to particular geometric locations of the respiratory tract to treat specific airway diseases. However, quantitative data on particle growth characteristics and factors regulating the hygroscopic behavior of airborne particles are very limited. This review examines the few available studies from the clinical perspective of targeting the deposition of inhaled pharmaceuticals to elicit optimum therapeutic effects.

DEFINITION OF TERMS

The hygroscopicity of an aerosol is a physicochemical property indicating its ability to assimilate moisture under defined conditions of temperature and relative humidity. A hygroscopic particle will change in physical dimensions and density as a function of its original size, chemical composition, and residence time in a particular environment of prescribed temperature and relative humidity (20). The hygroscopic growth per se of an aerosol (solid particles or droplets) is expressed in the change in particle size. Therefore, the expression of particle dimension must be defined, and it must be recognized that, in general, aerosols are polydisperse with regard to particle size. The most common parameter employed to characterize an airborne particle is termed the aerodynamic equivalent diameter (21,22). By definition, it is the geometric diameter of an equivalent sphere of unit density having the same Stokes terminal settling velocity as the considered particle.

The range of particle sizes emitted by metered-dose inhalers (MDIs) and nebulizers frequently approximates a log-normal distribution which can be characterized by a median diameter and geometric standard deviation \((\sigma_g)\). In the case of therapeutic aerosols, the distribution of drug mass is most relevant and is approximately described by a mass median diameter based on the aerodynamic equivalent size of individual particles, the mass median aerodynamic diameter (MMAD) and the \(\sigma_g\) (22).

The hygroscopic growth of a particle may be described by comparing its diameter at a high relative humidity, such as exists in the lung, with that at a low relative humidity, such as ambient conditions. Herein, a direct ratio of these two values, a dimensionless number, is termed the hygroscopic growth ratio and is used to designate a measure of aerosol hygroscopicity.

LUNG DEPOSITION MODELS

The scope and diversity of lung deposition modeling were reviewed by the Task Group on Lung Dynamics in an attempt to unify the experimental and theoretical data on inhaled particle dosimetry (23). The evolving mathematical models incorporate both empirical (24–26) and deterministic (27,28) efforts. The laboratory work involved deposition tests with airway casts, surrogates (29–31), and human subjects (32–39), with research directed toward improved drug delivery (40). The human inhalation exposure studies have been reviewed by Stahlofen et al. (1). However, while knowledge regarding the lung deposition of nonhygroscopic particles or stable droplets is at an advanced level, little information is available concerning aerosols which undergo dynamic changes while in transit through airways. Mathematical models have been developed that more accurately estimate lung deposition of aerosols. In some models relative humidity profiles for the range of airway generations have been constructed from clinical data and thermodynamic factors, and the effects of hygroscopicity upon deposition have been taken into account (41–57). Indeed, some studies have emphasized the behavior of aerosol-containing drugs (45,52,53). Lengthy reviews of this subject have been published (58,59).

Knowledge of the human lung’s temperature (T) and relative humidity (RH) atmospheres are central to the issue of aerosol hygroscopicity. To date, the transitory T and RH profiles within the lung have not been simultaneously and systematically mapped on an airway-by-airway basis. Perhaps the most technical attempts have been the in situ measurement protocols of McFadden et al. (60,61), but these studies were restricted to determining T values alone within the upper human bronchi. Other T and RH data are available only for selected individual airways; however, the exact measurement sites within the lung during the actual tests were often ambiguous. Moreover, the measurements were often made under a variety of unreported laboratory conditions; for example, Were human subjects anesthetized or were breathing patterns monitored? Limited T and RH data were obtained in a series of coordinated experimental investigations designed to simulate the internal environments of the human tracheobronchial (TB) tree (42,62–65). The T and RH profiles in the lung were estimated for a range of physiologically realistic breathing conditions and put into a format suitable for particle monitoring purposes. The data indicate that, for oral breathing of ambient T and RH aerosols, the RH pattern in the human lung may be suitable approximated in the following manner: RH = 90% in the trachea, and RH values increase monotonically by 1% increments for each downstream bronchial passage until a saturation level of 99.5% is achieved in generation \(I = 10\) airways (i.e., the peripheral TB bronchioles). Further, it is reasonable to assume a T value of 37°C in the TB network for most breathing conditions. For particle deposition modeling, the manner in which the hygroscopic behavior of inhaled aerosols is described mathematically must reflect, and is limited to, the specific formats in which growth data have been presented in the literature. This fundamental problem was analyzed here for two representative data bases, to establish whether the final or transitory particle sizes and densities are known. Regarding case 1 (i.e., final sizes), Tang and Munkelwitz (66) have measured the equilibrium parameters of sulfate aerosols under well-defined T and RH conditions. To use these data, therefore, it was necessary to define a priori the spatial T and RH distribution within the human lung. Martonen et al. (52) permitted particle sizes and densities to change in a stepwise manner as dictated by the local T and RH environment at a particular location while passing through the lung. Regarding case 2 (i.e., transitory sizes), the growth rates of medicinal aerosols have been measured in surrogate lung systems containing physiologically realistic T and RH atmospheres (42). In associated deposition calculations the inhaled particles were allowed to vary in size and density within the lung as a function of time and independent of location, thereby permitting effects of respiratory activity (i.e., time-dependent ventilatory parameters) to be simulated (52). The analyses indicated that information is needed de-