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Review

Behavior of Hygroscopic Pharmaceutical Aerosols and the Influence of Hydrophobic Additives[1]

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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, cetyl 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 (σg). 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 σg (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 ans 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 Stahlhofen *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 unregulated or 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 tracheobronchal (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-

scribing the growth rates of hygroscopic particles to simulate accurately related effects upon their deposition within the human lung.

HYGROSCOPIC GROWTH STUDIES

Theoretical Simulations

By application of Raoult's law with the inclusion of the van't Hoff factor, the equilibrium droplet size of particles may be calculated from the water activities of their components and a knowledge of the surrounding relative humidity and temperature (67,68). Table I shows theoretical values for the hygroscopic growth ratios of certain drugs commonly administered by inhalation. The computations assumed a relative humidity of 99.5%. These calculations are of limited utility, as they estimate growth under *equilibrium* conditions. Since hygroscopic growth is a dynamic phenomenon, it is the *rate* at which growth occurs that plays the critical role in lung deposition. To model lung deposition of aerosols more accurately, their behavior under physiologically realistic thermodynamic conditions should be analyzed *in vitro*. Therefore, the hygroscopic growth kinetics of pharmaceutical aerosols was studied in surrogate laboratory systems with controlled temperature and relative humidity profiles approaching those in different regions of the human lung.

Experimental Measurements

Early hygroscopic growth studies focused on the behavior of environmental sulfate compound aerosols (such as sulfuric acid, ammonium sulfate, and ammonium bisulfate) and sodium chloride (5,7,9,11,14,41). The sulfate aerosols are air pollutants and common emissions produced by the combustion of fossil fuels. The saline aerosols are common ingredients of marine atmospheres and are also the base of many aerosolized pharmacologic agents. These aerosols were frequently served in subsequent studies as control material because of the broad data base on their behavior (18,19, 55,68–70).

Initial studies regarding the hygroscopic growths of pharmaceutical aerosols employed β-adrenergic agonists, cromolyn sodium and adrenocorticosteroids. In practice they were delivered by nebulizers, dry powder generators (DPIs), and pressure-packaged MDIs (50–53). In Table II experimentally determined hygroscopic growth ratios are presented (71–74). The measured values are much smaller than the calculated values shown in Table I. A partial explanation for these differences may be related to the relative humidities for which each of the data were derived. The experimentally determined laboratory data were obtained under 90–98% relative humidity conditions, while the theoretical values correspond to a relative humidity of 99.5%.

Table I. Calculated Hygroscopic Growth Values of Pharmaceuticals Used in the Treatment of Lung Diseases

Drug	Particle growth ratio[a]	Ref. no.
Acetylcysteine	2.80	45
Atropine sulfate	2.24	45
Carbenicillin disodium	2.83	45
Dexamethasone sodium phosphate	2.46	45
Histamine dihydrochloride	3.55	45
Methacholine chloride	3.15	45
Disodium cromoglycate	2.60 (2.12)[b]	67
Isoproterenol hydrochloride	2.97 (2.85)	67
Isoproterenol sulfate dihydrate	2.59 (2.37)	67
Albuterol sulfate	2.50 (2.41)	67

[a] Assuming ideal solution behavior and full ionization.
[b] Ratio based on experimental isoosmotic concentrations in parentheses.

Hygroscopic Growth Behavior—Drug and Additives

Glycerol Effects

To study the hygroscopic behavior of inhaled aerosols, a series of surrogate lung systems has become increasingly realistic (42,62–65). The environments within the surrogate airways are intended to simulate *in vivo* conditions, and emphasis was placed upon maintaining the integrity of the following factors: (i) lung atmosphere—T and RH profiles; (ii) airway morphology—dimensions and branching; and (iii) fluid dynamics—R_e values, velocity patterns, and the laryngeal jet.

Hygroscopic growth studies have been performed (42,62,63) using monodisperse aerosols delivered at a flow rate of 1–3 L/min through a surrogate lung system. The key component of these studies was a growth chamber in which the TB environment was simulated. The aerosol was mixed with 50–100 L/min of clean, temperature- and relative humidity-regulated air. A Climet 208 optical particle counter sampled the aerosol at 7 L/min before and after passing through the growth chamber. Climet responses were pulse height-quantitated with a calibrated multichannel analyzer. Particle growth occurred during the time required to traverse the distance between the entrance to the growth chamber and the particle counter's sensing volume. Hygroscopic growths were regulated in the response tests by changing either the diluting airflow rate or the chamber's length to regulate particle residence times. The T and RH conditions were continuously monitored at the aerosol–air mixing site and at an exhaust port of the chamber. It was observed that hygroscopic growth to final sizes and, most significantly,

Table II. Measured Hygroscopic Growth Values of Pharmaceuticals Used in the Treatment of Lung Diseases

Aerosolized drug	Particle growth ratio	Relative humidity	Ref. no.
Cromolyn sodium (powder)	1.31	98	71
Metaproterenol sulfate	1.29	98	72
Isoproterenol sulfate	1.13	98	72
Beclomethasone dipropionate	1.33	98	73
Isoproterenol/phenylephedrine	1.24	90	74
Epinephrine	1.11	90	74
Metaproterenol	1.10	90	74
Albuterol	1.08	90	74
Isoetharine/phenylephedrine	1.10	90	74
Triamcinolone	1.17	90	74

growth *rate* were inhibited for isoproterenol hydrochloride aerosols by the presence of glycerin. Tables III and IV illustrate this point for two flow conditions, as defined by Reynolds numbers (Re), describing the upper TB airways during relatively light and heavy breathing conditions.

The chemical structures of the respective isoproterenol hydrochloride and glycerin molecules are depicted in Figs. 1a and b. They are presented to aid in a discussion of the observed growth rate inhibiting properties of glycerin. The hydrophilic and hydrophobic components of isoproterenol hydrochloride are indicative of surface-active characteristics. A possible mechanism for the role of glycerin in the retardation of water vapor uptake may be proposed. It is surmised that glycerin is originally concentrated over the surfaces of the particles entering the growth chamber. Hydrogen bonding between the glycerin and the water molecules would then promote the retention of the latter on the surface of an individual particle. Water molecules would consequently diffuse more slowly into the particle's core due to the presence of glycerin, thereby resulting in an inhibited rate of additional water absorption and commensurate particle growth. In this scenario, the hygroscopicity of a pharmacologic agent will decrease as its glycerin concentration increases. Therefore, glycerin may be a desirable additive to pharmaceuticals to control selectively their growth rates within the warm humid lung airways.

These data are consistent with recent results of studies of the dynamic behavior of single glycerin droplets in humid airstreams showing that the time required for maximum growth is longer than anticipated (75). These experiments were conducted in an electrodynamic balance where a charged droplet was suspended in the path of a He–Ne laser beam in a stream of air with precisely controlled humidity and temperature. The unusually slow growth rates of glycerin droplets were presumed to be due to interfacial resistance or the presence of other unspecified rate controlling mechanisms, similar to the process acting in the combined drug–glycerin droplets (42,62,63).

The concept of modified interfacial phenomena limiting the growth of aerosol droplets was considered in studies of the deposition of saline droplets covered with a monolayer of the surfactant cetyl alcohol (76,77). A polydisperse aerosol was preconditioned at a controlled temperature (20 or 36.5°C) and relative humidity (99.5%) and passed into a horizontal elutriator. The flow rate of the aerosol was 2 L/min and the mean residence time for droplets in the chamber was 3 min. The deposition efficiency of a sampled particle was used to estimate its degree of hygroscopic growth. The deposition efficiency was calculated from the ratio of the number of particles entering the elutriator to the number exiting as estimated using a sedimentation cell viewed by a camera through a microscope. Otanyi and Wang (76,77) concluded that the mechanism whereby cetyl alcohol reduced the growth rate of saline droplets in humid air (up to 99.5%) involved covering the droplets with a monolayer.

Table III. Hygroscopic Growth Ratio Values for Bronchodilator aerosols: The Airstream Reynolds Number in the Surrogate Lung During Laboratory Tests Was 2100–2300

Isuprel solution (%)	Additive	Particle growth parameter $t/(D_0)^2$ (sec/μm²)	Relative humidity (%)	Particle growth ratio	Ref. no.
1	None	0.010	93	1.40	42
		0.080	92	2.05	42
		0.150	93	2.45	—[a]
		0.215	93	2.70	42
		0.315	93	2.80	—
0.5	Glycerin	0.07	93	1.60	42
		0.21	93	2.05	—
		0.37	95	2.20	42

[a] Previously unreported data.

Table IV. Hygroscopic Growth Ratio Values for Bronchodilator Aerosols: The Airstream Reynolds Number in the Surrogate Lung During Laboratory Tests Was 1100–1200

Isuprel solution (%)	Additive	Particle growth parameter $t/(D_0)^2$ (sec/μm²)	Relative humidity (%)	Particle growth ratio	Ref. no.
1	None	0.010	93	1.15	62
		0.030	93	1.80	62
		0.045	92	1.65	62
		0.090	93	1.85	62
		0.250	93	2.15	62
0.5	Glycerin	0.020	93	1.10	42
		0.120	95	1.40	62
		0.225	94	1.60	42

Fatty Acid Effects

Disodium Fluorescein—In Vitro *Studies*. Surfactants are used as suspending agents and valve lubricants in aerosol formulations (78,79). Dry powder aerosols of disodium fluorescein (DF) were prepared with saturated fatty acid, lauric and capric acids, analogues of the commonly employed aerosol suspending agents (80). Each fatty acid was deposited on DF particles from nonaqueous solution by an adsorption/coacervation technique. Figures 1c and d show the structures of DF and capric acid (a 10-carbon molecule). Lauric acid differs from capric acid by two additional methylenes in

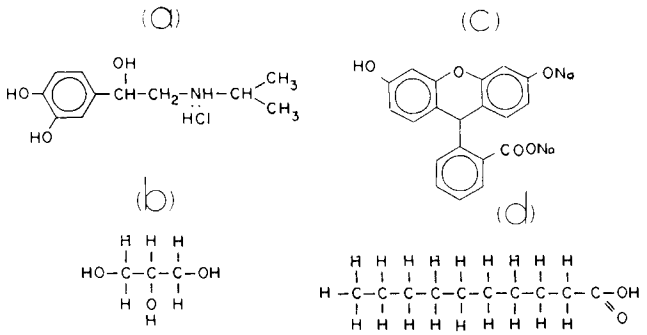

Fig. 1. Structure of (a) the active bronchodilator agent (isoproterenol hydrochloride), (b) an additive (glycerin) or Isuprel solutions, (c) disodium fluorescein, and (d) capric acid.

the aliphatic chain. The use of these particular saturated fatty acids yielded a solid product, and preparation and handling of these materials at room temperature were, therefore, facilitated. Chemical analysis of the powders indicated a fatty acid concentration-dependent, surface expansion effect during the adsorption process (80). The outcome of this procedure was a matrix-like product rather than a surface-coated powder. These powders were analyzed under controlled temperature (37°C) and relative humidity (20 and 97% RH) (81,82). Dry powder aerosols were projected mechanically into a preconditioned airstream initially flowing at 14.5 L/min. Air was sampled by a dew-point hygrometer monitoring the relative humidity. The remaining 12.5 L/min of this airstream was sampled by an inertial impactor which collected the entire aerosol. The residence time for the aerosol at the controlled conditions was approximately 40 sec.

Figure 2 shows the effect of the coatings on the growth ratio of DF (83). There was a significant reduction in the growth ratio as a function of increasing fatty acid concentration, from 1.5 for uncoated DF to 1.0 for 0.2 g/g lauric acid-coated DF. Since growth at only one residence time was examined in these experiments, the full scope of the application of this technique remains to be elucidated. By varying the residence time within this system, the kinetics of growth of these aerosols might be followed in future studies.

Disodium Fluorescein—In Vivo *Studies*. Studies of lung deposition of a lauric acid-coated DF aerosol in beagles indicated that enhanced uptake of fluorescein had occurred (84,85). Table V shows the rate constants for uptake of fluorescein in the beagle lung from particles of different sizes and from 0.23 g/g lauric acid-coated DF. It is possible that the coating of fatty acid might enhance absorption from the airways. However, it seems more likely that deposition of the aerosol particles took place at locations deeper in the lung, since they are not subject to rapid hygroscopic growth, thereby presenting them to a much larger surface for deposition and dissolution.

Disodium Cromoglycate. Disodium cromoglycate (DSCG), a hygroscopic drug (86,87), was subjected to the same treatment as DF described previously (88). In this case, the study of hygroscopicity was complicated by an additional physicochemical effect of fatty acid on the drug particles: A change in the shape of the particles is induced by the presence of fatty acid. This geometric change is likely to modify the aerodynamic behavior of the particles in the *absence* of any hygroscopic effects (89). Therefore, hygroscopic growth studies were performed on static bulk powders and not aerosolized powders, yielding information with respect to hygroscopicity alone. Nominal conditions of 37°C and 98% relative humidity were employed, with corresponding particle residence times of 24 hr. A DF sample was characterized using this system as a validation procedure; the growth ratio exhibited by DF was 1.38 ± 0.04. DSCG alone exhibited a growth ratio of 1.2 ± 0.04. Selected 0.1- and 0.2-g quantities of lauric acid, each in association with 1 g of DSCG, had growth ratios of 1.18 ± 0.00 and 1.17 ± 0.01, respectively. DSCG associated with 0.1 and 0.2 g of capric acid showed growth ratios of 1.20 ± 0.06 and 1.17 ± 0.05, respectively. The data suggest that the coating had little effect on the behavior of these prescribed powders. However, DSCG is known to have unusual colligative properties (90). The relationship between water activity and molality of DSCG solutions shows marked nonideality. A nematic mesophase (91) is formed which has constant water activity and is in equilibrium at 99.4% relative humidity and 37°C. The extent of hygroscopic growth of DSCG particles is crucially dependent on particular temperature and relative humidity values. The relative humidity atmosphere employed in these studies may not have been high enough to observe significant effects because of the colligative properties of the drug.

Further investigations in this field may give rise to a physicochemical approach permitting the control of hygroscopic growth and, ultimately, to targeted lung deposition.

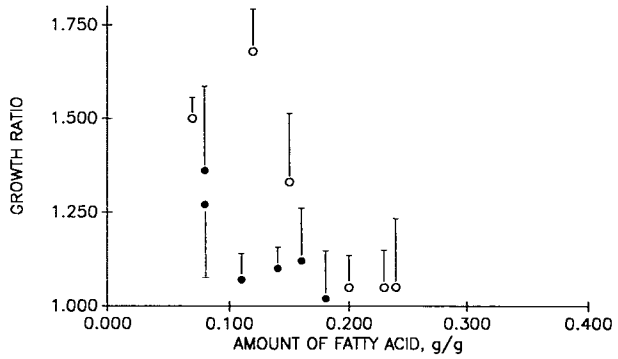

Fig. 2. Hygroscopic growth of disodium fluorescein particles as a function of lauric (○) and capric (●) acid content.

Table V. Absorption Rate Constants for DF and a 0.23-g Lauric Acid/g DF, from Aerosols Deposited in the Lungs of Two Beagles

Particle composition	MMAD (μm)	Absorption rate constant (min^{-1}) Dog 1	Dog 2	Ref. no.
DF alone	1.1	0.036	0.065	84
	3.5	0.042	0.047	84
	4.4	0.030	0.058	84
0.23 g LA/g DF	4.1	0.044	0.069	85

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