Study of the Hygroscopic Properties of Selected Pharmaceutical Aerosols Using Single Particle Levitation

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Purpose. To use a single particle levitation technique to investigate the equilibrium water sorption characteristics in both the evaporation and growth of four respiratory drugs at 37°C: atropine sulfate (AS), isoproterenol hydrochloride (IPHC) and isoproterenol hemisulfate (IPHS) and disodium cromoglycate (DSCG).

Methods. The equilibrium water content was measured as a function of relative humidity (RH) by a single particle levitation technique using an electrodynamic balance (EDB). The change of water content was determined by the voltage required to balance the weight of the levitated particle electrostatically. The water activities of bulk samples were also measured. Growth ratios were determined and compared with values in the literature.

Results. Crystallization or deliquescence was not observed for AS, IPHC and IPHS. The hysteresis in the water cycle was not observed for any of the drugs. At RH ~ 0%, AS particles still contain about 5% water but IPHC and IPHS particles do not contain any residual water. The aerodynamic growth ratio from RH 0% to 99.5% is 2.60, 2.86, 2.42 and 1.26 for AS, IPHC, IPHS and DSCG, respectively. Supersaturated droplets of IPHC and IPHS are expected to exist in the ambient conditions. DSCG is in a solid state in the RH range of 10–90%.

Conclusions. It is expected that some aerosolized drugs of low solubility may experience supersaturation before they enter the human body and this could exert a significant influence both on particle loss before inhalation and on the deposition of the drugs in the lungs. The EDB is a convenient and reliable tool for studying the hygroscopic properties of pharmaceutical aerosols, especially for supersaturated solutions.

KEY WORDS: hygroscopic property; water activity; particle growth; atropine sulfate; isoproterenol hydrochloride; isoproterenol hemisulfate; disodium cromoglycate.

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ABBREVIATIONS: a_w, water activity; GR_A, aerodynamic growth ratio; α, thermal diffusivity of air (cm^2s^{-1}); α_p, thermal diffusivity of the particle (cm^2s^{-1}); c, total molar concentration (mol cm^{-3}); C_0, balance calibration constant; c_p, molar density of the particle; D_1 diffusivity of solute in the droplet (cm^2s^{-1}); D_g, diffusivity of solvent vapor in air (cm^2s^{-1}); g, gravitational constant; mfs, mass fraction of water-free solute; ρ, particle density; R, gas constant; q, charge on a particle; R_p, particle radius; x_{A_∞}, molar fraction of solvent vapors far from the droplet; $X_{s\text{-}25}$, saturated molar fraction of solute in water at 25°C; $X_{s\text{-}37}$, saturated molar fraction of solute at 37°C; ΔS_f, entropy change associated with fusion; T_m, melting point in K; V, balancing voltage with air flow at time t; V_{85}, balancing voltage at RH = 85%; V_0, final balancing voltage in dry air with RH of about 5%; Vdc, balancing DC voltage without air flow; Z_0, distance between top and bottom electrodes.

INTRODUCTION

The use of aerosolized drugs via the respiratory route has been demonstrated to be an effective method of treating respiratory diseases (1). The hygroscopic property of pharmaceutical aerosols is an important parameter in the administration (2). Following the definition used in the aerosol science community, aerosols are strictly defined as airborne particles, in the form of either solid particles or liquid droplets in this paper. Most therapeutic aerosols are hygroscopic in nature. Other drugs, though non-hygroscopic themselves, are usually administered in normal saline solutions, which are hygroscopic. A hygroscopic solid particle becomes a liquid particle, i.e., a droplet, when it absorbs a sufficient amount of water to form a solution. Respiratory aerosols grow soon after they enter the warm and humid respiratory tract at a temperature of 37°C and RH of up to 99.5%. Growth affects the aerosols' size, density, and shape, and hence their deposition in the lungs, which is crucial to the therapeutic outcome of drugs.

In recent years, the single particle levitation technique using an electrodynamic balance (EDB) has been demonstrated to be a valuable method for studying hygroscopic properties of atmospheric aerosols. It is also well suited for studying pharmaceutical aerosols, as demonstrated by Chan et al. (3). In essence, this technique enables the study of growth (and evaporation) of an individual levitated particle. The single particle levitation technique has a few advantages over the conventional approaches of gravimetric measurement of water sorption using bulk solutions (4,5) and size distribution measurements (6). For example, the mass change in a particle can be monitored continuously, thus providing unambiguous *in situ* characterization of the aerosol. Supersaturated droplets can be studied since heterogeneous nucleation is suppressed when a droplet is levitated without contacting any foreign surface. Although supersaturated droplets do not exist in human airways because of the high RH of airways, they may exist before the generated aerosols enter human airways, especially for drugs of low solubilities which become saturated at high RH (e.g. RH = 95%). Despite its potential EDB has seen limited use in the study of the water sorption characteristics of pharmaceutical aerosols. Chan et al. (3) measured the water activities of two common pharmaceutical excipients, NaCl and disodium fluorescein (DF) using an EDB. However, the EDB is not suitable for studying the hygroscopic properties at RH > 90% because the droplets will grow to a size too large to be levitated. Bulk measurements at high RH are needed to complement the single particle measurements at low RH.

In this paper, we utilize the single particle technique to study the water sorption of four respiratory drugs: atropine sulfate (AS), isoproterenol hydrochloride (IPHC), isoproterenol hemisulfate (IPHS) and disodium cromoglycate (DSCG). They can be used in aerosol form via oral or nasal inhalation (7–9). Water activities of bulk samples were also measured. The objective of the present study was to demonstrate the capability of the EDB to serve as a convenient and reliable tool for estimating the supersaturation level of aerosolized drug droplets, since this has an important factor affecting their deposition in the lungs. Although the size of the particles we studied (~ 10 microns in diameter) is much larger than that of pharmaceutical aerosols in practice, the water

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sorption equilibrium data we obtained in this study are applicable to particles of all sizes.

MATERIALS AND METHODS

An EDB, designed and fabricated by our group, was used to investigate the equilibrium relationship between concentration of selected respiratory drugs and ambient RH. Bulk dilute (0.1–0.5 mol kg^{-1}) aqueous solution of the species studied was introduced into a piezoelectric droplet generator (Uni-Photon Inc., NY., USA, Model 201), which emitted droplets of about 20 μm in diameter. The droplets were then charged by induction before they fell into the EDB. A single particle was then levitated and equilibrated to RH = 85% in the EDB by evaporation of water. The particle, illuminated by a He-Ne laser, was observed with a microscope. In general, a particle can exist as an aqueous droplet or a solid particle at RH = 85%, depending on the species studied. In this study, all the species exist as aqueous droplets except DSCG. To determine the water sorption characteristics of the particle, the RH in the EDB was then changed.

Figure 1 shows the design of the EDB used in this study. It is identical to that used by Chan et al. (3). The EDB basically consists of two DC electrodes and a ring of an AC electrode. A charged particle inside the EDB experiences an electrostatic force due to the DC field, a time varying force due to the AC field, gravitational force, and any drag force due to relative movement with the ambient air. Because of the inertia of the particle, any particle off the center of the balance will experience a force, which on an AC cycle average, points to the center of the balance. When the electrostatic force due to the DC balances the weight and the drag force of the particle, the particle can be held stationary. When there is no air flow, the electrostatic force will be equal to the weight of the particle,

$$m = \frac{C_0 q}{g Z_0} V_{dc} \tag{1}$$

Effectively, the EDB serves as a highly sensitive gravimetric balance, with the mass (m) of the stationary droplet being proportional to the applied balancing DC voltage (V_{dc}). Any mass change of a levitated particle with the change of RH will result in the change of the balancing DC voltage. The mass fraction of solute of the particle (mfs = mass of solute / mass of (solute + water)) can be determined by measuring the ratio of V_{dc} to that of the same particle at a reference state of known composition. There are two possible reference states for known compositions: high RH where the equilibrium composition is known, or a water-free dry particle at RH = 0%. The former would be a good reference state if water activity (a_w) vs composition data were available (10). Unfortunately, the solubility of the drugs we studied is so low that there is no overlap between the available bulk data (at high RH) and the single particle data (at low RH). Hence, the latter reference state of a water-free dry particle at RH = 0% was used. However, levitated particles may not always form anhydrous particles at RH = 0%, even for binary solutions (11). The validity of the assumption of water-free particle at RH = 0% was evaluated. It should be noted that there has been no reported effect of charges on the a_w of droplets studied using an EDB.

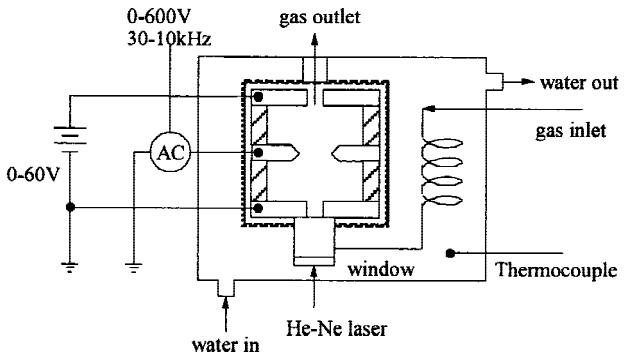

Fig. 1. A temperature controlled electrodynamic balance (EDB).

The *mfs* of a particle equilibrated as a function of RH was determined. The RH of the feed to the EDB was changed by varying the mixing ratio of a stream of dry air to a saturated stream after passing through a water bubbler. Air flow for controlling RH in the EDB was momentarily stopped when the balancing voltage was measured. The RH was determined by a dew-point hygrometer (EG&G DewPrime model 2000), and ambient temperature was measured with a digital thermocouple.

When a particle is equilibrated with its ambient environment, its a_w is related to RH by a_w = RH/100. So in this paper a_w and RH will be used interchangeably. Usually several particles were studied for each drug. Since our particles studied are in the order of 10 μm in diameter, the correction of vapor pressure due to curvature, i.e. the Kelvin effect, can be ignored in this study. Measurement at each a_w (or *RH*) typically takes about 40 minutes. The experimental details can also be found in Chan et al. (3).

The water activities of bulk solutions were measured by an AquaLab instrument (Model, 3TE, Decagon devices, USA), which measures the dew-point of the vapor phase in equilibrium with a bulk solution of known concentration in a sealed chamber. The AquaLab water activity meter has an accuracy of within 0.003 in a_w. The materials used in our study were obtained from Sigma Chemical Co. and were used as received without further purification. Because some of these chemicals are hygroscopic and may contain water under ambient conditions, the water content of the solid samples was determined by thermogravimetric analysis (TGA) (TA Instrument, DSC 2910, USA) before the samples were used for the bulk a_w measurement.

It is useful to know the saturation concentration of the drugs so that the existence of supersaturated solutions can be confirmed. Since the solubility data of the drugs at 37°C ($X_{s\text{-}37}$) are not available, they were estimated using the equation (12,13):

$$\log \frac{X_{s-25}}{X_{s-37}} = \frac{\Delta S_f T_m}{R} \left(\frac{25 - 37}{298.15 \cdot 313.15} \right) \tag{2}$$

where ΔS_f is assumed to be 13 cal/mol-°C, an average value for organics (13).

RESULTS AND DISCUSSION

Time Required to Achieve Equilibrium

In studying the water sorption and evaporation of pharmaceuticals, it is imperative to distinguish equilibrium and

mass transfer limited measurements. Equilibrium measurements are size-invariant when the Kelvin effect is ignored. On the other hand, mass transfer limited measurements would show particle size dependence. In fact, a distinct advantage of using a single particle in a water sorption experiment is the shorter response time of an individual particle than bulk sample particles to changes in ambient RH. Therefore equilibrium measurements can be made in a much shorter time.

Liang and Chan (15) compared the time scales of associated heat and mass transfer processes of evaporation of droplets in an EDB, upon a step change in the RH of the feed to the EDB. These time scales are listed in Table 1. Although the time scale of the change in the RH inside the EDB, which is the rate limiting step in particle growth and evaporation, varies depending on the residence time in the EDB, it is in general much longer than the time scales for other processes and it is short compared to the hours or even days required for a bulk water sorption experiment.

Figure 2 shows the results of drying experiments in which the RH of the stream to the EDB is changed from RH = 85% to RH = 5%. The relative voltage change, the F factor, is defined as $F = (V_{85}\text{-}V)/(V_{85}\text{-}V_0)$. It is can be seen that AS, IPHC, IPHS and DSCG all attain their final values, i.e., the equilibrium values, within 40 minutes. In the following discussion, the water cycle, i.e., equilibrium water sorption data during both evaporation and growth is presented in the form of the *mfs* as a function of a_w (=RH/100), shown in Figure 3–6. The saturation points at 37°C calculated by Equation (2) are also included in the figures. The bulk data and the EDB data are presented and compared with available data from literature.

Atropine Sulfate (AS)

Figure 3 shows the water cycle of AS, including the measurements of single droplets and bulk measurements. Also shown is the water cycle of NaCl at 37°C. The descriptions of

Table 1. Comparison of Characteristic Times of Processes Involved in the Evaporation of a $R = 10$ μm Droplet

Processes	Characteristic time definition[a]	Characteristic time (second)
1. Change of *RH* inside the EDB	$\frac{L^b}{u}$	120
2. Vapor diffusion in air	$\frac{R_p^2}{D_g}$	1.0×10^{-5}
3. Particle growth	$\frac{c_p R_p^2}{D_g X_{A\infty} C}$	0.54
4. Liquid diffusion in a droplet	$\frac{R_p^2}{D_1}$	0.10
5. Heat conduction in air	$\frac{R_p^2}{\alpha}$	1.2×10^{-5}
6. Heat conduction in a droplet	$\frac{R_b^2}{\alpha_p}$	1.0×10^{-3}

[a] See Abbreviations for details (Seinfeld (14)).
[b] Liang and Chan (15).

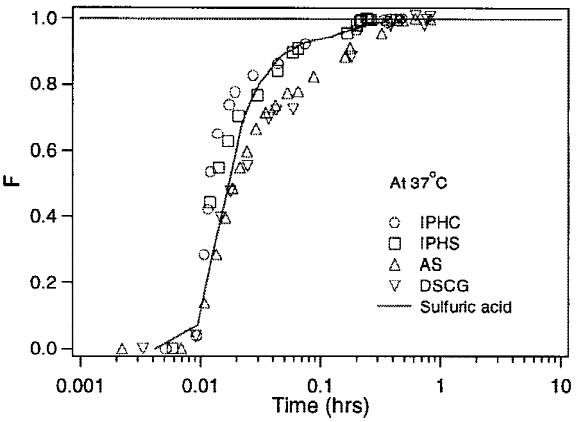

Fig. 2. Relative mass change of AS, IPHC, IPHS, DSCG and H_2SO_4 as a function of time at 37°C (from 85% to 5%).

"evap" and "cond" represent data measured during evaporation and condensation, respectively. When RH decreases from a high value (e.g. 90%), an aqueous NaCl droplet loses water and its *mfs* increases gradually until an RH of 45% is reached when the droplet effloresces and crystallizes to form an anhydrous particle of *mfs* = 1. When RH increases from a low value (e.g. RH = 10%), the anhydrous particle remains dry until an RH of 75% is attained when it abruptly absorbs water and becomes a droplet. This sudden change of state from a solid particle to a droplet at a particular RH as RH increases is called deliquescence. The deliquescence RH (DRH) is identical to the RH that is in equilibrium with a saturated solution (*mfs* = 0.266) at 37°C. Between RH= 75% and 45%, a NaCl particle exists as a supersaturated droplet when RH decreases but exists as a solid particle when RH increases. Such hysteresis is a common characteristic of many deliquescent salts (11).

Unlike NaCl, the AS particle neither crystallizes nor deliquesces. It continuously absorbs and desorbs water at increasing and decreasing RH, respectively. We found that the *mfs* calculated from the raw balancing voltage data are discordant with our measured bulk data if an anhydrous salt was assumed at RH = 0%. On the other hand, the presence of 5 *wt*% residual water in the particle at RH = 0% gives results that best follow the trend of the bulk data. A similar observation has been made for disodium fluorescein (DF) at 37°C

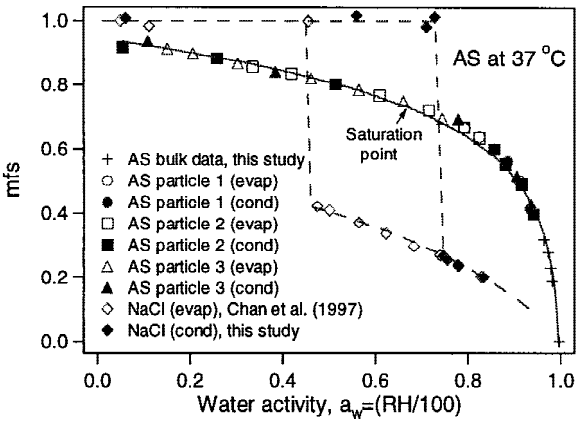

Fig. 3. Water activity data of atropine sulfate (AS) at 37°C compared with NaCl.

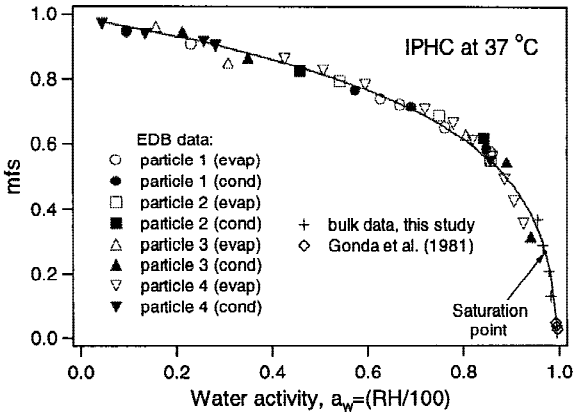

Fig. 4. Water activity data of isoproterenol hydrochloride (IPHC) at 37°C.

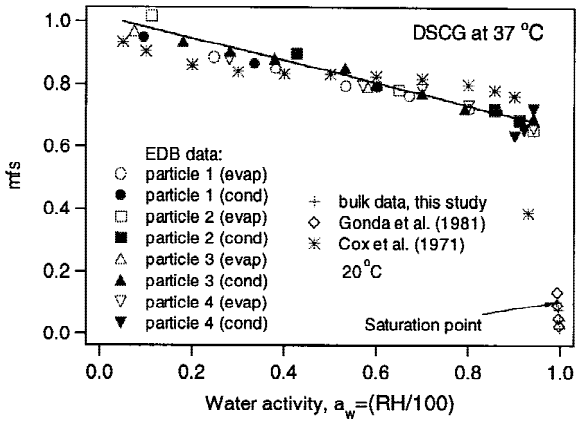

Fig. 6. Water activity data of disodium cromoglycate (DSCG) at 37°C.

by Chan et al. (3). DF contains 20% water by mass when the RH decreases to 10%. Because of the absence of an abrupt increase of *mfs* which is indicative of crystallization, it appears that crystallization, if it occurs, occurs at a very low RH and results in the evaporation of little water and a negligible change in *mfs*. At RH = 0%, the extrapolated *mfs* corresponds to a di-hydrate of AS, instead of the monohydrate specified by the manufacturer. No information of the most thermodynamically stable state in bulk study is available in literature. We cannot disgard the possibility that AS crystallizes at RH <5%.

Isoproterenol Hydrochloride (IPHC)

Figure 4 shows the water cycle of IPHC, including the single particle and bulk measurements. Like AS, the levitated IPHC particle neither crystallizes nor deliquesces. Again, hysteresis was not observed in the water cycle. An IPHC particle gradually loses water as RH decreases and finally achieves a water-free state without crystallization. In this case, assumption of a 100% water-free particle is valid. Our bulk measurements and the single particle measurements at high RH are consistent with measurements made by Gonda et al. (9). Although AS and IPHC show similar water sorption characteristics, IHPC is much less soluble in water than AS and therefore has a wider range of RH for which supersaturated droplets can exist. Since the a_w of solution is in general not a strong function of temperature (16), we can use Figure 4 to predict the behaviors of these particles at ambient temperatures. At 25°C, the saturation concentration of IPHC corresponds to *mfs* = 0.25 (17) which has a a_w of 0.975. Hence, droplets in an ambient environment of RH < 97% will be supersaturated solutions. To generate aerosols from solutions, for example by using a nebulizer, particles need to travel in an ambient environment with an RH that is likely below 97% before they would be humidified in the human airways. Hence, supersaturated droplets instead of anhydrous crystallized particles of IPHC may be formed. The aerosols generated from a nebulizer may deposit on the internal walls of the delivery tubing, within a spacer if applicable, and even in the nasal region before they grow and become subsaturated solution droplets. Since particle deposition depends on aerodynamic diameter, supersaturated droplets will have a larger particle loss than smaller anhydrous crystallized particles. Furthermore, since we did not observe deliquescence in the water cycle, modeling of drug particle growth in the respiratory system may not need to incorporate deliquescence. It is interesting to note that IPHC has a low solubility in bulk samples but can attain a very high supersaturation in levitated droplets.

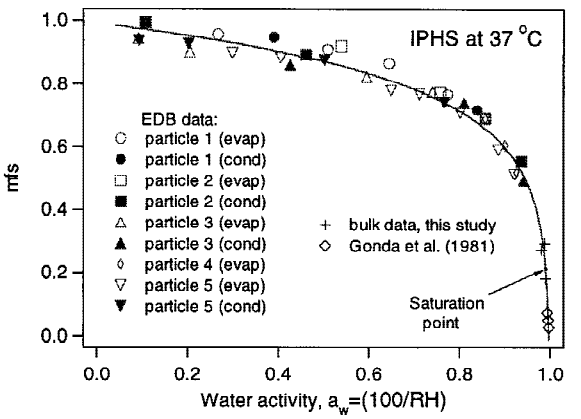

Fig. 5. Water activity data of isoproterenol hemisulfate (IPHS) at 37°C.

Isoproterenol Hemisulfate (IPHS)

Figure 5 shows that the single particle measurements, bulk measurements and the data from Gonda et al. (9) follow the same trend. Again, crystallization or deliquescence was not observed for the levitated particles. As RH decreases, the particle loses water until finally reaching an anhydrous state at RH = 0%. The assumption of a water-free particle is valid. Like IPHC, IPHS is slightly soluble and has a *mfs* of 0.2 (17) at the solubility limit at 25°C. Using the a_w data shown in Figure 5, an aerosol droplet of IPHS will be supersaturated at RH < 99%. Hence, supersaturated droplets of IPHS are expected to exist in ambient conditions after nebulization.

Disodium Cromoglycate (DSCG)

The water sorption characteristics of DSCG are very different from the other three drugs. After a droplet is introduced into the EDB, it quickly loses water and becomes a solid even at RH = 85%. For AS, IPHC and IPHC particles,

the light scattering signal at a fixed angle does not change dramatically unless the particles change size, indicating that these particles are in the form of homogeneous droplets. However, the light scattering signal of DSCG particles is random even at RH = 85% because of the particle rotation, indicating the formation of a solid phase in the particle.

Using a "quartz spring" balance, Cox et al. (18) found that the amount of water absorbed in the lattice of DSCG crystals is roughly proportional to the ambient RH up to 90% at 20°C, and that many forms of DSCG hydrate can exist at any given RH. In general, our measurements at 37°C are consistent with the measurements at 20°C taken by Cox et al., as shown in Figure 6. Although it is a solid particle, DSCG absorbs water continuously and reversibly without crystallization and deliquescence. Cox et al. (18) observed hysteresis in their measurements but they acknowledged that it might be due to mass transfer limitation. The levitated particle appears to be water-free at RH = 0%. The *mfs* is inversely proportional to RH in the range we studied. DSCG particles absorb 12 water molecules per DSCG molecule between RH of 0% to 90% at 37°C. The crystalline unit cell of DSCG can expand to accommodate up to about nine molecules of water (18). At RH > 93% more water is absorbed and a mesophase emerges, consistent with the phase composition diagram reported by Cox et al. (18). A few researchers (19,20) have reported different states of hydration of levitated particles of other species in an EDB.

Growth Ratio

Using the *mfs* at RH_1 and RH_2 the aerodynamic growth ratio (GR_A) can be estimated by the equation:

$$GR_A = \frac{R_{p,2}}{R_{p,1}} \cdot \sqrt{\frac{\rho_2}{\rho_1}} = \left(\frac{mfs_1}{mfs_2}\right)^{1/3} \left(\frac{\rho_2}{\rho_1}\right)^{1/6} \quad (3)$$

as presented by Chan et al. (3). R_p is the particle radius and ρ is the particle density. The density ρ of a particle is estimated from $\rho = \Sigma \rho_{io} mfs_i$, where ρ_{io} and mfs_i are the density of water or solute and the corresponding mass fraction in solution respectively (9,21). Since there is no data available in the literature for AS, the density of AS was estimated from $\rho = \Sigma \rho_{io} mfs_i$ and density measurements taken with the mass-volume method at 22°C. As shown in Table 2, the calculated results of IPHC, IPHS and DSCG at 37°C are consistent with those reported by Gonda et al. (9), Hiller (8) and Hickey (4). However, the GR_A of AS is about 15% larger than that reported by Ferron et al. (22). In their calculation of the growth ratio, Ferron et al. assumed unity density of AS although typical organic species have a density of 0.9–1.5 g cm^{-3}. However the error in density cannot lead to the relatively large difference in the growth ratio because of the weak dependence of GR_A on ρ in Eq. (3). We note that the calculated GR_A is very sensitive to the choice of RH_2 since *mfs* is very sensitive to a high RH. For example, the growth ratio would be 2.32, which is close to Ferron et al.'s estimation if RH_2 = 99.4% and density = 1.33 were used. Water activity data of supersaturated solutions were not reported in the literature cited above.

Table 2. Aerodynamic Growth Ratio (GR_A) for AS, IPHC, IPHS, and DSCG

Species	RH_1 (%)	RH_2 (%)	GR_A[a]	GR_A from literature
AS	0	99.5	2.60	2.24[b]
IPHC	0	99.5	2.86	2.85[c]
IPHS	0	99.5	2.42	2.37[c]
IPHS	17	96	1.26	1.13 ± 0.24[d]
DSCG	0	99.5	2.13	2.12[c]
DF	20	97	1.52[e]	1.45 ± 0.18[f]

[a] Based on the Equation (3).
[b] Ferron et al. (22).
[c] Gonda et al. (9).
[d] Hiller et al. (6)
[e] Chan et al. (3).
[f] Hickey et al. (4).

CONCLUSIONS

We have investigated the hygroscopic properties of four aerosolized drugs: AS, IPHC, IPHS and DSCG, at 37°C by using an EDB in air environment with well-controlled RH (5~93%). Neither crystallization nor deliquescence exist in the water cycle of AS, IPHC, and IPHS. DSCG is in a solid state in the RH range of 10–90%. At RH = 0%, AS still contains about 5% water (di-hydrate) but IPHC and IPHS do not possess any residual water. DSCG appears to be water-free at RH = 0%. The aerodynamic growth ratio from an RH of 0% to 99.5% is 2.60, 2.86, 2.42 and 1.26 for AS, IPHC, IPHS and DSCG, respectively. Supersaturated droplets of IPHC and IPHS are expected to exist in ambient conditions. The level of such supersaturation (which represents the driving force for particle growth) will likely influence the extent and rate of the deposition of these drugs in the lungs.

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