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Study of Hygroscopic Properties of Aqueous Mixtures of Disodium Fluorescein and Sodium Chloride Using an Electrodynamic Balance

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Purpose. The purposes of this study are: a) to demonstrate the use of an Electrodynamic Balance (EDB) to investigate the hygroscopic properties of pharmaceutical aerosols; and b) to evaluate the applicability of the Zdanovskii-Stokes-Robinson model (ZSR) in the associated data analysis with multicomponent pharmaceutical aerosols.

Methods. The compositional dependence of the water activity of two model materials commonly employed in the study of pharmaceutical aerosols, namely, NaCl and Disodium Fluorescein(DF), was investigated using an EDB. The water contents of single levitated droplets of NaCl and DF and their mixtures at mass ratios of 1:3, 1:1, 3:1, and 6:1 from dilute concentration to high supersaturation were determined as a function of relative humidity (RH).

Results. At decreasing ambient RH, supersaturated aqueous NaCl droplets lose water and crystallize to form dry solid particles at an RH of ~50%. Aqueous DF droplet continues to lose water until it reaches a final state containing about 20% by mass of residual water. Mixed solutions of DF and NaCl crystallize at an RH of ~50% and then continue to lose water at lower RHs. The resulting "dried" particle still contains water whose amount depends on the mass ratios of DF and NaCl in the mixture. Good prediction of water activity of the DF-NaCl mixture can be achieved with the ZSR model. Collection of a full set of water activity-composition data at each mass ratio of DF-NaCl requires only a few hours.

Conclusions. The EDB, together with the application of the ZSR model in data treatment, appears to be a valuable tool for studying the hygroscopic properties of pharmaceutical aerosols.

KEY WORDS: electrodynamic balance; single particle levitation; water activity; hygroscopic aerosol growth; disodium fluorescein; sodium chloride.

INTRODUCTION

The amount of water contained in pharmaceutical products is a critical parameter in their production, storage, and applications (1–3). The water activity-concentration equilibrium relationship of aerosols is frequently measured for new drug entities. Most of these studies rely on gravimetric methods to determine the amount of water in drug powders equilibrated over different standard saturated salt solutions which provide constant RHs (4,5). However, because of the need for accurate mass determination in grams of powder, the equilibration time can take from several hours to days. The use of a powder bed can also lead to mass transfer limitations, thus complicating the equilibrium sorption measurements (5). An alternative approach commonly used is to measure the size changes of a flowing stream of aerosols as a result of humidification in a growth chamber. For droplets which may have significant growth retardation (e.g. coated droplets), the equilibrium measurement may be compromised by mass transfer limitations as the residence time in such system is usually limited to 1 minute (6). The lack of control of aerosol residence time to ensure the attainment of equilibrium undermines the application of this latter approach in water sorption studies. Both the aforementioned gravimetric technique and particle size measurement use stepwise change of RH, making equilibrium water activity measurement very time-consuming. In addition, these approaches measure the bulk or "average" properties of the aerosols which are subject to interparticle variations.

In recent years, study of deliquescent and hygroscopic properties of atmospherically related droplets has been made possible by the development of a novel single particle levitation technique. Using a device called electrodynamic balance (EDB), the water activity of a wide variety of single and multicomponent aerosols has been quantified. The EDB has wide applications in aerosol research including the characterization of optical properties of droplets and spectroscopy, thermodynamic properties, evaporation and growth, and chemical reactions (7). This technique is ideal for the study of water activity and evaporation/growth of aerosols since: a) the mass change of a droplet can be monitored continuously; b) it provides unambiguous *in-situ* characterization of the aerosol; c) it facilitates the study of supersaturated droplets; and d) the equilibration time for the particle is very small compared to that for bulk samples. The use of only a small but well characterized sample ($\sim 10^{-9}$ g for a 10 μm particle *vs* 0.1–1 g for typical bulk sample studies) will tremendously reduce the mass transfer limitations. Many single and mixed electrolyte solutions have been studied using the EDB by various researchers (8–11).

Despite its wide acceptance as an ideal tool for studying hygroscopic properties of aerosols in atmospheric applications, the EDB has not been applied to the study of pharmaceutical aerosols. The objectives of the present investigation were twofold: a) to apply this technique to determine the water activity-composition relationship of aqueous mixtures of disodium fluorescein (DF) and sodium chloride (NaCl), both of which have been employed as model materials in the study of pharmaceutical aerosols (4); and b) to evaluate the utility of the Zdanovskii-Stokes-Robinson (ZSR) model (12) in the associated data analysis. The ZSR model is an empirical model widely used in the aerosol science for prediction of water activity of multicomponent atmospheric aerosols.

PRINCIPLE OF ELECTRODYNAMIC BALANCE

In an EDB, a combination of AC and DC fields is required to trap and levitate a particle (Figure 1). A charged particle

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ABBREVIATIONS: a_w, water activity; GR_A, aerodynamic growth ratio; m, mass of droplet, kg; m_i, molality of species i in electrolytic solution, molal kg^{-1}; *mfs*, mass fraction of solute; p, particle vapor pressure, Nm^{-2}; V_{dc}, balancing DC voltage, V; V_{dry}, balancing DC voltage of a completely dried particle, V; R, particle radius, m; RH, relative humidity; x_i, mass fraction of species i in droplet.

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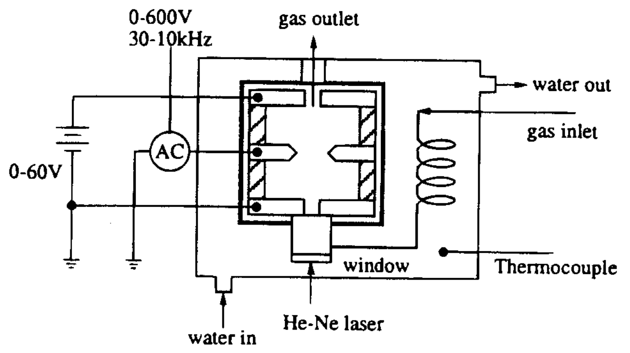

Fig. 1. A temperature controlled electrodynamic balance.

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, a particle can be held stationary. When there is no air flow, the electrostatic force will be equal to the weight of the particle. Effectively, the EDB serves as a very sensitive gravimetric balance, with the mass of the stationary droplet proportional to the applied balancing DC voltage (V_{dc}). The mass fraction of solute (*mfs* = mass of solute/mass of (solute + water)) of the particle can be determined by measuring the ratio of V_{dc} and that of the same particle at a reference state of known compositions. It should be noted that there is no reported effect of charges on the water activity of droplets studied using the EDB.

MATERIALS AND METHODS

Reagents and Materials

NaCl (ACS Certified, >99%) and DF were obtained from Aldrich Chemicals, and used as received. The DF raw material contains about 10% of bound water, as estimated by thermal gravimetric analysis (Perkin-Elmer TGA7 system). Bulk solutions of known DF/NaCl ratios were prepared with deionized water (>18M ohms). The solutions were introduced into a piezoelectric droplet generator (Uni-Photon Inc., NY., USA, Model 201) which can emit droplets of about 50 μm in diameter. The droplets were then charged by induction before being introduced into the EDB. In the EDB, the droplet will equilibrate with the ambient environment.

Calculation of Water Activity

At equilibrium, the chemical potential of water in the vapor phase is equal to that in the liquid. Assuming ideal gas behavior, the water activity, a_w, of the droplet is given by

$$a_w = p_w / p_{w,sat} = \mathrm{RH}/100 \qquad (1)$$

where p_w is the ambient vapor pressure of water and $p_{w,sat}$ is the saturation water vapor pressure at the same temperature *T*. Hence, in response to changes of ambient relative humidity (RH), a droplet attains an equilibrium composition such that its water activity is identical to the RH. The Kelvin effect (curvature effect on vapor pressure) can be neglected if the droplet size is greater than 0.5 μm.

Equilibrium Water Activity—Composition Studies

In this study, the water content of droplets as a function of water activity (*i.e.* ambient RH) was determined. The relative humidity was controlled by varying the dew point of the stream going into the EDB (Figure 2). High purity nitrogen at 70kPa was used as a carrier gas for water vapor. The dew point of the stream was controlled by varying the ratio of the stream going to the bubbler and that bypassing it and was measured by a dew point hygrometer (EG&G DewPrime model 2000). The ambient temperature was measured by a digital thermocouple thermometer. The precision of the dew point hygrometer and the digital thermocouple thermometer are 0.2°C and 0.1°C, respectively. The temperature of all experiments was set at 37.0 ± 0.1°C. The balancing voltage of a droplet initially equilibrated at an ambient RH of ~70% was determined. Equilibrium was achieved when a constant balancing voltage was obtained. Since the flow rate to the EDB was high enough to produce significant drag force on the particle, the balancing voltage was measured after stopping the flow momentarily. The flow was resumed with a new RH and the balancing voltage of the droplet equilibrated to the new RH was recorded. Equilibration of the particle mass required about 20–30 min at each RH setting. Typically, several hours were needed for collecting a set of data of the mass fraction of a specified solute as a function of water activity. A He-Ne laser was used to illuminate the particle for balancing voltage determination.

It should be noted that while the droplets we used (20 μm dia) are much larger than typical therapeutic aerosols (1–5 μm dia), the water activity-concentration equilibrium relationship obtained by this method can be directly applied to hygroscopic growth of therapeutic aerosols as the Kelvin effect can be neglected in both cases.

RESULTS AND DISCUSSIONS

Presented in this section are the water activity data of both single and binary component solutions. Single component data are required for comparison with those of mixture and serve as inputs to the ZSR model for predicting water activity of mixture solutions.

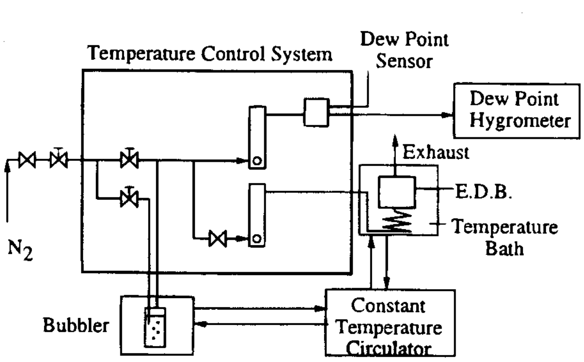

Fig. 2. Control and monitoring of the relative humidity.

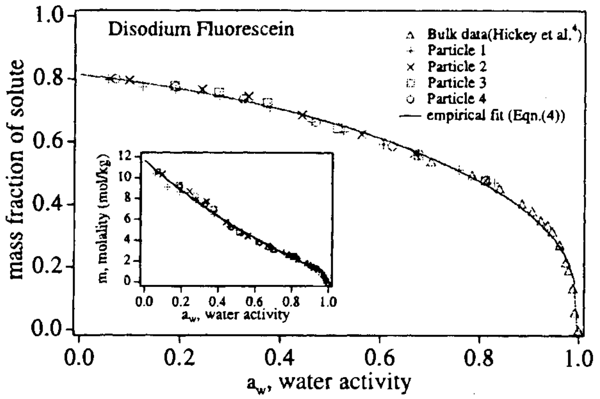

Fig. 3. Water activity of aqueous disodium fluorescein droplets.

Figure 3 shows the dependence of the mass fraction of solute (*mfs*) of aqueous DF droplets (and molality in insert) on the water activity (a_w). Bulk data from Hickey *et al.* (4) are shown for comparison. The *mfs* of droplets are calculated from the balancing voltages and a proper choice of reference state of known composition. There are two logical choices of the reference state: a dried particle at low RH or a droplet at high RH for which literature *mfs* − a_w data are available. Cohen *et al.* (8) have shown that solid particles formed by drying of levitated droplets can attain a state which is different from the thermodynamically most stable state in the number of water of hydration. In their studies of water activities of NH_4NO_3-$(NH_4)_2SO_4$ solutions, Chan *et al.* (11) have demonstrated that droplets at high RH can be used as accurate reference states. Using the dry particle as a reference state, we have found that the water activity data at high RH become discordant with bulk data. Hence, we used the measured balancing voltages and droplet concentrations at high RH (>80%) estimated from bulk data (4) to calculate the V_{dry} (the balancing voltage of a hypothetical *water-free* dry particle) of the DF/H_2O droplet. The *mfs* at other RHs can then be obtained from $mfs = V_{dry}/V_{dc}$.

Figure 4 shows the compositional dependence of water activity of NaCl-H_2O solutions. As water activity of electrolyte solutions is a weak function of temperature, the measured a_w at 37°C are similar to those at 25°C[13] which were used to estimate the reference state concentrations from the experimental data. As expected, the *mfs* of both solutions increase at decreasing RH. However, at an RH of about 50%, NaCl solution crystallizes and becomes a solid particle while DF solution continues to lose water until a final value of *mfs* = 0.8 is obtained. The "dried" particle of DF still contains about 20% by mass of water. The presence of water in the "dried" particle is consistent with the observation that the DF raw material invariably contains about 10% of bound water, as determined by Thermal Gravimetric Analysis.

Solutions of DF and NaCl at mass ratios (MR) of 1:3, 1:1, 3:1, and 6:1 have been studied. For each MR, the water activities of 2 particles have been measured. The typical behaviors of water activity of the mixtures can be illustrated in Figure 5 for MR = 1:1. The filled symbols are *mfs* calculated assuming the dried particle at low RH is completely water-free, i.e. using the "dried particle" as a reference state. The open symbols are *mfs* calculated using the reference states at high RH whose concentrations are estimated by the ZSR equation (12)

$$\sum_i \frac{m_i}{m_{o,i}(a_w)} = 1, \qquad (2)$$

where m_i is the molality of species i in a multicomponent solution having a water activity of a_w, $m_{o,i}(a_w)$ is the molality of the single component solution of water activity a_w, which equals that of the solution mixtures. The $m_{o,i}(a_w)$ for NaCl and DF aqueous solutions are obtained from empirical fits of data in Figures 3 and 4 using the following equations:

$$\text{DF:} \quad m = -0.12109 + 3.7152(1 - a_w)^{0.38622} + 8.0235(1 - a_w)^{1.7003} \ (\text{for } 0 < a_w < 0.97) \qquad (3)$$

$$\text{NaCl:} \quad m = 0.024625 + 21.828(1 - a_w)^{0.90769} \ (\text{for } 0.45 < a_w < 0.98) \qquad (4)$$

It is clear that *mfs* based on the dry particle as a reference state cannot match the model even at high RH, suggesting that the "dried" particle is not water-free. The standardized data, based on a reference state at high concentrations, agree well with the ZSR predictions. At RH = 45%, the particles crystallize from the DF-NaCl solutions, similar to aqueous NaCl droplets. However, the dried particles in this case still contain water which evaporates as the *RH* decreases further. The presence of water in the "dried" particle at DF:NaCl mass ratio of 1:1 is likely due to the water associated with DF, similar to the case for a

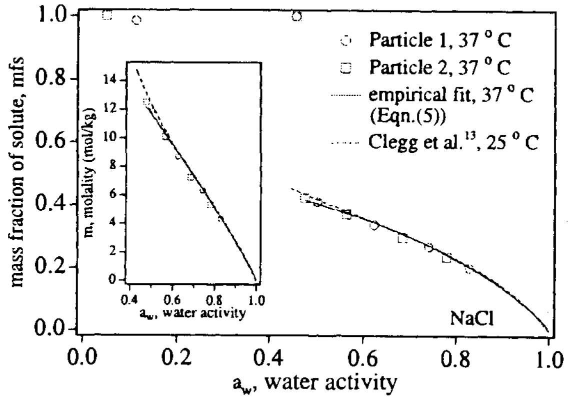

Fig. 4. Water activity of aqueous sodium chloride droplets.

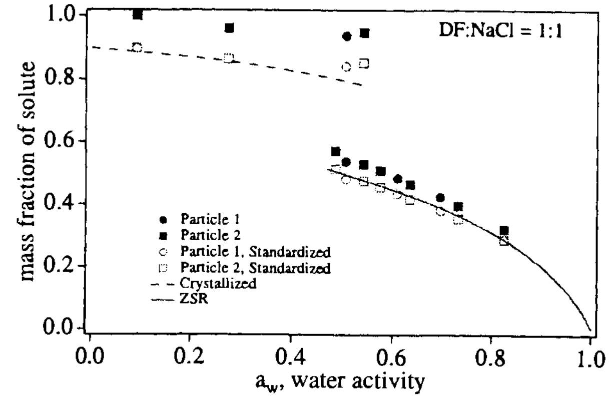

Fig. 5. Water activity of aqueous DF:NaCl (1:1) droplets.

single-component DF solution. If we postulate that the dried particle consists of completely water-free NaCl solid and aqueous solutions and that the water contained in the droplet can be represented by Equation (3), *i.e.*, it is not affected by the presence of NaCl in the particle, the *mfs* of the crystallized particles can be estimated (labeled as "crystallized" in Figure 5). Good agreement between the predicted and the observed data can be found at low RH. At higher RH, the data show a higher *mfs* suggesting that the particle contains *less* water than calculated based on the simple NaCl crystallization model. Such discrepancy is most prominent right after crystallization and decreases as RH decreases. A possible explanation for this observation is formation of DF/NaCl complex in the crystalline state, resulting in less free DF for water absorption. Hickey and Byron (14) studied the dissolution characteristics of co-precipitated DF-$Mg(OH)_2$ mixtures and found that the release rate of DF in water can be tremendously reduced when it is co-precipitated with $Mg(OH)_2$. They concluded that DF adsorbs on $Mg(OH)_2$ sols, which hinders the release of DF in water. The actual structure of DF-NaCl-H_2O complex at low RH will need to be verified by definitive means such as spectroscopic techniques.

Figure 6 summarizes the water activity data of mixed solutions at various mass ratios. Empirical fits of data of DF and NaCl droplets (*i.e.*, Equations (3) and (4)) are also included for comparisons. The data points shown have all been standardized using reference states at high RH. As NaCl is more hygroscopic than DF, *mfs* increases with the DF:NaCl ratio at a fixed RH. All the data show the expected trend of increasing *mfs* at decreasing RH. The mixture droplets crystallize at an RH of about 50% and continue to lose water at decreasing RH. After crystallization, droplets containing more DF have a larger water content and lower *mfs* since only DF can absorb water.

The solid lines and dotted lines are predictions based on the ZSR model and the simple NaCl crystallization model, respectively. The ZSR model can predict *mfs* of mixed droplets to within 0.02 in *mfs*, comparable to the level of accuracy of the experiment. It can be concluded that the ZSR model is accurate for predicting the water activity of the DF-NaCl-H_2O system. Further studies will be needed to evaluate the applicability of this model to therapeutic aerosols. After crystallization, the difference between measured and calculated *mfs* based on NaCl crystallization becomes smaller at higher DF:NaCl ratio. At any fixed mass ratio, the difference decreases with decreasing RH, consistent with the trend shown in Figure 5.

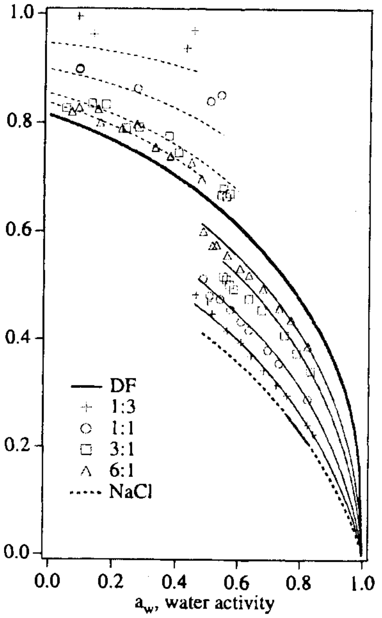

Fig. 6. Water activity of aqueous DF:NaCl mixture droplets.

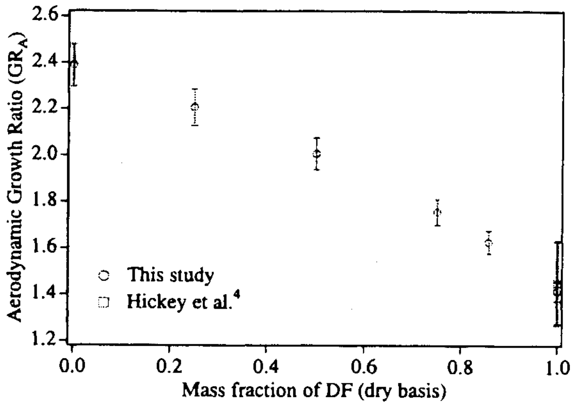

Fig. 7. The aerodynamic growth ratio of DF:NaCl mixture droplets.

Using *mfs* of mixed solutions at $RH = 20\%$ and 97%, the aerodynamic growth ratio (GR_A) can be estimated by the following material balance equation of the mass of the solute in the particle:

$$\frac{4}{3}\pi R_{20}^3 \cdot mfs_{20} \cdot \rho_{20} = \frac{4}{3}\pi R_{97}^3 \cdot mfs_{97} \cdot \rho_{97} \qquad (5)$$

where ρ and R are the density and the radius of the particle. The subscripts '20' and '97' represent the conditions at RH = 20% and 97%, respectively. GR_A is defined as:

$$GR_A = \frac{R_{97}}{R_{20}} \cdot \sqrt{\frac{\rho_{97}}{\rho_{20}}} = \left(\frac{mfs_{20}}{mfs_{97}}\right)^{1/3}\left(\frac{\rho_{97}}{\rho_{20}}\right)^{1/6} \qquad (6)$$

The density term in the above equation is to correct the density to unity density in accordance with the definition of aerodynamic size. The density of a particle, ρ, is estimated from:

$$\rho = \sum_i \rho_{io} x_i \qquad (7)$$

where ρ_{io} and x_i are the density of single component i and the mass fraction of i in the mixture, respectively. Using $\rho_{H2O} = 0.993$, $\rho_{NaCl} = 2.163$, and $\rho_{DF} = 1.49$ g/cc (4,15) and the *mfs* estimated by the ZSR and the NaCl crystallization models for mfs_{97} and mfs_{20} respectively, GR_A at various mass ratios are plotted in Figure 7. The error bars include errors due in the determination of mfs_{20} (± 0.02), mfs_{97} (± 0.002), ρ_{20} ($\pm 0.1\rho_{20}$) and ρ_{97} ($\pm 0.01\rho_{97}$). Liang and Chan (16) found that the density estimated from Equation (8) is within 10% of the experimentally measured density of supersaturated NH_4HSO_4 solutions. Hence, the present study used 10% for the error in the density estimation. The GR_A increases with decreasing x_{DF} as NaCl is more hygroscopic. Hickey *et al.* (4) have determined the GR_A (from RH of 20% to 97%) of DF to be 1.45 ± 0.18, which is in close agreement with the calculated value based on *mfs* determinations in the present study.

CONCLUSIONS

The ZSR model affords good prediction of *mfs* of the DF-NaCl-H_2O droplets before crystallization to within 0.02. Water sorption of the mixture after crystallization is dominated by the presence of DF, but is limited possibly by the entrapment of DF in NaCl crystals. By virtue of its simplicity and its accurate prediction of water activities, the ZSR model may prove valuable for estimating the hygroscopic growth of multicomponent pharmaceutical aerosols.

In this study, a set of $mfs - a_w$ data can be obtained in several hours, which is a significant improvement over conventional gravimetric measurements which normally take days. The rapid technique developed by Liang and Chan (16), which enables measurement of a full set of $mfs - a_w$ data in about an hour, can be modified to accommodate studies at 37°C.

The electrodynamic balance can prove to be an efficient, convenient, and powerful tool for evaluating the hygroscopic properties of pharmaceutical aerosols.

ACKNOWLEDGMENTS

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