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An automated controlled atmosphere microbalance for the measurement of moisture sorption

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Summary

A controlled atmosphere microbalance system has been constructed for the measurement of moisture sorption in pharmaceutical materials. The system is automated, and the user can program arbitrary changes of relative humidity (RH) under computer control. The sample is suspended in an isothermal chamber at 20–25°C, and the RH is regulated from 1 to 98% RH by adjusting the flows of dry and moist gas. A commercial sensor system is used to determine the relative humidity of the flowing gas. Over most of the range, the absolute RH accuracy is ±3%, the RH reproducibility is ±1%, and the RH stability is ±0.2%. Sample masses as large as 1 g can be accommodated. For a typical sample mass of 10 mg, the reproducibility of the weight uptake measurement is typically better than 0.05% of the dry weight over the entire working range of relative humidity. The data collection software employs a weight stability criterion for equilibrium to allow data collection at the maximum rate permitted by the sorption kinetics of the material under investigation. Three examples are presented of applications to pharmaceutical powders.

Introduction

Moisture uptake is a significant concern for many powdered industrial materials. In particular, the processing characteristics and stability of organic, biological, and polymeric materials are altered by the uptake of moisture (Gal, 1983; Hageman, 1988; Slade et al., 1989; Ahlneck and Zografi, 1990). In amorphous materials, moisture frequently plasticizes the solid and lowers its glass transition temperature. In crystalline materials, moisture can promote deliquescence or solid-state phase transformations (Osawa et al., 1988; Vadas et al., 1991). In the pharmaceutical and food industries, the susceptibility of a material to atmospheric moisture is often a key factor in decisions related to packaging, storage, handling, and shelf-life. The successful development of novel medicinal compounds, in particular, requires that we understand the influence of atmospheric moisture on the properties of these materials.

Moisture sorption isotherms are fundamental thermodynamic tools for the investigation of moisture sensitive materials. They relate the equilibrium water content of the solid to the water activity. Isotherms yield abundant information. Features in the moisture sorption isotherm may

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expose regimes of relative humidity where important structural changes take place. Isotherms that differ between different preparations of the same chemical substance reflect solid-state structural differences between the preparations. Isotherms that exhibit hysteresis reveal a dependence of the physical state of the system on the history of its exposure to moisture.

Frequently, even when moisture is sorbed in bulk regions, moisture sorption can be modeled effectively as a type II multilayer sorption process (Gregg and Sing, 1982). In these situations, moisture is sorbed slowly and predictably as the water activity is increased, and the classical 'batch' equilibration methods are usually effective for the collection of isotherm data. The batch methods register changes in weight for a material after isothermal equilibration in a chamber of fixed relative humidity. Batch procedures are arduous, however, if the sorption and desorption profiles are examined sequentially for a single sample. Furthermore, not all materials have simple type II sorption profiles. Some crystalline materials, for instance, exhibit sharp changes in water content over narrow ranges of relative humidity (Osawa et al., 1988). Under these conditions, the coarse increments in the typical batch sorption profiles fail to represent the true shape of the isotherm. Batch methods are not convenient techniques for the evaluation of sorption profiles at high resolution on the relative humidity axis.

Numerous alternatives exist for the dynamic measurement of moisture uptake by solids (Gal, 1967, 1975, 1981)). Gravimetric methods with electronic microbalances are well developed, and recent descriptions of automated systems are available (Rasmussen and Akinc, 1983; Astill et al., 1987). Most of the online gravimetric methods rely on vacuum systems to evacuate the atmosphere surrounding the sample. The absence of inert gas eliminates a diffusive barrier to transport and enables the user to measure the water activity via the system pressure. Good vacuum techniques and equipment are required. The system must be free of leaks and the entire vacuum chamber must be thermostatted at a temperature above the maximum dewpoint. Heat transport and thermomolecular flow are additional concerns in vacuum based sorption experiments (Czanderna and Wolsky, 1980; Robens, 1985; Astill et al., 1987).

As an alternative to vacuum based measurements, moisture uptake can be measured dynamically in atmospheres of controlled composition. Several systems of this type have been reported (Gal, 1967, 1975, 1981; Best and Spingler, 1972), and Teng et al. (1991) have recently applied this technique to measure the isotherms for protein powders. Controlled atmosphere microbalance (CAM) systems feature simple designs that are relatively easy to automate. These systems rely on an inert carrier gas to transport moisture rapidly to the sample. The microbalance can operate at room temperature, even during measurements at high water activity, because gas flows can restrict the high dewpoint gas to the sample region. Water activity can be tightly controlled, and stepped changes in water activity can be achieved without overshoot. Water activity is more difficult to measure in these systems however, because the system pressure is no longer a direct measure of water activity. Instead, dewpoint instruments or electronic relative humidity sensors must substitute for direct measurements of water vapor partial pressure.

This report describes a particularly simple automated CAM system that exploits the advantages of modern electronic microbalances and electronic flow controllers. If intraparticle sorption kinetics are favorable, complete, high resolution isotherms can be obtained in less than 1 day on as little as 10 mg of material.

Experimental

System overview

A schematic of the system is shown in Fig. 1. The sample is suspended from a microbalance in a flowing gas stream at a constant temperature, T_s. The moisture content of the flowing reaction gas is controlled by mixing dry nitrogen with moisture saturated nitrogen. The mixing ratios are varied while the total flow is held constant. The moisture content in the reaction gas stream is measured at the exhaust port of the sample

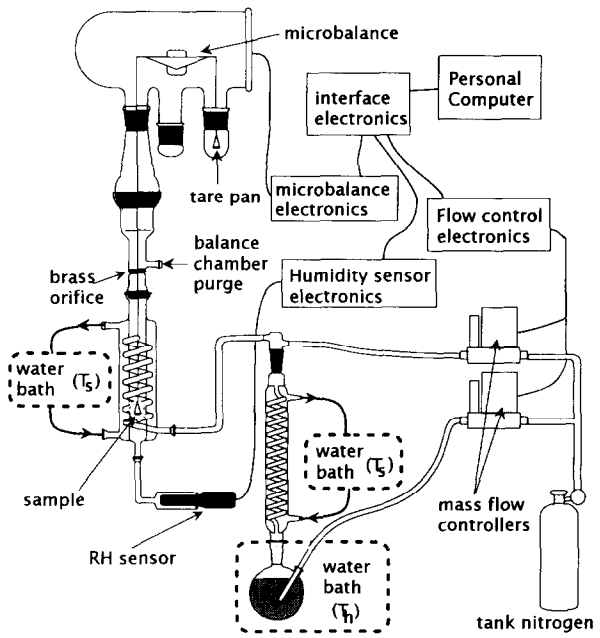

Fig. 1. Schematic outline of the controlled atmosphere microbalance system. Key components are identified in the text.

chamber. The water activity and sample weight are logged in computer memory as a function of time. The flows are altered under computer control to generate arbitrary changes in the water activity of the reaction gas. The sorption isotherm is constructed from the time dependent data at the end of the experiment.

Balance subsystem

The electronic microbalance (Cahn Instruments, Model C2000) is a taut band suspension, electromagnetic compensation type balance. The balance is mounted inside a glass vacuum bottle (Cahn Instruments), which is sealed at all points above the sample hangdown port to prevent the flow of moisture back through the balance chamber. The entire assembly is mounted on a rigid stand attached to a cement table. The sample is held in a 11 mm diameter flat bottom platinum pan, which is suspended inside a glass vapor chamber (Cahn Instruments, gas permeation tube assembly) with about 55 cm of 0.025 mm diameter tungsten wire. Water from a constant temperature bath (Lauda RCS-6) circulates in the outer jacket of the vapor chamber to maintain the sample at a constant temperature T_s. The reaction gas stream enters the spiral coil in the outer water jacket at the bottom of the vapor chamber. As gas flows through the coil, it equilibrates at the sample temperature T_s. The equilibrated gas enters the inner tube of the vapor chamber about 12 cm above the sample. It flows vertically downward across the sample and exits the chamber. Nitrogen is typically used as a carrier gas at a total flow of 100 cm^3/s. This flow translates to a linear velocity of about 25 cm/min in the 22 mm inner diameter tube of the vapor chamber.

The exchange of water vapor between the sample chamber and the balance chamber is suppressed by a brass disk with a 3 mm diameter orifice. Just above this disk, a constant flow of 1–2 cm^3/s nitrogen purges the balance chamber and sweeps the orifice. The balance chamber purge is controlled by an electronic mass flow controller (MKS Instruments, Model 1259C). The relative humidity of the balance chamber is typically maintained between 40 and 60% by passing the dry nitrogen purge gas through the headspace over a saturated solution of sodium chloride.

Flow subsystem

The ratio of dry nitrogen to humidified nitrogen determines the water concentration in the reaction gas. The flow in each stream is maintained by a mass flow controller (MKS Instruments, Model 1259C) with a full scale range of 100 sccm. The flow controllers are typically supplied with dry nitrogen gas, regulated at 15 lb/$inch^2$. The flow control electronics (MKS Instruments, Model 147) provide a 0–10 V analog setpoint control input for each valve. During normal operation, the total flow from the two controllers is maintained at the maximum full scale flow for a single controller. The moisture content of the reaction gas is adjusted by changing the ratio of the flows. That is, both valve setpoints are changed simultaneously by amounts that are equal in magnitude but opposite in sign.

The saturator assembly provides a source of humidified gas at pressure close to atmospheric pressure. This water activity at the saturator out-

let is close to the saturation vapor pressure for water at the temperature T_s, so a broad range of relative humidities can be covered by the mixing process. Dry nitrogen is bubbled through a fritted disc in a sealed, jacketed, round-bottom, flask containing liquid water. The water is maintained at a temperature about 25°C above the sample temperature T_s. The moisture laden gas stream traverses a 30 cm Graham condenser, which contains circulating water at the temperature T_s. A water bath (Lauda RCS-6) with a stability of ± 0.02°C provides the requisite temperature stability for the condenser water jacket. The excess moisture in the gas is deposited in the lower coils of the Graham condenser. At the top of the Graham condenser, the humidified nitrogen blends with dry nitrogen to yield the lower dewpoint reaction gas that is transported to the sample. Glass tubing and stainless steel connectors couple the Graham condenser and the sample chamber. These materials minimize the moisture sorption in the flow lines and reduce the time needed to stabilize the water activity of the reaction gas. This coupling section is wrapped with heating tape to prevent condensation in the lines when the dewpoint of the reaction gas rises above room temperature.

Relative humidity measurement

The relative humidity of water in the reaction gas is measured downstream of the sample. A variety of sensors are suitable for this measurement. The system currently uses an inexpensive polymer based capacitance sensor (Vaisala Corp., Probe Model HMP35 and Digital Relative Humidity Indicator Model HMI 32) that responds directly to RH. The sensor has a response time of about 5 s, and the analog output signal is readable to better than 0.05% RH. The accuracy of the polymer sensor is specified as ± 2% over the 0–90% range when the probe is calibrated against reference solutions. The calibration is checked against saturated solutions (Wexler and Hasegawa, 1954) of LiCl (RH = 12.0% at 25.0°C) and NaCl (RH = 75.8% at 25.0°C) at intervals of about 2 months or less.

Relative humidity for this sensor system is defined as the ratio of the partial pressure of water vapor, p, to the partial pressure of water vapor at saturation, p_s.

$$\mathrm{RH} = p/p_s \tag{1}$$

The relative humidity thus defined differs by less than 0.1% from the water activity, a_w, at 25°C. (Water activity is defined as the analogous ratio of fugacities.) This definition of relative humidity will apply throughout this paper.

The temperature of the RH probe usually differs from the sample temperature by several degrees. In addition, the RH probe temperature may vary by several degrees during the course of an experiment. The temperature of the RH probe is monitored continuously by a platinum resistance sensor mounted close to the polymer RH sensor on the same probe. The probe temperature is used by the software to correct the RH readings for the difference in temperature between the sample and the probe.

Control and interfacing

The experiment is controlled by an 80386 based PC compatible computer with ASYST (Keithley-ASYST) software. A GPIB interface board (IOTech Co., Personal 488) is the system controller for the GPIB bus, which is used to communicate with the digital multimeters. The analog voltage signal from the balance is converted to a digital format with a $6\frac{1}{2}$ place digital multimeter (Keithley Instruments, Model 196), and the digital data is communicated to the computer over the GPIB bus. The analog outputs for RH and sensor temperature are converted to digital format with a scanning digital multimeter (dmm) (Keithley Instruments, Model 199), and the dmm data are communicated to the computer over the GPIB. The control voltage setpoints for the flow control valves are established through two 12-bit D/A converters mounted in a general purpose instrument interface box (Keithley Instruments, Series 500). These D/A converters provide a 0–10 V control signal divided into 4096 discrete steps. The minimum step interval corresponds to a nominal change of about 0.025% of the full scale voltage.

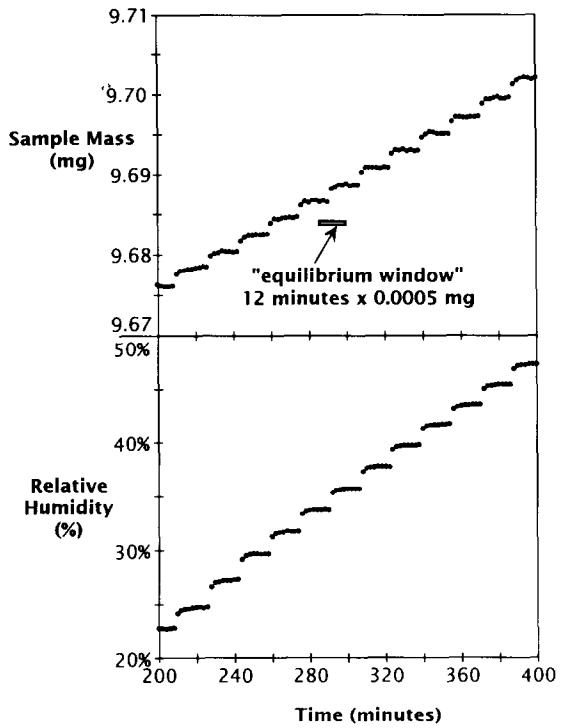

Fig. 2. The mass (upper frame) and relative humidity (lower frame) are plotted as a function of time during the measurement of a typical equilibrium moisture sorption isotherm. Individual data points are separated by 2 min intervals. The relative humidity is held at a predetermined level until seven consecutive data points fit within a 0.0005 mg window. These data were collected for U-88,943E (see Fig. 6) at 25.0°C.

Briefly, the sorption experiment consists of a series of discrete steps. A portion of a typical step sequence is shown in Fig. 2. Prior to a step change in relative humidity, the sample weight is in equilibrium with the reaction gas. This gas has a fixed dewpoint, and therefore a fixed relative humidity (RH) at the stable sample temperature. During the step change, the flows are changed, and the RH of the reaction gas relaxes toward a new value with some characteristic response time. While the RH approaches a new plateau, the sample responds to the 'step' change in RH by changing weight. The step is complete when the sample achieves a new equilibrium weight value. The software checks for equilibrium by requiring that a predefined number of successive points lie within a predefined weight interval. When equilibrium is reached, the software proceeds with the next RH change.

Typically, the time interval between data points is about 2 min. At each point, the software stores the time, the sample weight, the relative humidity, the temperature of the relative humidity sensor, and the mass flows registered by the flow control valves. The experiment is complete when the software has stepped through the entire, user-specified profile of relative humidity. At the end of the experiment, the software calculates the relative humidity at the sample from the RH probe readings and the sample temperature. The saturation vapor pressure of water is calculated from one of the equations given by Wexler (1976):

$$\ln(p_s) = \sum_{i=1}^{4} g_i T^{i-2} + g_t \ln(T) \qquad (2)$$

$$g_1 = -0.60951748 \times 10^4,$$

$$g_2 = 0.2116173595 \times 10^2,$$

$$g_3 = -0.27222404 \times 10^{-1},$$

$$g_4 = 0.16840790 \times 10^{-4},$$

$$g_5 = 0.24505058 \times 10^1.$$

No correction is applied for the difference between saturation pressure and atmospheric pressure, because this correction is less than 0.1%.

Moisture sorption isotherms are typically constructed in a personal computer spreadsheet program (Microsoft EXCEL) spreadsheet. The equilibrium endpoints in each step interval are selected and assembled into plots of equilibrium weight uptake vs relative humidity. The data are plotted as weight uptake vs relative humidity. With some assumptions, or with additional supporting data, plots of equilibrium moisture content (EMC) vs relative humidity can also be constructed. EMC is normally expressed as the amount of water relative to a fixed amount of dry solid. The equilibrium moisture content (EMC) cannot be calculated unless the moisture content of the sample is known at a given relative humid-

ity. In many cases, moisture can be stripped completely from the sample by purging with dry nitrogen for several hours. Frequently however, more exhaustive drying changes the solid irreversibly. If the moisture sorption data must be expressed in terms of EMC, and if large amounts of water are retained in the sample throughout the moisture sorption experiment, then the EMC is determined at a reference point by some independent method. Frequently, this information is obtained from thermogravimetric analysis or Karl Fischer analysis on samples that are equilibrated in atmospheres of known relative humidity.

Results and Discussion

Relative humidity – control and stability

The relative humidity is controllable from about 1% up to about 98% RH. Portions of a typical RH profile for a moisture sorption experiment are shown in Fig. 3. An empty pan was used for this example, and the duration of RH steps was set at 90 min. Single data points in Fig. 3 are spaced at 2 min intervals. The RH plateaus are flat to within 0.2% RH on this time scale. The typical rise time for the RH change is about 5–10 min for most of the RH range. Below about 4% RH, longer times are needed for the RH to stabilize.

In the presence of a moderately hygroscopic sample, the RH profiles are similar to those shown in Fig. 3, but the step lengths are adjusted as necessary to compensate for slow sorption kinetics in the sample. A normal sample sorbs only a small fraction of the moisture from the flowing reactant gas. A typical sample size is about 10 mg, so a weight increase of 1% corresponds to an actual weight gain of 100 μg. By comparison, the gas flow of 100 cm^3/min provides about 1.1 mg of water vapor per min at 50% RH and 25°C. Under these conditions, the sample will not perturb the RH response of the system until the RH drops below about 5%. The influence of the sample becomes progressively larger as the RH step size increases, or as the sample capacity increases.

Stable water activity at the sample depends on

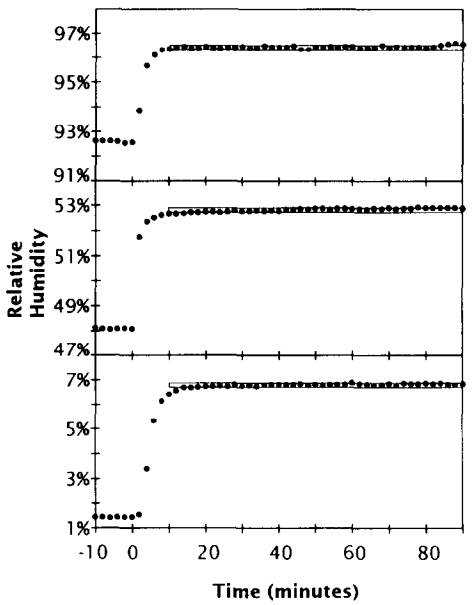

Fig. 3. Relative humidity at the sample as a function of time at 25.0°C. The response of the system to relative humidity changes is plotted for three different ranges of relative humidity. For each relative humidity level, the gas flows were changed at time = 0 min to yield a nominal change in relative humidity of 5% RH. Points in the figure are spaced 2 min apart.

stable gas flows, a stable sample temperature, and a stable dewpoint at the saturator outlet. Fig. 3 illustrates the typical short term RH stability over 80 min. 10 min were allowed for the RH to settle after the 5% RH change. The boxes around the points in each figure have a height of 0.2% RH. Typical values of the standard deviations are 0.06–0.07%, with the exception of the region where the RH is lowered below 4%. In this region, the system responded more slowly.

The variability in the calculated RH values does not include the variability in the sample temperature, which is maintained constant throughout the sorption experiment. The chamber temperature was checked with a calibrated portable thermistor probe (Omega Model 5831A with THX-700-AP probe), which was inserted through the exhaust port. The temperature variation in the chamber was monitored with this probe throughout a cycle from 1 to 90% RH. At 25.00°C, the measured standard deviation was

about ± 0.04°C. This variation in sample temperature translates to a variation of about $\pm 0.2\%$ in relative humidity for a fixed dewpoint reaction gas at a nominal relative humidity of about 80% RH.

Sample weights provide a more direct measure of RH stability, although the weight responds more slowly than the RH sensor to changes in the RH. For a hygroscopic sample, the sample weight is a sensitive function of water activity, and it can be used to probe the RH stability of the system. Sulfuric acid solutions are convenient for this purpose, because water activity has been tabulated as a function of composition for the sulfuric acid/water system at 25.0°C (Stokes and Robinson, 1949). For ease in calculation, the tabular data of Stokes and Robinson (1949) were fitted to an analytic expression consistent with a three term Redlich-Kister equation for the excess free energy (see, for example, Rowlinson and Swinton, 1982):

$$a_w = (1 - x)e^{(Ax^2 + Bx^3 + Cx^4)} \qquad (3)$$

$$A = -42.296;\ B = 36.281;\ C = 13.300$$

a_w is the activity of water, and x denotes the mole fraction of sulfuric acid in the mixture. Between $0.05 < a_w < 0.80$, this equation reproduces the tabulated a_w values of Stokes and Robinson (1949) to better than ± 0.002. This equation was used to translate mass changes for sulfuric acid solutions into changes in water activity, a_w. The mass of the sulfuric acid solutions thereby provide a useful indicator of the stability of the water activity in the immediate environment of the sample.

Fig. 4 illustrates the stability of the water activity over a 30 h period at three different RH values between 15 and 80%. Because of slow sorption kinetics, the samples were equilibrated for about 6 h at the target RH prior to the periods shown in Fig. 4. During the final 3 h of the 30 h period, the RH was increased by 0.2% to illustrate the response of the sulfuric acid solution to small, sudden RH changes. Prior to this increase, water activity varied by less than ± 0.001 over the preceding 27 h. This variation in water activity translates into an equivalent variation in relative humidity at the sample.

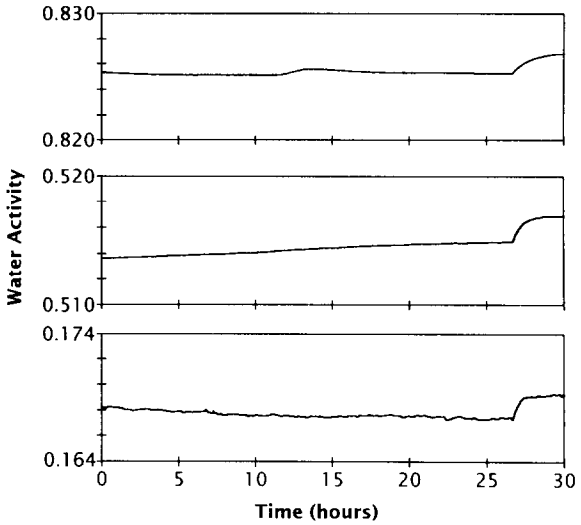

Fig. 4. Long term RH stability is illustrated by the water activity as a function of time for sulfuric acid solutions at three different nominal relative humidities. The relationship between vapor pressure and composition of sulfuric acid/water mixtures was used to translate solution masses into water activity. After 27 h, the water activity was increased by 0.2% RH to illustrate the response of the sulfuric acid sample.

As a general requirement for moisture sorption experiments, the RH should be stable over the time needed for the sample to reach equilibrium. Otherwise, RH fluctuations may prevent the equilibrium condition from being reached or, rarely, they may cause the equilibrium condition to be reached prematurely. If the RH drifts on a longer time scale, the effects are relatively unimportant, because the equilibrium sample weight will track the RH. For kinctic studies, the RH must be stable over the timescale of the transformation. Frequently, for instance, the kinetics of equilibration must be checked for a particular sample to verify the that the endpoint criterion for equilibrium is adequate. This check is accomplished by allowing the sample to equilibrate over a period as short as an hour or as long as several days. RH stability is critical for the success of this experiment.

Relative humidity – measurement accuracy

The accuracy of the RH sensor system is listed as ±2% in the manufacturer's literature. This specification covers the range of 0–90% RH when the unit is calibrated relative to standard saturated salt solutions. The accuracy of the RH also depends on the accuracy of the sensor probe temperature relative to the sample temperature because of the calculation used to convert probe RH into sample RH. The combined bias between the probe temperature and the sample temperature is less than 0.2°C. This value translates to an maximum RH bias of 1.2% at 25°C and 100% RH. Hence, a realistic estimate of the absolute RH accuracy is ±3%. The reproducibility of the probe readings is ±1% RH. This value is an estimate based on repeat measurements of sorption isotherms and based on calibration measurements over saturated solutions of lithium chloride and sodium chloride. The sensor system holds the two point calibration within ±1% at 25°C for periods well over 1 month. In principle, improvements in accuracy could be obtained at higher cost with alternative sensors.

Baseline stability

The baseline response of the instrument is influenced by two factors: moisture sorption by balance components and zero drift in the CAHN 2000 balance. In principle, gas flow variations are a source of problems, but in practice these variations contribute negligibly to the baseline performance. At a flow of 100 cm^3/s, the gas stream contributes a force equivalent to 0.015 mg at the sample pan. Hence, even a 1% change in the total flow results in a response change of less than 0.0003 mg. This value is small compared to the variability from the other sources.

Typical baseline response is illustrated in Fig. 5. The results in Fig. 5 were collected over 30 h, so the contribution of long term zero drift is minimal. The balance was ramped from 1–90% RH and back in increments of 1% RH. About 10 min were allowed for the RH to stabilize after each flow change. The sorption of moisture on the balance components contributed about 0.002–0.004 mg at 90% RH. The zero point drifted 0.002 mg between the beginning and the

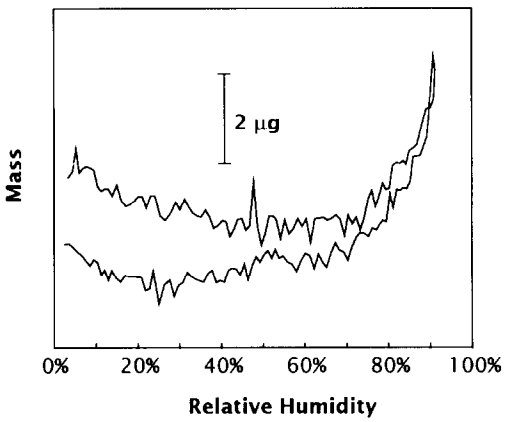

Fig. 5. Baseline sorption response of the CAM system at 25.0°C. An empty platinum pan was mounted in the vapor chamber, and the relative humidity was stepped in increments of 1% RH. 10 min were allowed for equilibration at each RH value.

end of the experiment, as shown by the difference between the initial and final points at the lowest RH. The sorption of moisture by instrumental components was significantly higher, about 0.02 mg, when aluminum sample pans were used instead of platinum sample pans. This increase may be attributable to the sorption of water by the oxide coating on the aluminum pans. Over periods of 1 week or longer, the balance zero point has drifted as much as 0.01 mg.

For samples more massive than 10 mg, the instrumental limitations to weight accuracy are well under 0.1%. Barring contributions from sample variability, the isotherms are reproduced to within 0.1% on the weight uptake axis, if the 1% variability in the RH sensor is taken into account on the RH axis. Over the RH range from 1 to 90%, the baseline contribution from moisture sorption on balance components is small enough that it can be neglected for most samples. The error in neglecting the background sorption is less than the error attributed to zero point drift in the balance. Reproducibility is improved at low moisture uptakes if larger sample sizes are used. With samples as large as 100 mg, I have reproduced isotherms to better than 0.01%. The sample size is limited by the balance capacity, which is 1.5 g, and the slow sorption kinetics in the

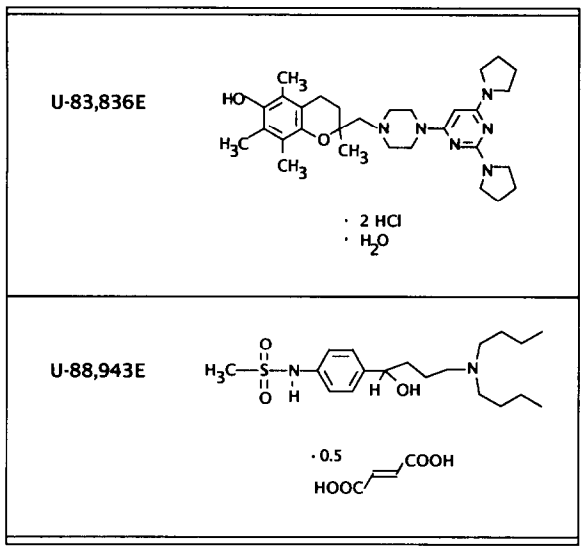

Fig. 6. Chemical structures of the two of research drug compounds used in moisture sorption studies. (These compounds were synthesized by Upjohn Laboratories, The Upjohn Co.)

larger powder beds. When sample availability is a greater concern than measurement reproducibility, I have obtained adequate results from 1 mg samples.

Examples of applications to pharmaceutical powders

U-88,943E is an experimental antiarrhythmic drug with the molecular structure shown in Fig. 6. U-88,943E is typical of many crystalline organic salts that sorb a moderate amount of water (1–2% by weight) over a broad range of relative humidity. These solids typically equilibrate rapidly over the entire range of relative humidity. The rapid equilibration of U-88,943E is illustrated by the experimental data in Fig. 2. Fig. 2 illustrates the 'window' that was used to define the endpoint criterion for equilibrium. This height of this window is 0.0005 mg, which is about 0.005% of the sample mass. If the measurement noise is neglected, the window defines the magnitude of the maximum rate of acceptable weight change at 'equilibrium'. In this case, the window corresponded to a maximum rate of change of 0.005%/12 min, or 0.025%/h.

The sorption isotherm for U-88,943E, at a temperature of 25.0°C, is shown in Fig. 7. The complete sorption/desorption isotherm contained 99 points between 1 and 95% RH. The data set was collected in less than 26 h. Because the hysteresis in this isotherm is negligible, the

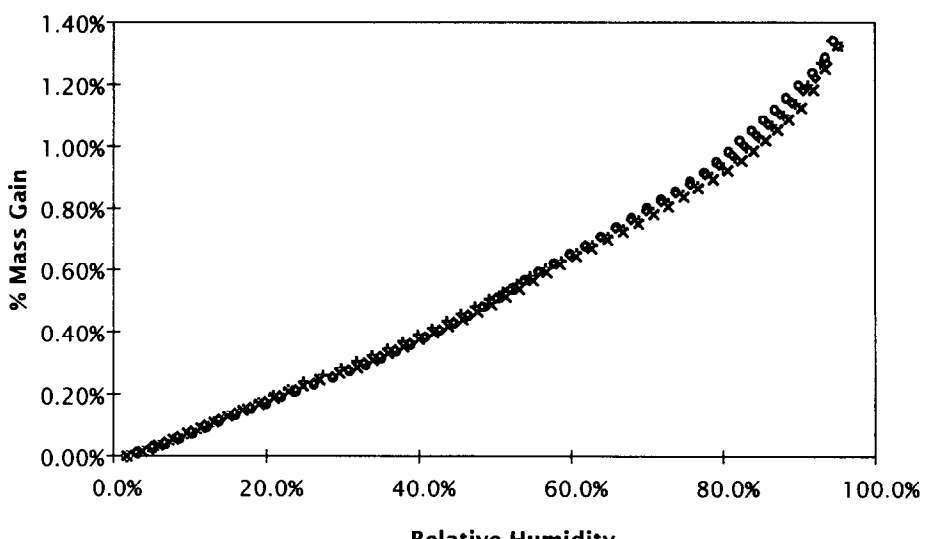

Fig. 7. Moisture sorption as a function of relative humidity for U-88,943E at 25.0°C. U-88,943E is a crystalline organic molecular solid under experimental investigation for use as a human therapeutic agent. Sorption (+, ○) and desorption (×, ◇) profiles are shown for two independent experiments.

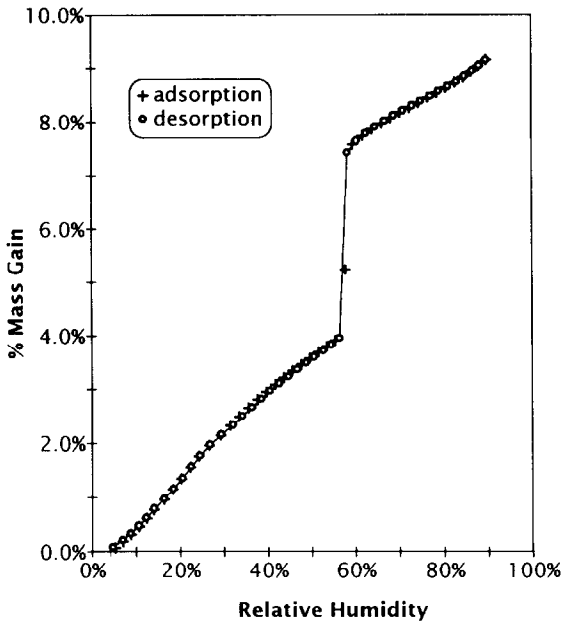

Fig. 8. Moisture sorption as a function of relative humidity for U-83,836E at 25.0°C. U-83,836E is a crystalline solid.

moisture sorption profile reflects equilibrium conditions. The relevant time scale for equilibrium is the duration of the experiment, or about 1 day. The data in Fig. 2 clearly illustrate that U-88,943E powder responded rapidly to changes in humidity. The reproducibility of the U-88,943E isotherm is illustrated in Fig. 7 by the agreement between points taken from two independent experimental runs. Each run used about 10 mg of sample. The independently determined isotherms are reproduced to better than 0.05% in this example.

A second experimental drug compound, U-83,836E, illustrates the utility of high resolution moisture sorption studies. The molecular structure of U-83,836E is shown in Fig. 6. The compound has several crystalline polymorphs, which have been characterized by XRD. As shown in Fig. 8, one of the crystalline polymorphs sorbed water in excess of 9% by weight over the range of 5–90% RH. The region from 56 to 58% RH is noteworthy, because the extent of sorption is greater than 3% by weight over this narrow interval. The reversibility of the entire sorption process is reflected by the absence of significant hysteresis in the isotherm. This isotherm has been quantitatively reproduced in samples that were crystallized independently. The complete isotherm in Fig. 8 was collected in less than 36 h with about 10 mg of sample. The detailed isotherm served as a useful guide in the development of handling procedures for this drug and in the design of experiments that probe the relationship between water activity and solid-state stability. Structural studies of the moisture-induced transformation are in progress and will be reported in detail elsewhere.

The CAM system is particularly valuable for the measurement of isotherms that require high resolution on the relative humidity axis. This resolution is essential for a materials that sorb large amounts of water over a small RH interval, such as U-83,836E. A large increase in water content over a narrow interval suggests that water is associated with a major structural change in the material. Such changes are qualitatively distinct from the incremental changes in structure that takes place over a broader range of relative humidity. Physical processes associated with these dramatic changes include deliquescence, the formation of crystalline hydrates, and the dehydration of crystalline hydrates.

As a final example, the isotherm for microcrystalline cellulose (Type PH101, FMC Corp.) is shown in Fig. 9. In contrast to the solids shown in Figs 7 and 8, the moisture sorption profile for this

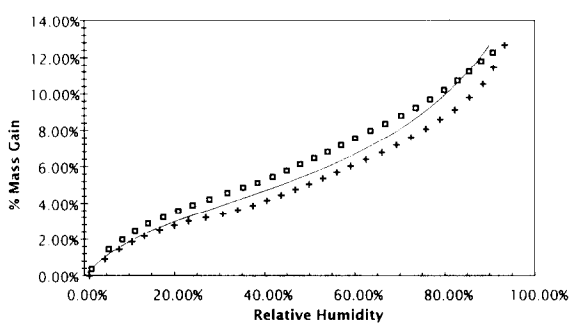

Fig. 9. Moisture sorption in microcrystalline cellulose (Type PH101) at 25.0°C. Sorption (+) and desorption (□) data are compared with the line given by the isotherm of Spiess and Wolf (1987).

partially amorphous, cellulosic polymer exhibited considerable sorption hysteresis. It has been common practice among a number of investigators (Zografi et al., 1984; Spiess and Wolf, 1987) to fit the sorption isotherm for microcrystalline cellulose to one of several different multilayer sorption equations. The results in Fig. 9 are in general agreement with the isotherm equation given by Spiess and Wolf (1987), who based their equation on the results from a large inter-laboratory batch equilibration study. In contrast to the two previous examples, the isotherm in Fig. 9 required about 8 days of data collection. Despite the relatively long equilibration periods, most, if not all, of the hysteresis may originate from slow sorption kinetics. Under these circumstances, batch sorption methods may be advantageous for the measurement of the equilibrium isotherms. The stable water activity within the CAM system, however, provides favorable conditions for detailed studies of the slow sorption kinetics.

Conclusions

An automated, controlled atmosphere microbalance system is easily assembled from commercial components. This system works well for the measurement of moisture sorption at room temperature. With minor modifications, such as heating of the exhaust lines or repositioning of the relative humidity sensor, the design should be readily extensible to the measurement of isotherms at higher temperatures. In contrast to vacuum based moisture sorption systems, the dewpoint changes are restricted to the sample region, and the balance mechanism is not exposed to high dewpoint gases. A pair of electronic flow controllers provide a convenient source of flowing gas with an adjustable dewpoint. The relative humidity of the atmosphere surrounding the sample is stable to better than 0.2% RH for periods of several hours or longer. The rapid response of many samples to RH changes suggestions that instrumental limitations to sorption kinetics are minimal as long as moderately small sample sizes ($\approx$ 10–20 mg) are used. For samples of this size, moisture sorption can be measured reproducibly to better than 0.1% on the weight uptake axis.

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