Moisture Sorption Analysis of Pharmaceuticals

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ABSTRACT

This paper describes the design features of the Q5000 SA, a new analyzer designed for evaluating moisture adsorption / desorption behavior of materials, and its use in the analysis of pharmaceuticals.

INTRODUCTION

Because moisture affects the properties of many pharmaceutical materials, manufacturers must understand not only the quantity of moisture present in their materials, but also their moisture adsorption / desorption behavior as they are exposed to humidity during processing, storage and in end-use.

Q5000 SA

Figure 1 shows a schematic of the Q5000 SA. The analyzer is based on a vertical nulling microbalance in which the sample and reference hang-down wires and pans are enclosed in a humidity- and temperature-controlled chamber. The balance is thermally isolated from the measurement zone and maintained at a constant 35ºC during experiments to provide the long-term baseline stability required for sorption analysis (Figure 2). The hang-down wires and sample pan / boat (metallicized quartz, platinum or sealed aluminum) are grounded to the balance enclosure to eliminate static effects. A dry nitrogen gas purge at 10 mL/minute assures the dryness of the balance housing. A separate dry nitrogen purge stream at 200 mL/minute is split into two components for generation of the desired percent relative humidity (%RH) environment. One part of the stream remains dry while the other is passed through a water saturation chamber, where it is brought to 100 %RH at the temperature of the analysis. High precision mass flow controllers regulate the proportions of dry and wet gas to obtain the %RH desired for the analysis. Capacitance-type sensors located near the sample and reference pans monitor the %RH to confirm that it is at the desired level. The temperature of the oven enclosure, which surrounds the humidity chamber, is tightly regulated by four Peltier elements on the outside of the enclosure.

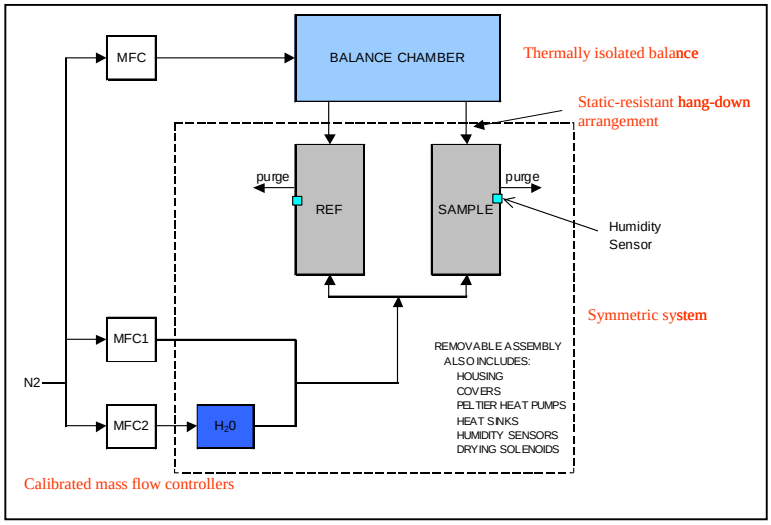

Figure 1: Q5000 SA Simplified Schematic

The whole enclosure is very compact, and hence highly responsive to changes in %RH or changes in temperature. The Q5000 SA can run isothermal experiments in the range of 5-85ºC, where the humidity is stepped (in steps of 0.1 %RH or larger) or ramped at 0.1-0.2 %RH/minute. It can also perform isohumidity (isohum) experiments, where the temperature is stepped or ramped at rates of up to 0.5 ºC/minute. The humidity range covered is 0-98 %RH.

Figure 2 shows the excellent Q5000 SA baseline as judged by the Y-axis displacement (4 µg) on an isothermal, constant humidity experiment over nearly 64 hours at ambient temperature.

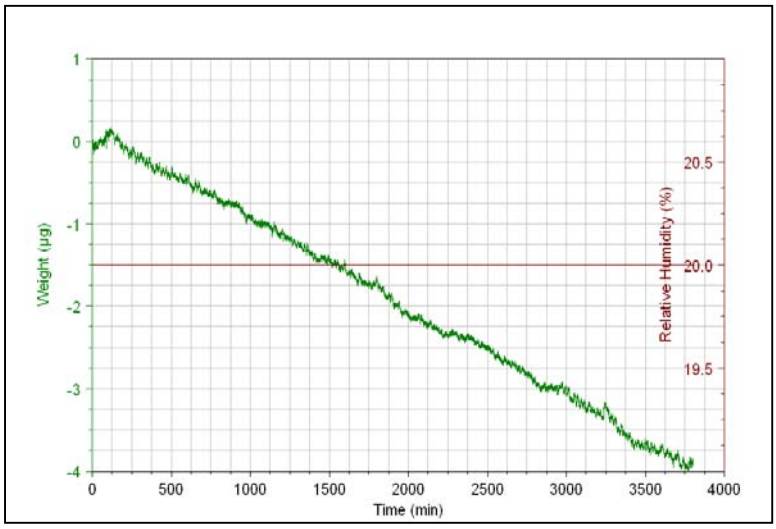

Figure 2: Q5000SA Baseline Drift over 2.5 Days

APPLICATIONS

Most moisture sorption analysis experiments are performed by stepping the humidity (%RH) over a broad range at constant temperature. Since many materials do not desorb water at the same rate as they originally adsorbed the water, the actual experiments often consist of a more complex stepped humidity experiment, where the humidity is increased, then decreased, and finally increased a second time to determine if the material's structure and behavior are changed during the initial exposure to higher humidity. Faster water adsorption on the second set of increasing humidity steps usually indicates that the material's structure has changed. Most results are plotted as "% weight change" versus %RH, and materials can be evaluated either "as received" or dried. If the molecular weight of the sample material is known, the results can be reported as "weight (moles) of adsorbed water per weight (moles) of sample". To obtain those values, however, the sample must be dried prior to analysis and a true "dry weight" obtained. Drying prior to analysis is achieved by holding the material at 0 %RH for multiple hours at modest temperatures (25-60ºC). Drying under more strenuous conditions such as high temperature or vacuum is avoided because those conditions could change the structure of the material (e.g., waters of hydration could be lost).

Figure 3 shows the raw experimental data for a typical stepped humidity - constant temperature experiment. The sample is PVP (polyvinylpyrollidone), a common excipient used in pharmaceutical formulations. The blue curve shows the humidity steps, while the green curve displays the resultant weight gains that occur as the humidity is increased. Note the long experimental time. Moisture sorption analyses are usually lengthy because of the time required for the material to reach equilibrium at a specific humidity. Typically, the equilibrium time increases as the %RH increases. With appropriate software, sorption experiments can be programmed so that either total elapsed time (dwell time), or the decay of the weight derivative signal, determines when equilibrium at each humidity step has occurred. The latter approach helps reduce the total experimental time, while maintaining the accuracy of the results. Figure 4 is the final adsorption curve for PVP. This plot is generated by taking a single point after equilibrium at each humidity level. The value of interest in assessing PVP is the total % weight change of 42 +/- 2% at 80 %RH. The amount of water adsorbed by PVP is large by pharmaceutical standards, but is typical of excipients. Crystalline materials used as active ingredients in pharmaceutical formulations commonly adsorb <5 % water.

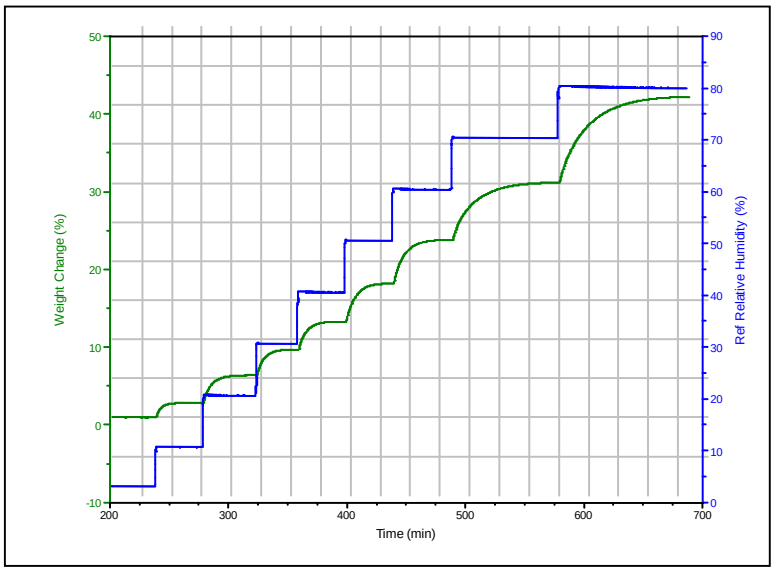

Figure 3: PVP Experimental Data

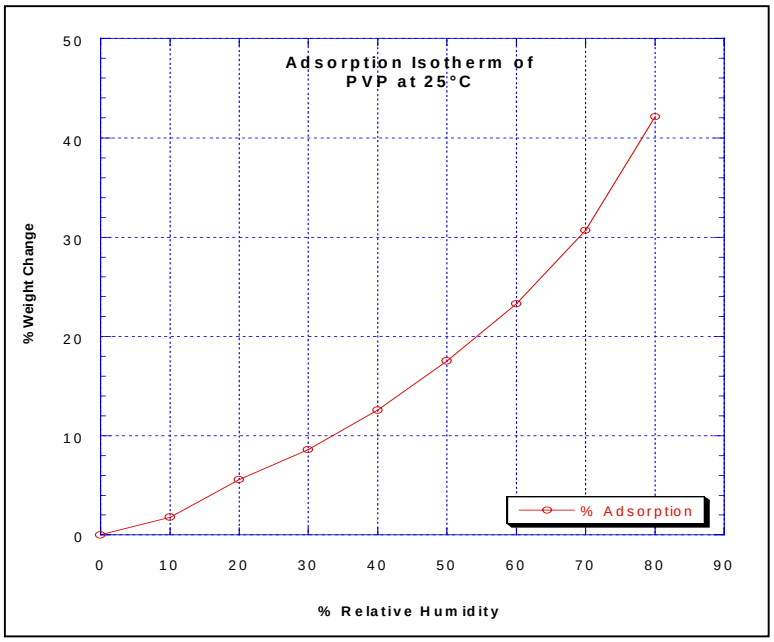

Figure 4: PVP Sorption Isotherm

Deliquescence is another common behavior, which can be exhibited by pharmaceutical materials when exposed to moisture. Deliquescent materials absorb very little water as the humidity is raised until the %RH reaches a "critical" (deliquescence) level. At that %RH and temperature, the material suddenly starts absorbing any available moisture. Lithium chloride (Figure 5) represents "ideal" onset of deliquescence from an analysis perspective because the % weight change with humidity is so abrupt that it is easy to determine the deliquescence point as either the first deviation from baseline or as the extrapolated onset of adsorption. Materials like urea, however, exhibit a more gradual deliquescence point (green curve in Figure 6) and hence its determination is more subjective based on where the extrapolated onset of uptake (weight gain) is measured. This difficulty can be eliminated by plotting the change in mass, with respect to the change in humidity during a ramped humidity experiment. The point where that curve (blue curve in Figure 6) crosses zero (i.e., the point where the material is neither adsorbing or desorbing water) during the decreasing humidity ramp is recognized as the deliquescence point. There is a third method used to

determine the deliquescence point. That method is based on raising the humidity above the onset of deliquescence and then stepping down in humidity. The maximum point in the downward %weight change curve is considered the deliquescence point (Figure 7). Since the region of interest in this latter type of plot is often only several %RH wide (as is the case with urea), it is necessary to use small (0.1 %RH) steps to obtain accurate results.

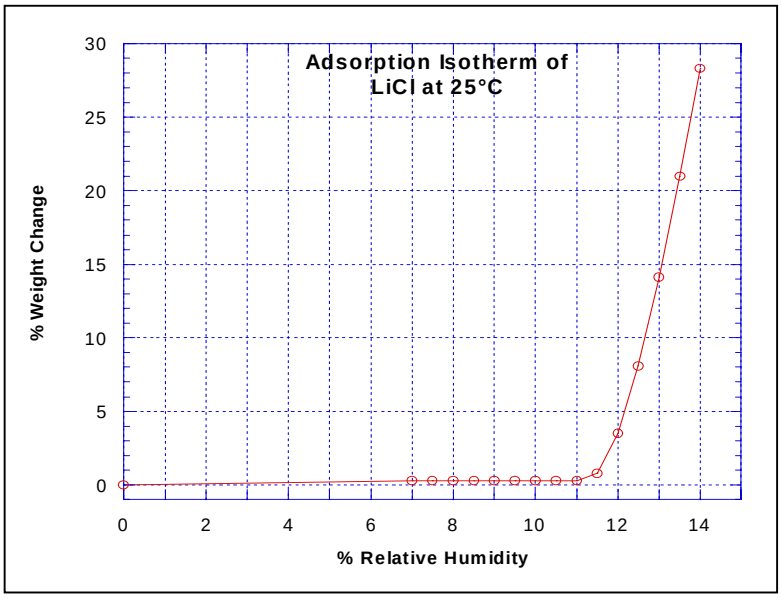

Figure 5: Lithium Chloride Deliquescence

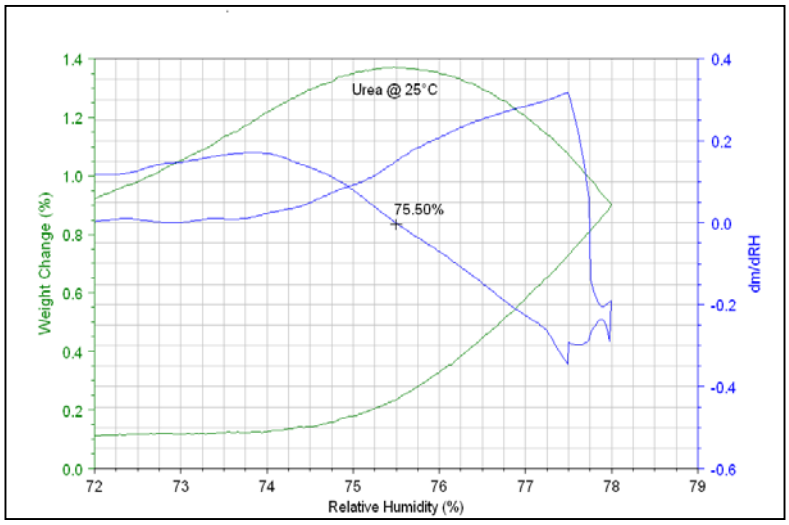

Figure 6: Urea Deliquescence (Ramp Humidity) at 25 ºC

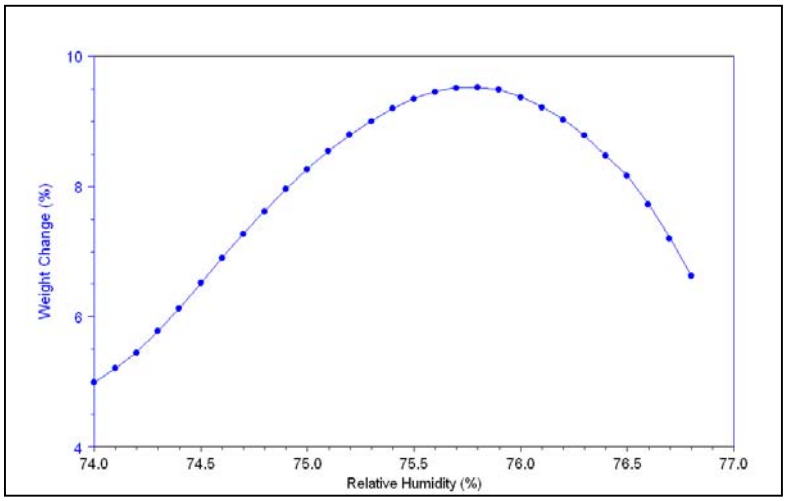

Figure 7: Urea Deliquescence (Step Down Humidity) at 25ºC

When evaluating pharmaceuticals, particularly in the active ingredient screening and preformulation stage, it is common for only small amounts of material to be available for conducting multiple analytical tests including sorption analysis. Hence, the ability to work with small samples is beneficial. In addition, working with smaller samples allows the material to equilibrate more rapidly at the various humidity steps, thereby shortening the experiment. The low baseline drift of the Q5000 SA (Figure 2) means that good results can be obtained on as little as10-20 milligrams of crystalline drugs such as prednisone (Figures 8-9), which adsorb <1% moisture over a broad humidity range. The sorption results shown in Figure 8 represent about 15 micrograms of weight change full-scale. The larger sample shown in Figure 9 yields the same general profile indicating that the results on the smaller sample are valid. The reversibility (lack of hysteresis) in the sorption / desorption profile for prednisone indicates that the moisture is adsorbed on the surface of the material rather than being absorbed into its structure.

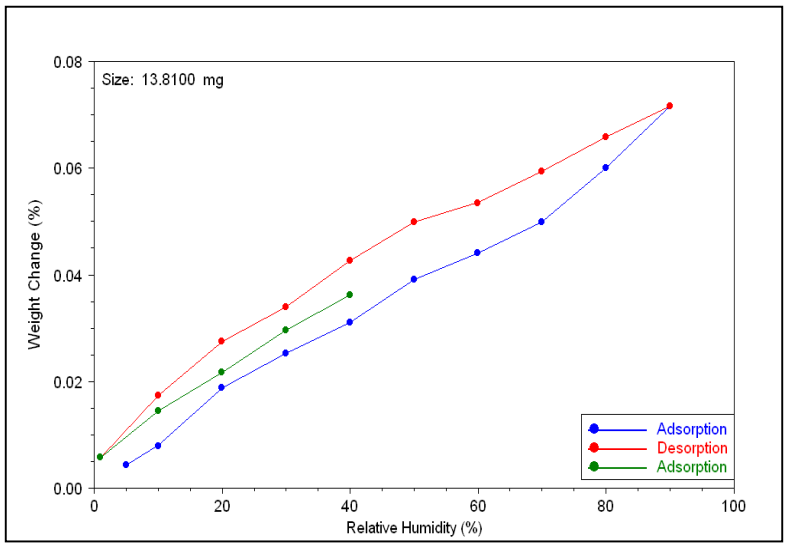

Figure 8: Prednisone...small sample (25°C)

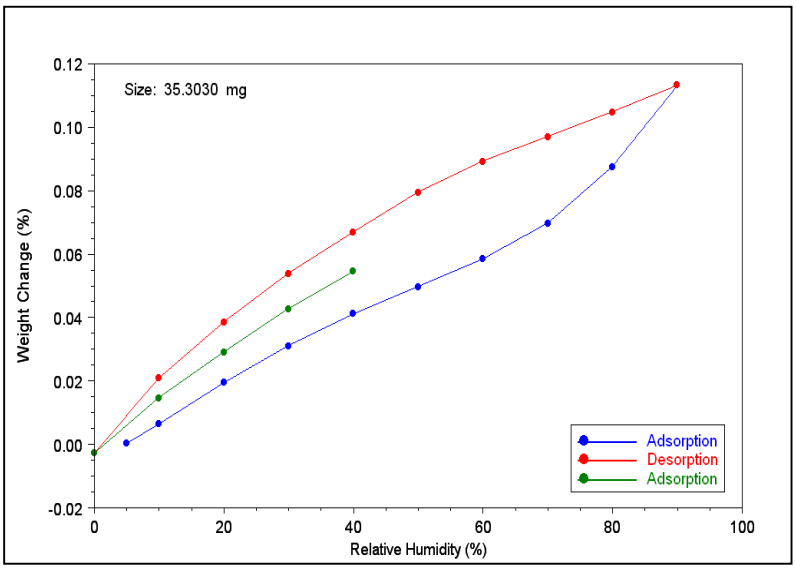

Figure 9: Prednisone…large sample (25°C)

Choline (Figure 10) is another material, which exhibits an adsorption / desorption profile without appreciable hysteresis. In this case, however, the amount of moisture absorbed is extremely large (150% weight change at 90 %RH) implying that the material essentially forms an unsaturated solution. Since there is no evidence that the structure of choline is changed during this large uptake of moisture, the overall structure of the material must be very open. Two other cases where bulk absorption of water occurs are shown in Figures 11 and 12. Fluphenazine exhibits some hysteresis during the desorption process. However, the pore sizes within the material are sufficiently large to allow all the moisture to "escape" by the time the relative humidity is decreased to 60%. This curve is similar to results reported in the literature for materials with mesopores (2-50nm). Trifluoperazine, on the other hand, releases the adsorbed water more slowly. In addition, the structure of the material changes as a result of the initial absorption because the second absorption curve follows the desorption profile rather than the original absorption profile.

Diphenylhydantoin (Figure 13) also changes structure on exposure to moisture. The desorption profile exhibits significant hysteresis from the initial sorption profile and there is a sharp step change in weight as the humidity decreases below 30 %. Profiles like this are indicative of the formation of hydrates, and at 5 %RH, the residual weight gain agrees well stoichiometrically with what is expected for the monohydrate form of this material. Since the hydrated form has a more open structure, its subsequent sorption profile shows more rapid uptake of moisture than the original sample.

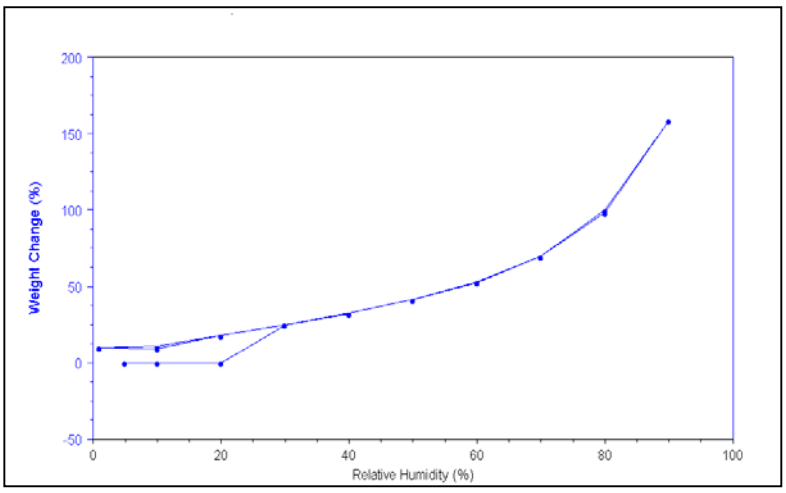

Figure 10: Choline (25°C)

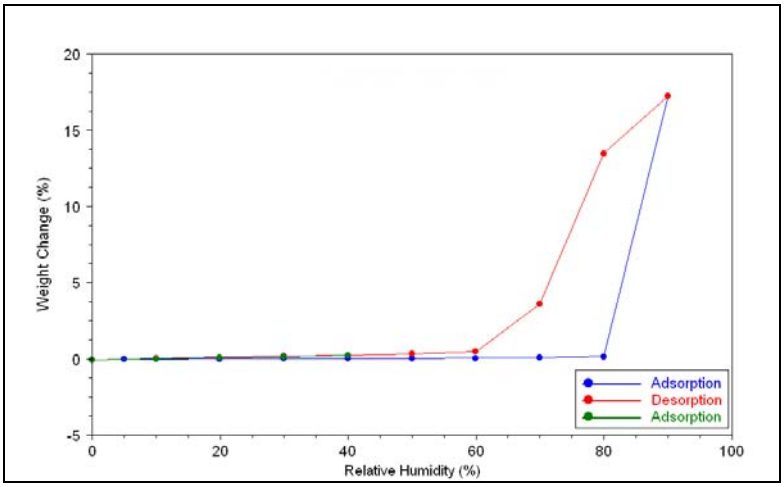

Figure 11: Absorption into Mesopores (2-50 nm)

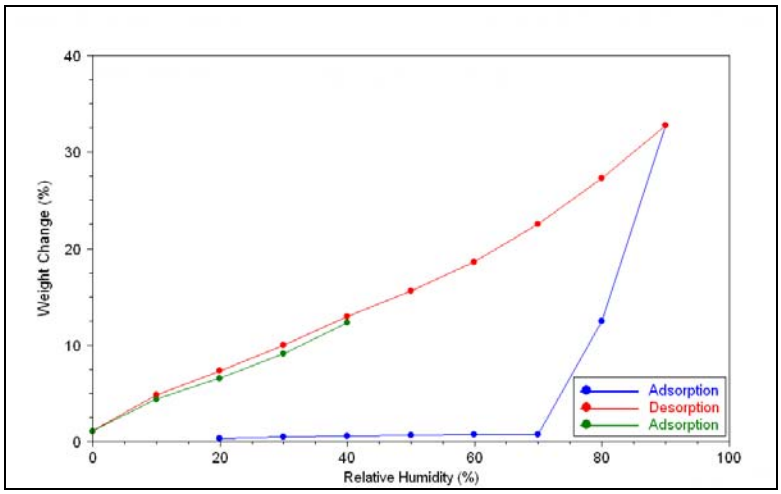

Figure 12: Bulk Absorption…Trifluoperazine Dihydrochloride (25°C)

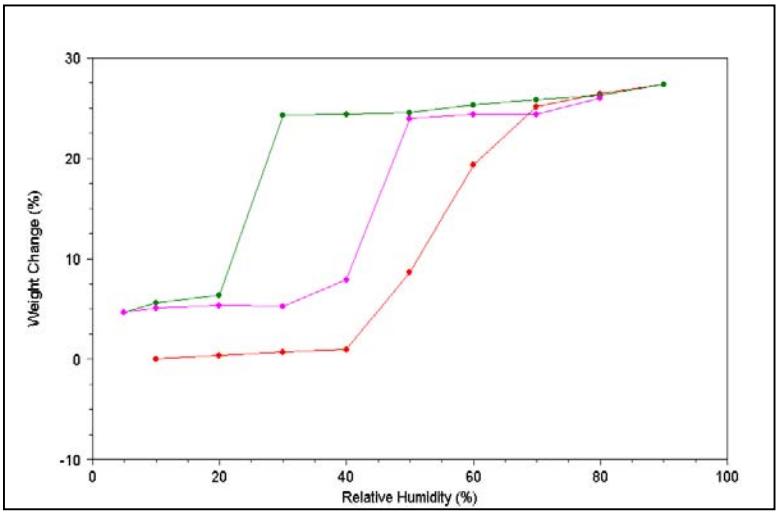

Figure 13: Diphenylhydantoin Sodium Salt (25°C)

Sorption analyses can be performed on the material “as received” or after drying under specific conditions. Figure 14 compares the results for diclofenac “as received” and after drying at 60 ºC and 0 %RH for 4 hours. The general shape and level of moisture adsorption / desorption are the same with and without drying, indicating that the drying conditions chosen, while sufficient to remove 1-2 % of adsorbed surface water, are sufficiently mild that the structure of the material is unaffected. In situations where the results from sorption analysis are used “qualitatively” to determine the general shape of the sorption profile as well as to provide a general indication of the level of moisture adsorbed, drying the sample often does not increase the amount of useful information obtained. That is the case with diclofenac. On the other hand, in situations where more exact quantification of the amount of moisture adsorbed at a specific humidity level is required such as for microcrystalline cellulose (BCR-302), drying the material before analysis becomes more important. Microcrystalline cellulose is another common pharmaceutical excipient. BCR-302 is a standard developed in Europe via an interlab study, where microcrystalline cellulose was equilibrated over well-characterized, saturated deliquescent salt solutions at 10 different humidities and the weight gains accurately measured. Figure 15 shows a table of results for the first three weight steps for BCR samples dried differently prior to analysis. As expected, sample size, temperature, and time are important considerations during drying. Typically, the larger the sample, the more time which must be allowed for proper drying. Increasing temperature reduces the time required to appropriately dry the sample. As shown in the table, if the BCR sample is not properly dried prior to analysis, the weight gains observed at each humidity level are lower than found in the interlab study. This is, of course, because the undried material already contains some of the total moisture, which it can adsorb at the humidity levels being tested, and hence yields low results.

As mentioned earlier, care must be taken in drying materials prior to analysis because it is possible to change the structure of the material during drying and affect the resultant sorption profile. Figures 16 and 17 are the results for a drug monohydrate run “as received” and after drying at 80 ºC for 6 hours at 0 %RH. The profile for the “as received” material is indicative of a crystalline drug. The dried material loses roughly 5 % weight during drying, probably corresponding to loss of the water of hydration. The anhydrous material adsorbs about 5 times the amount of moisture adsorbed by the original material.

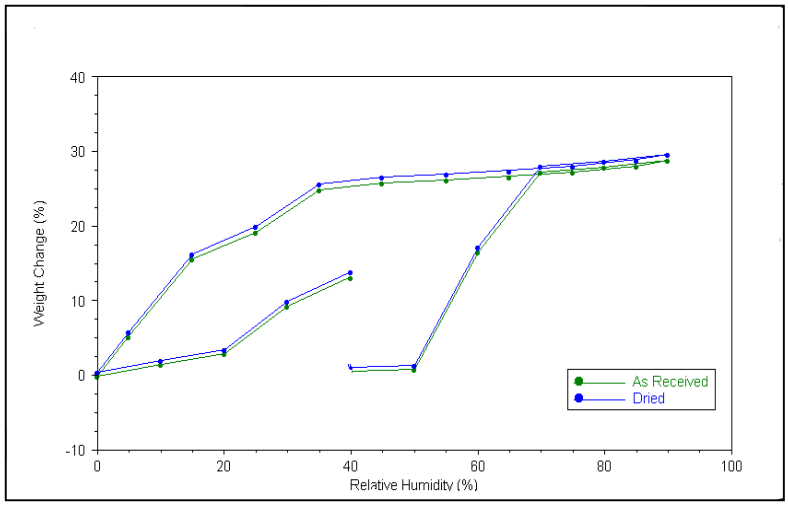

Figure 14: Diclofenac Sodium Salt (25°C)

%RH	Weight Gain	Confidence Interval	Dried at 60C (10mg)	Dried at 25C (10mg)	Dried at 25C (2mg)	As received
11.1	2.13	+/-0.11	2.06	1.95	2.04	1.44
22.5	3.24	+/-0.12	3.25	3.12	3.24	2.67
33.0	4.15	+/-0.09	4.25	3.89	4.05	3.60

Figure 15: Microcrystalline Cellulose (BCR) Results

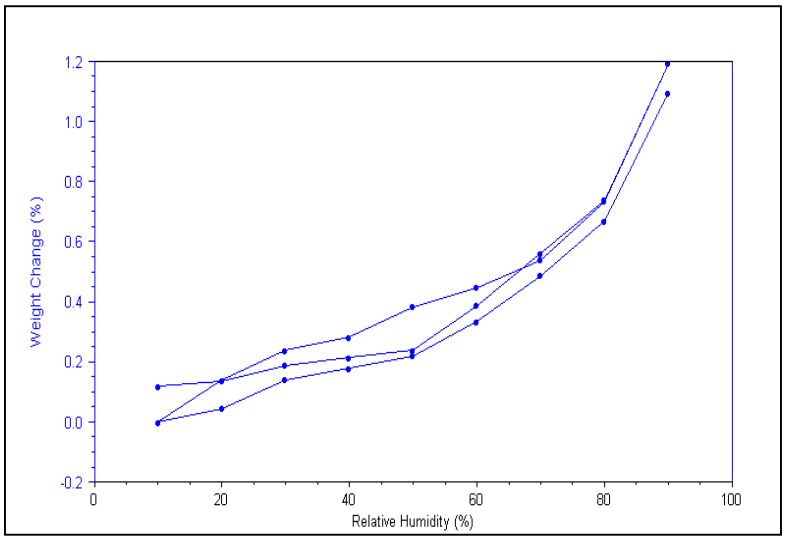

Figure 16: Drug Monohydrate (as received)

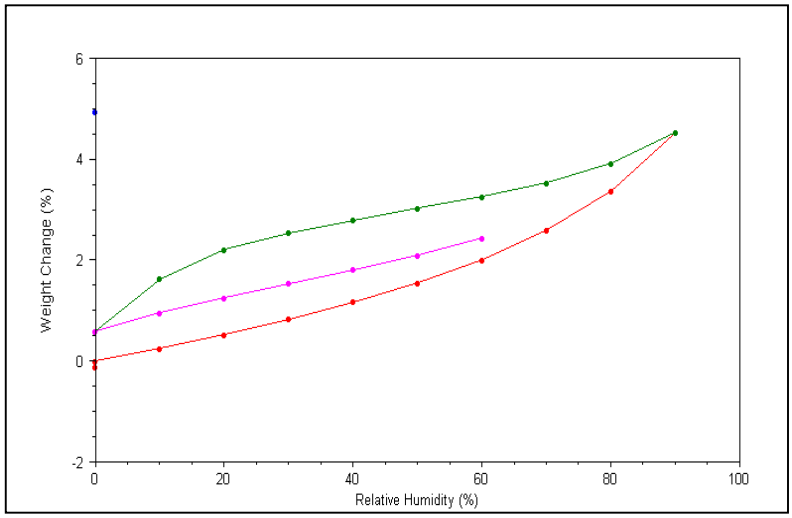

Figure 17: Drug Monohydrate (after drying)

Further examples, which illustrate other types of measurements that can be made on pharmaceuticals, are shown in Figures 18-24. Samples that readily adsorb moisture (hygroscopic materials) are often difficult to evaluate since their weight changes dynamically in the process of determining the initial starting weight for the purposes of expressing later weight changes as "%weight change". Another way to evaluate those materials is to expose them to different humidity levels until the material comes to equilibrium, and designate that point as the starting weight for subsequent comparisons. Then, the "moisture-equilibrated" materials are "dried" by raising them to an elevated temperature at 0 %RH until equilibrium is attained. The weight losses during "drying" provide an indication of the total amount of water adsorbed by the material at each humidity level. Drying the material before analysis is another potential approach. However, the peptide material shown in Figure 18 could not be evaluated that way since it was known to readily lose waters of hydration, which changed the material's structure.

In Figure 19, the goal is to determine proper drying parameters for a hydrated material during processing (i.e., the lowest humidity which can be used at a specific drying temperature **without** changing the structure by removing any weakly held water(s) of hydration). The results were obtained by stepping humidity from a high starting level to a lower level (right to left in the Figure). The humidity where a significant weight change occurs indicates loss of the water of hydration. At 25ºC drying temperature, humidities as low as 10 %RH can be used. At 40ºC and above, the humidity during drying must be at least 15 %RH to avoid issues. In this material, the impact of sample form (milled versus unmilled) has little effect on the drying properties.

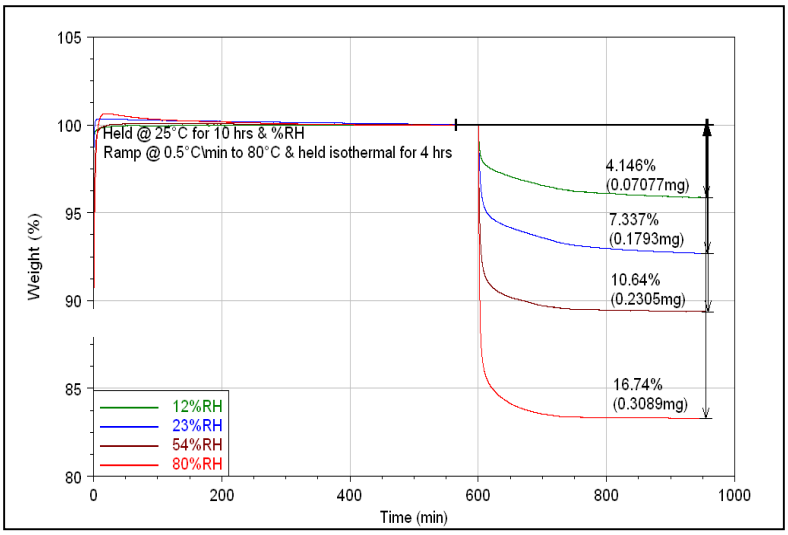

Figure 18: Peptide Hygroscopicity

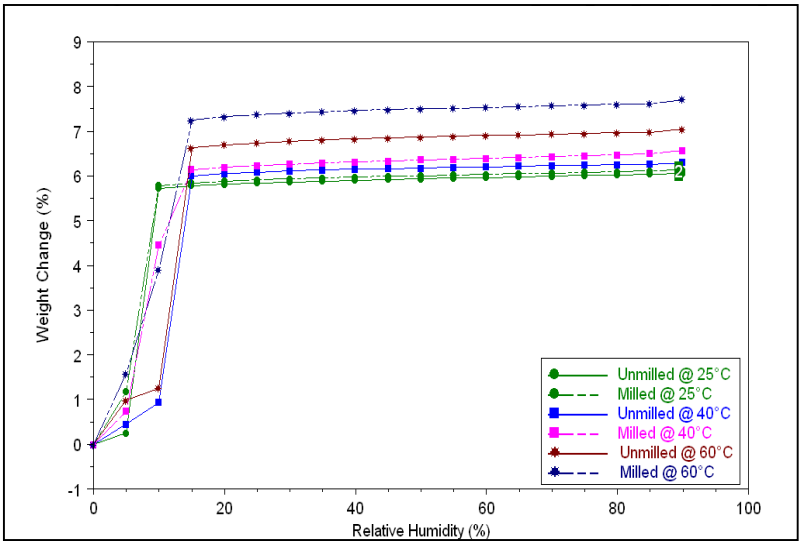

Figure 19: Drying of Weak Hydrate

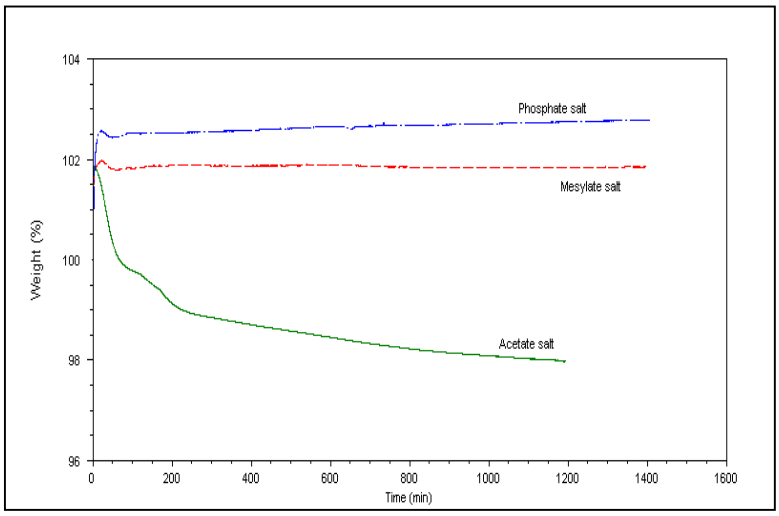

Figure 20: Stability Comparison of Salt Formulations

Long-term stability of different formulations of the same active ingredient when exposed to moisture can be assessed by exposing the materials to constant humidity at higher temperature to accelerate the onset of "degradation". In the example shown in Figure 20 several different salts of the same base compound are exposed to 50 %RH at 25ºC, then raised to 80 ºC while maintaining 50 %RH. All three salts rapidly pick up about 2 % moisture at 25ºC and 50 %RH. However, when the temperature is raised to 80 ºC, the phosphate and mesylate salts retain the adsorbed water and the weight remains constant over the next 24 hours. The acetate salt, on the other hand, rapidly gives-up the initial weight gained as the temperature is raised to 80 ºC and the material continues to lose weight with time indicating that it is the least stable formulation.

The amount of material available for sorption analysis is limited in situations like screening of active ingredients and preformulations, and hence smaller samples are analyzed. There are, however, other situations (e.g., evaluation of tablets) where sample size will be much larger. Figure 21, for example, shows a comparison of the raw sorption results for uncoated (chewable) and coated (slow-release) pain relief tablets. The uncoated tablet loses more moisture on initial drying and adsorbs more moisture on exposure to increasing humidity than the coated tablet. Since these tablets weighed 300-400 mg, the results were obtained by taring out a portion of the total weight in order to keep the weight loss/gain within the dynamic range of the instrument. Figure 22 compares the rate of absorption for the whole uncoated tablet versus the tablet after powdering. The larger surface area after powdering results in more moisture absorption. This figure also shows the effect of pan type on the results. Running the powder in mesh pans where the material is exposed on all sides to the humidified environment results in an additional increase in moisture absorption.

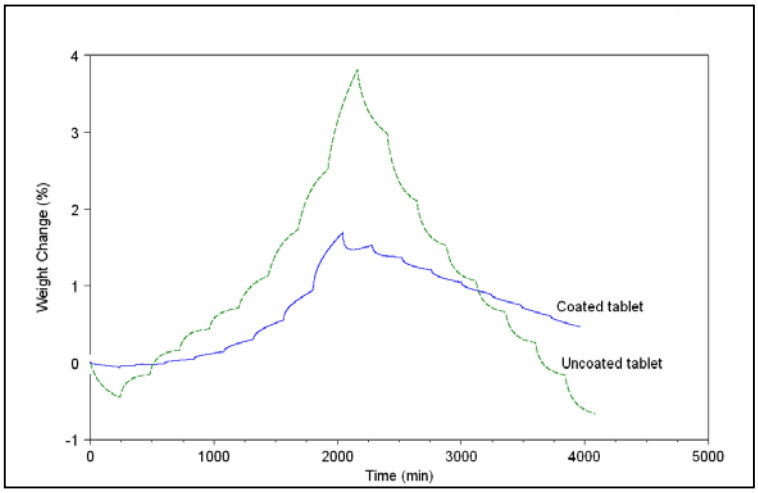

Figure 21: Evaluation of Pharmaceutical Tablets

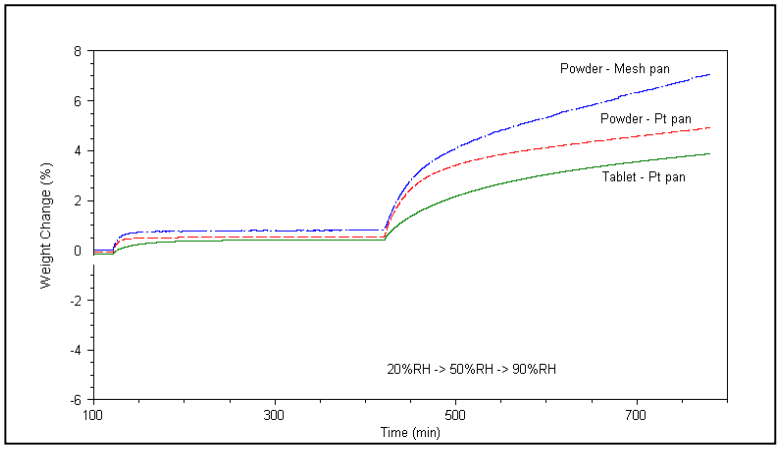

Figure 22: Tablet Form & Pan Influence on Moisture Uptake

Concerns about unwanted interaction of sample materials with the laboratory environment, while waiting for analysis, (e.g., hygroscopic materials) can be eliminated by sealing the materials in aluminum pans that are designed to be opened automatically just prior to the sorption analysis. The benefit of this approach is illustrated in Figure 23. Dried PVP readily picks up moisture on exposure to most laboratory environments. A lower than expected weight gain at 80 %RH indicates that the PVP has in fact previously picked up water from the environment. These results indicate that PVP equilibrates at roughly 6% weight gain (moisture pick-up) after 8 hours at 25°C and 25 %RH. But, sealing the dry PVP in pans for 24 hours and then opening the pan for sorption evaluation, yields the expected results (42 +/-2 % weight gain at 25°C and 80 %RH). Sealed pans are the best choice for evaluating materials "as received."

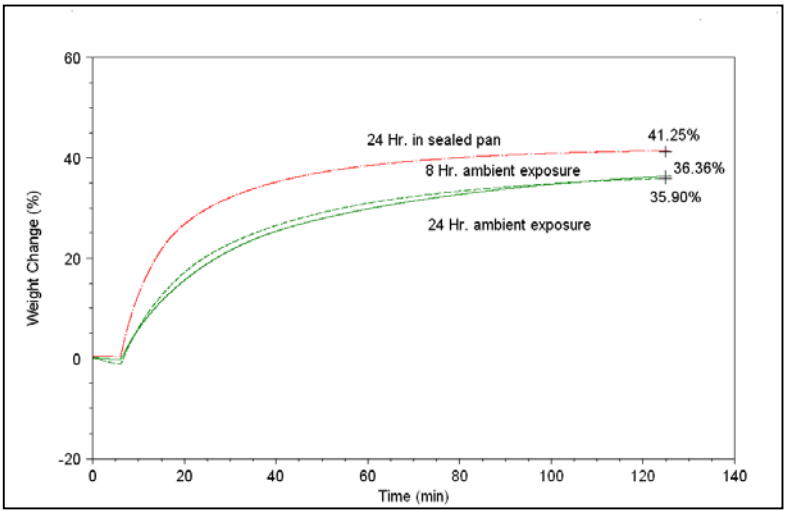

Figure 23: Dried PVP After Exposure to Ambient Conditions

Evaluation of the glass transition temperature for amorphous pharmaceutical materials is another measurement, which can be made using sorption analysis. The glass transition is the point where an amorphous material becomes less stable and rearrangement to the more stable crystalline structure occurs. The glass transition is affected by temperature and humidity. Hence, it can be determined using either ramped temperature experiments at constant humidity or using ramped humidity experiments at constant temperature. The amorphous material gains weight until the glass transition is reached. Then, as the material rearranges to the crystalline form, there is a significant decrease in weight since crystalline materials have less affinity for water than amorphous materials at the same temperature and humidity conditions. A similar application for ramped temperature/constant humidity experiments is shown in Figure 24. The deliquescence humidity for most salts decreases as temperature increases. Therefore, if the humidity selected is below the deliquescence point at 25°C, the weight change indicating the onset of deliquescence does not occur until the temperature is raised to the appropriate level. Sodium bromide deliquesces at 41°C and 53 %RH. The onset temperature of weight gain measured from a ramped temperature experiment agrees well with theory. The results here represent duplicate runs. [Note: The

derivative weight signal is used and in the Q5000 SA the sign of that signal is reversed, which means that weight gains yield a downward sloping curve.]

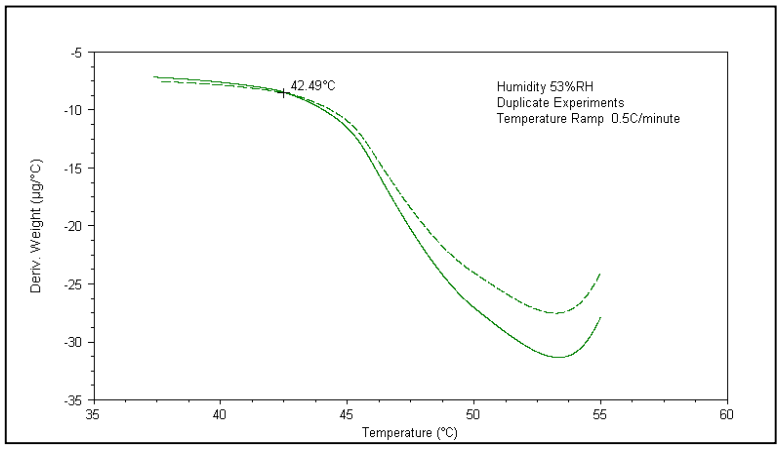

Figure 24: Sodium Bromide Deliquescence…Temperature Ramp

In addition to evaluation of the actual pharmaceutical formulations, sorption analysis can also be valuable in comparing the polymeric films, which are being considered for packaging the drugs. Figures 25 and 26 show comparative profiles for different packaging materials. In Figure 25, Film A (dashed line) adsorbs and desorbs moisture at a more rapid rate than the other film evaluated. In Figure 26, the adsorption-desorption profiles for two PET (polyethyleneterephthalate) films indicate low levels of surface adsorption occur in both films, but the copolymer film adsorbs more water, if higher humidities are present.

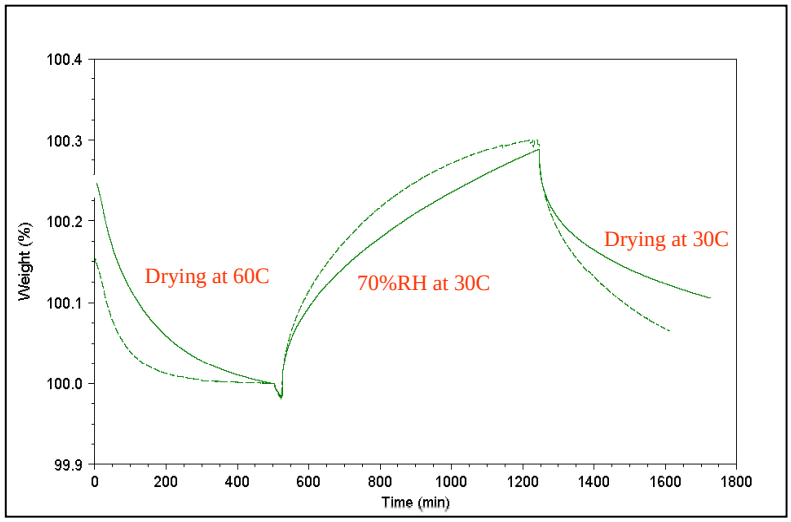

Figure 25: Comparison of Rate of Adsorption-Desorption in Packaging Films

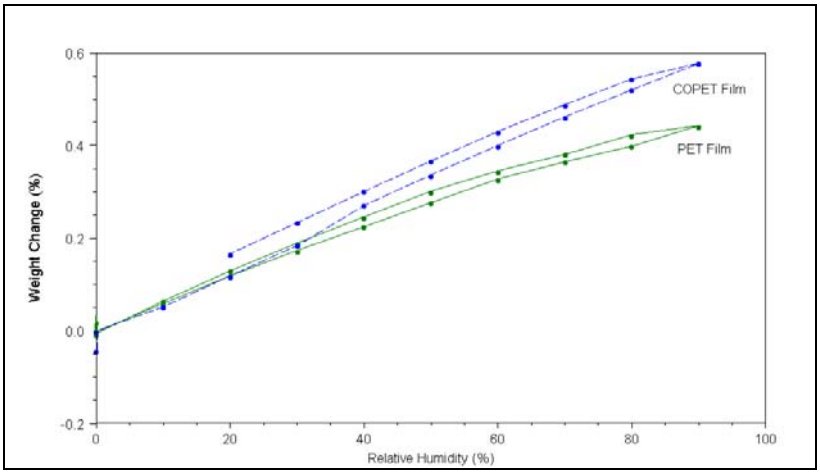

Figure 26: Comparison of Film Adsorption-Desorption Properties

SUMMARY

Sorption analysis is an important analytical tool for the characterization of pharmaceuticals during the screening of active ingredients and preformulations. The new Q5000 SA from TA Instruments (Figure 20) incorporates many unique features, including a ten-position Autosampler and software for scheduling automatic unattended validation of performance and calibration, which should make obtaining these important results faster and easier. Furthermore, the instrument is totally self-contained and requires minimal bench space compared to traditional sorption analyzers.

Figure 27. Q5000 SA

KEY WORD

Q5000 SA, sorption analysis, moisture sorption analysis, adsorption, desorption, humidity, relative humidity, pharmaceuticals, active ingredients, preformulation

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