Application Bulletin #1

Pharmaceutical Applications for VTI's Series of SGA Sorption Analyzers

The Models SGA-100 and SGA-CX Symmetrical Gravimetric Analyzers from VTI are designed to handle a variety of pharmaceutical sorption applications in research, development, quality control and packaging evaluations. Here is a sampling of technical topics and applications data which demonstrates VTI's unique experience in pharmaceuticals…

Symmetrical Microbalance Design

The SGA-100 and SGA-CX Analyzers are symmetrical sorption instruments…that is, both the sample and reference chambers are exposed to the same conditions of temperature and humidity. This is a very important feature when testing non-hygroscopic solids or when small amounts of samples are available for analysis, both cases frequently encountered in pharmaceutical studies. Since both sides of the system are almost identical, water or organic vapor sorption onto the hang-down wires and sample holders cancel each other and the water sorption data represents the water uptake by the sample alone.

By contrast, in non-symmetrical systems, the water adsorbed by the hang-down wire and sample holder is added to the water adsorbed by the sample. The only way to determine the true water uptake by the sample is to subtract the water adsorbed by the hang-down wire and sample holder, as determined in a separate blank experiment. In addition to the obvious increment in experiment time, for samples with small water uptakes, the experimental uncertainty is quite high. This is due to the sample's water uptake being determined by the small difference between two relatively large numbers.

Resolution and Stability of the Microbalance

The standard microbalance for the SGA-100 and SGA-CX has a 0.5 microgram resolution. However, for pharmaceutical applications, we normally recommend one of our optional microbalances with a resolution of 0.1 micrograms. Also, for more effective work in pharmaceutical studies, the SGA's design provides an enhanced stability of the balance by maintaining the balance compartment at a constant temperature, independent of the sample temperature. To accomplish this, we use a dry nitrogen purge of the balance compartment, so the humidity around the balance beam and components is always below 5%RH. Because the balance is maintained at constant temperature, the user has the option of drying the sample at temperatures other than the experimental temperature, or to run different temperature and RH profiles without removing the sample from the chamber or re-calibrating the balance. Our Isohume© program takes full advantage of this feature allowing for changes of RH and temperature within a given run.

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Sample Chamber Design

In the SGA Analyzers the sample and reference chambers are located within an aluminum block which is maintained at constant temperature (within 0.01 C) by a circulating constant temperature bath. Our unique aluminum block design has two distinct advantages. First, due to the high thermal conductivity of the aluminum, thermal gradients within the chambers are minimal. Secondly, because the chamber is a metal block, the issues of static electricity are eliminated. This feature is especially useful when analyzing finely divided powders, as is often the case with pharmaceuticals. The sample temperature is measured with a highly accurate calibrated platinum resistance thermometer.

Precision Humidity Measurements

As part of our standard design, both the SGA-100 and SGA-CX use a chilled-mirror dew point analyzer to determine the humidity at the sample. In contrast with polymer-based, relative humidity monitoring probes, a dew point analyzer is a primary standard for humidity. In applications where humidity is critical (as in most pharmaceutical studies), chilled-mirror dew point analyzers are the preferred method, because of the absence of drift and long term stability. The dew point analyzer offers another important feature…complete inertness to organic vapors. RH probes with their polymer sensor are very susceptible to organic vapors and their calibration can change drastically, if exposed accidentally to an atmosphere containing organic vapors.

Sorption Testing Using an Organic Vapor

The SGA Analyzers are routinely used for water sorption analysis, but also can be used for organic vapor sorption…if VTI's Organic Vapor option is purchased. Since there is no universal organic vapor sensor in the SGA, the concentration of the organic vapor in the gas stream reaching the sample is determined by the fraction of gas going through the organic solvent evaporator and the fraction of dry gas. The assumptions made in competing systems are that the evaporator is 100% efficient and that the temperature of the evaporator is constant from low to high concentrations. The SGA system measures the temperature of the organic solvent in the evaporator and uses this information together with the vapor pressure equation for the particular solvent (using the Wagner equation) to control the organic vapor concentration in the gas phase. This method solves the issue of the adiabatic cooling of the solvent, a major source of error in other systems. The solvent containers/evaporators are easily removed so there is no need for decontamination or cleaning of the system when changing organic solvents or reverting to water adsorption experiments. For safety, the evaporator compartment is purged with dry nitrogen and fitted with a combustible gas sensor with an audible alarm that when triggered shuts down the power to the analyzer.

Examples of experimental data

Shown below are several examples of water sorption data of pharmaceutical materials with a brief explanation of the experimental observations…

Example #1 - This example shows a typical adsorption/desorption isotherm and the corresponding time-course data for a pharmaceutical material. From the time-course data one can obtain sorption kinetics and from the equilibrium sample weight and RH, the isotherm is obtained.

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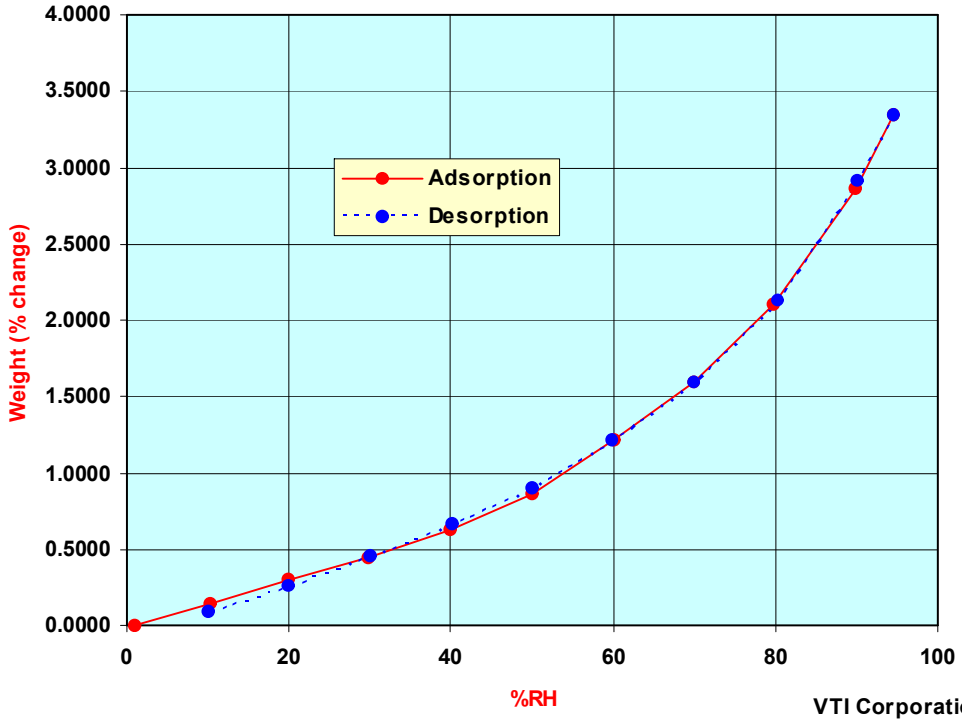
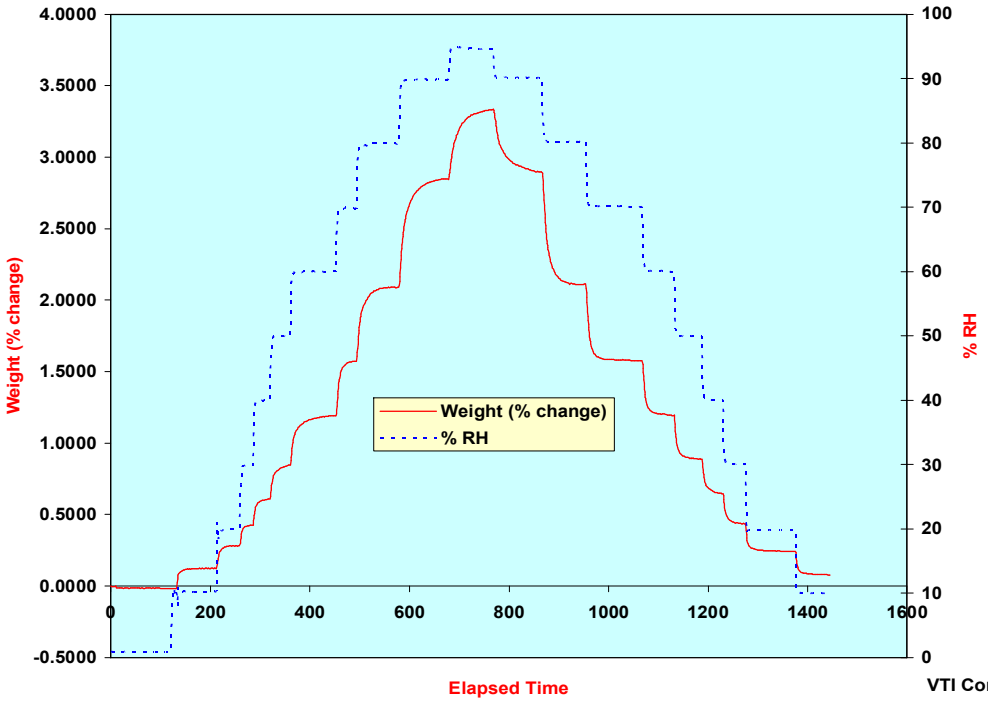
Example #1-Sorption Isotherm



VTI Corporation SGA-100 Data

Example #1- Tme-Course



VTI Corporation SGA-100 Data

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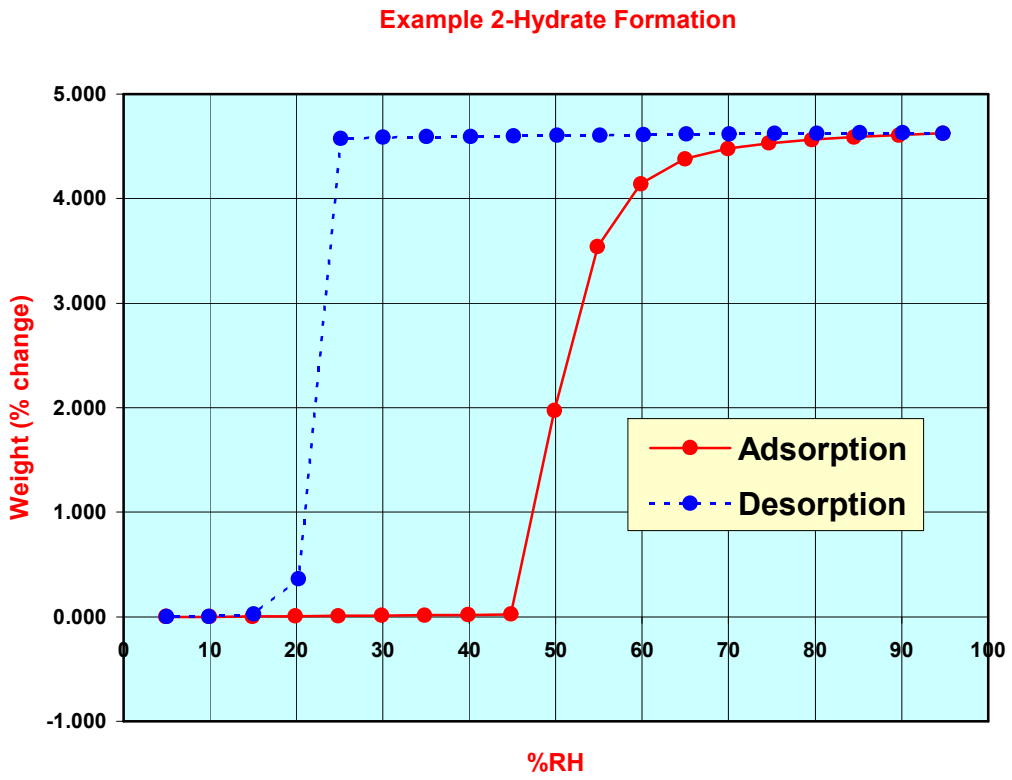
Example #2 - In Example # 2, we show the formation of a hydrate. The hydrate formation is characterized by a plateau in the desorption branch of the isotherm.



In this example the hydrate is formed at around 45%RH. The sample adsorbs about 4.5% by weight water and does not lose the water of hydration until the RH is lowered below 25%. This hydrate would be considered as a labile or unstable hydrate.

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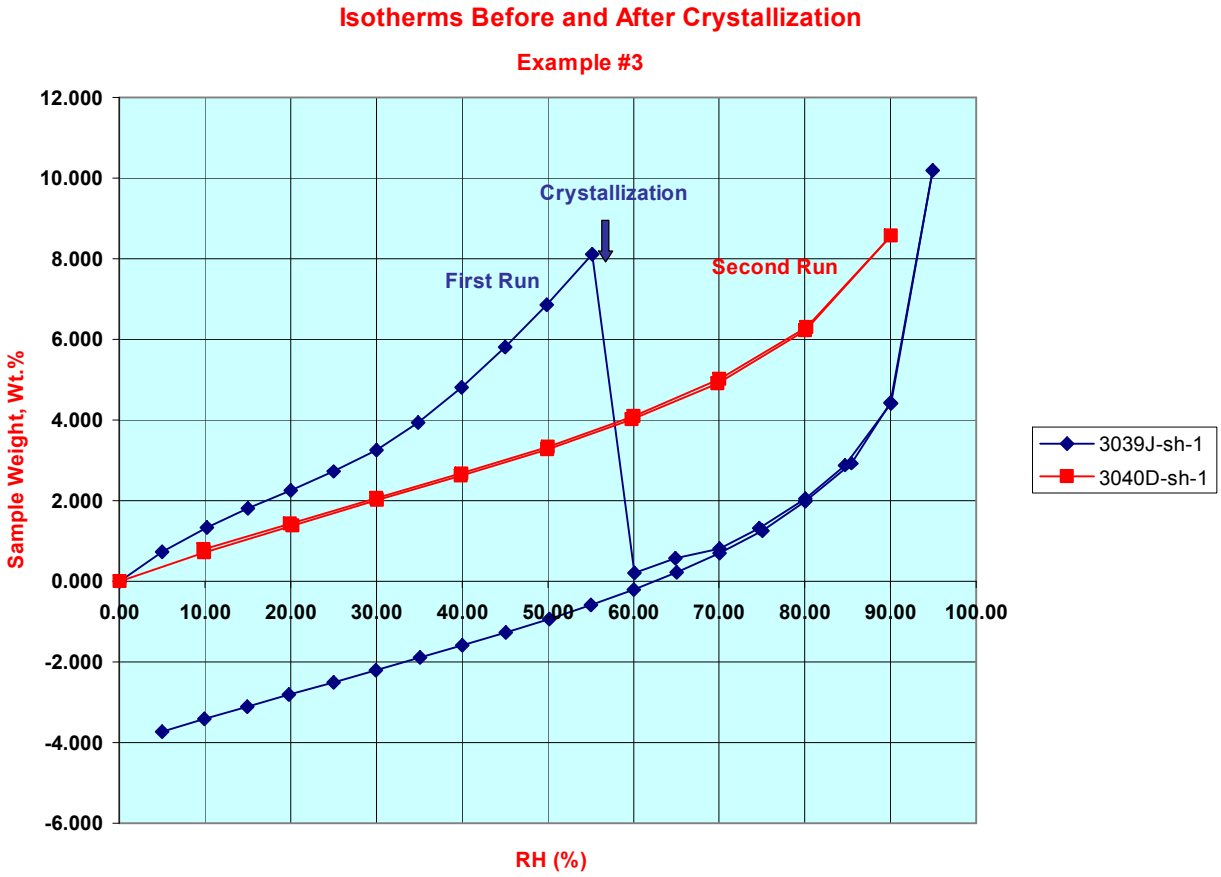
Example #3 - Water acts as a plasticizer for many amorphous solids of pharmaceutical importance by lowering the glass transition temperature of the amorphous phase. Once the glass transition temperature is lowered to the experimental temperature, the increased molecular mobility makes possible the crystallization of the amorphous phase. At the re-crystallization of the amorphous phase is characterized by a sudden loss is sample weight. This weight loss is caused by the ejection of water associated with the amorphous phase: once the material crystallizes there is no room to accommodate this water.

In Example #3 we show the adsorption isotherms of a material containing some amorphous material that undergoes crystallization. We have shown the sorption isotherms before and after re-crystallization. One can observe that after the material is re-crystallized, the isotherm does not show the weight loss observed in the amorphous material.



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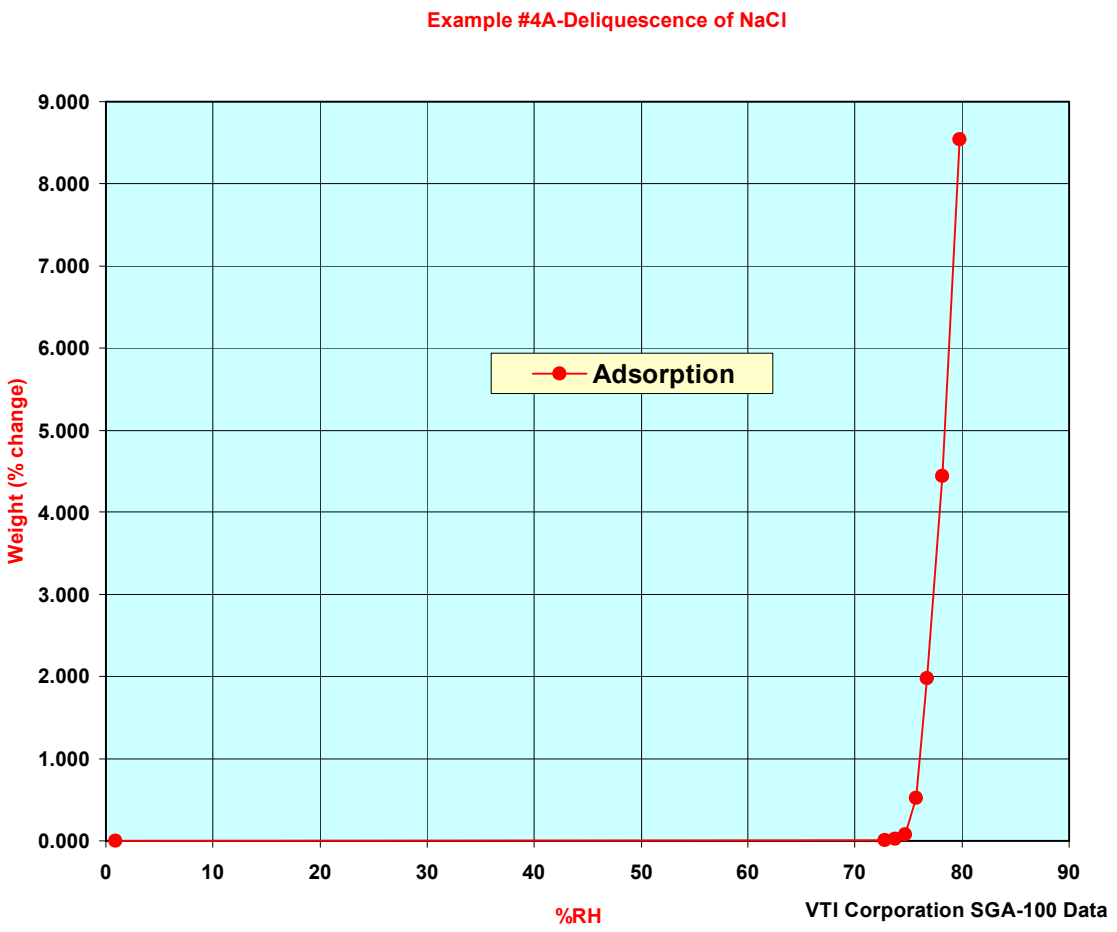
Example # 4 - Deliquescence, the phenomena of a solid absorbing water vapor to form a solution, is a common occurrence in many pharmaceutical solids. Since deliquescing takes place at or above a critical RH, the deliquescence of well-known salts like NaCl and MgCl2.6H2O are commonly used for calibrating humidity sensors.

In Example 4A the sorption isotherm of NaCl is shown. The rapid water uptake above 75%RH is an indication of the deliquescing of the solid. Since the substance absorbs water rapidly above this critical RH and looses water below it, it is sometimes easier to determine the deliquescing point of the solid by first exposing it to a high RH well above the suspected critical RH and then start lowering the RH at small intervals. As long as the RH is above the critical RH for deliquescence, the solid will continue to absorb water but once the RH is below this critical RH, the solid will start loosing water. In Example 4B this is exactly what we can observe for NaCl.



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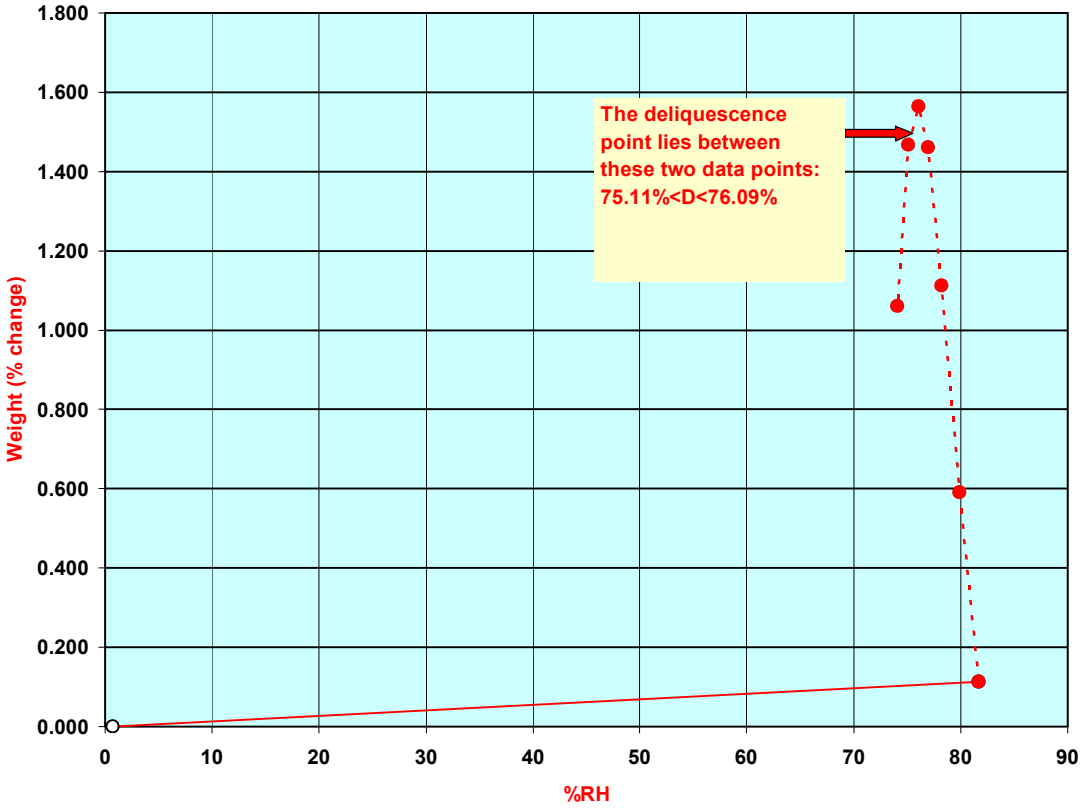
Example # 4B-Deliquescence of NaCl



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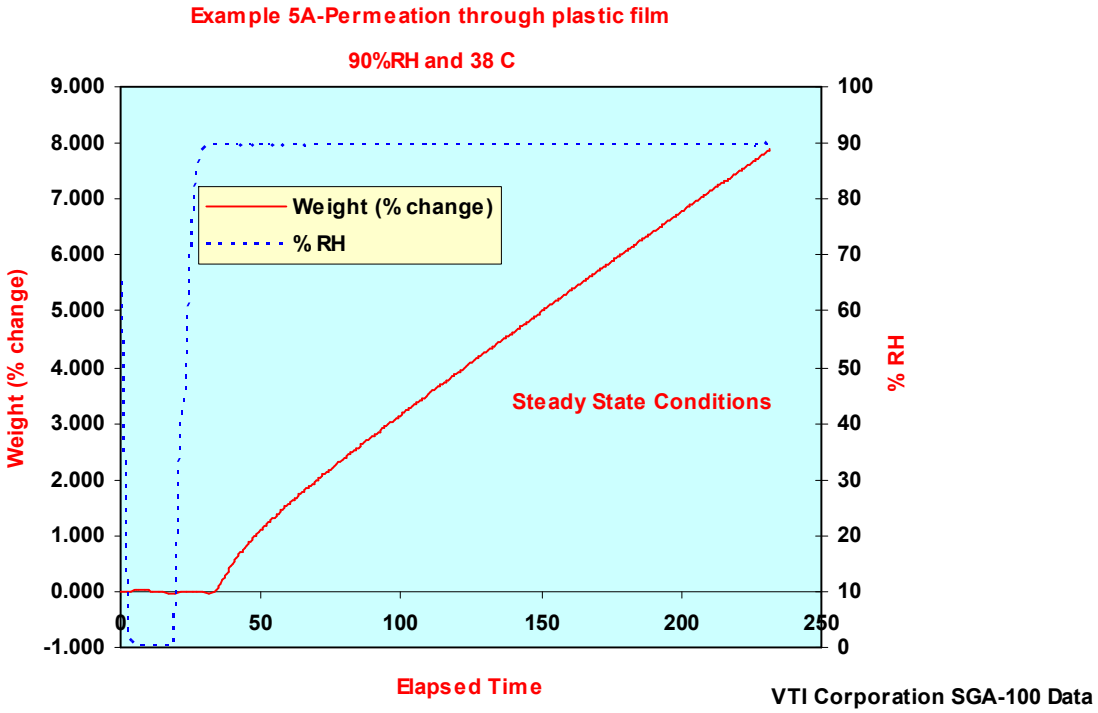
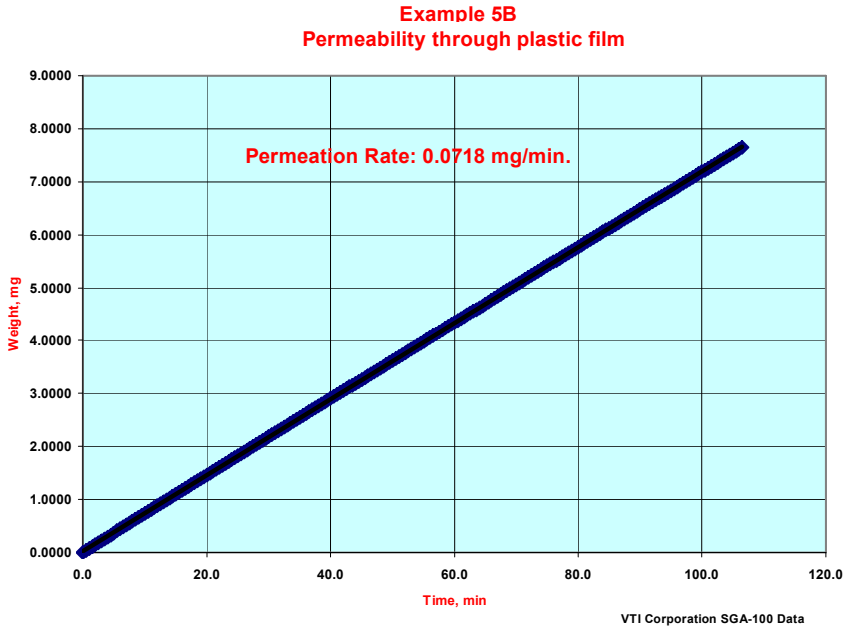
Example # 5 - Application of the SGA to packaging issues: The SGA systems have been successfully used by pharmaceutical departments to determine water and organic vapor permeability through different types of packaging and films. We have designed a special permeation cell onto which we can seal a polymer film or membrane. Inside the cell we can place a desiccant material (silica gel, MgCl2), hang the cell from the balance and determine the permeation of water through the film at different relative humidities. The permeation of the cell is calculated from the steady state weight increase and from the known area of the film. Examples 5A and 5B show the results of such experiment.





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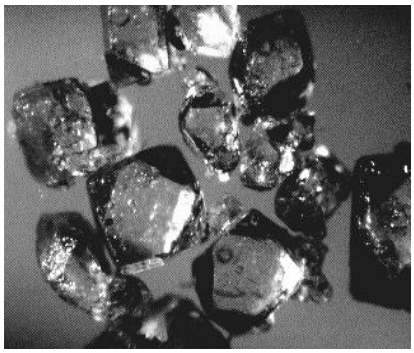
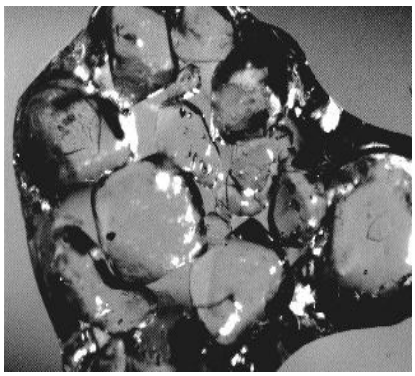
Example # 6 - Using the CCD Camera Option: The Model SGA-100 can be fitted with a 3CCD video camera to take pictures of the sample during the sorption experiment. The lens magnification ranges from 80X to 180X and pictures can be taken automatically with our Windows software. In Example 6A we see crystals of NaCl before deliquescing and Examples 6B and 6C show crystals of a pharmaceutical solid, before and during deliquescing, respectively.

Example 6A. NaCl Crystals

Example 6B. Crystals at 10% RH



Example 6C. Crystals at 95%RH, showing dissolution



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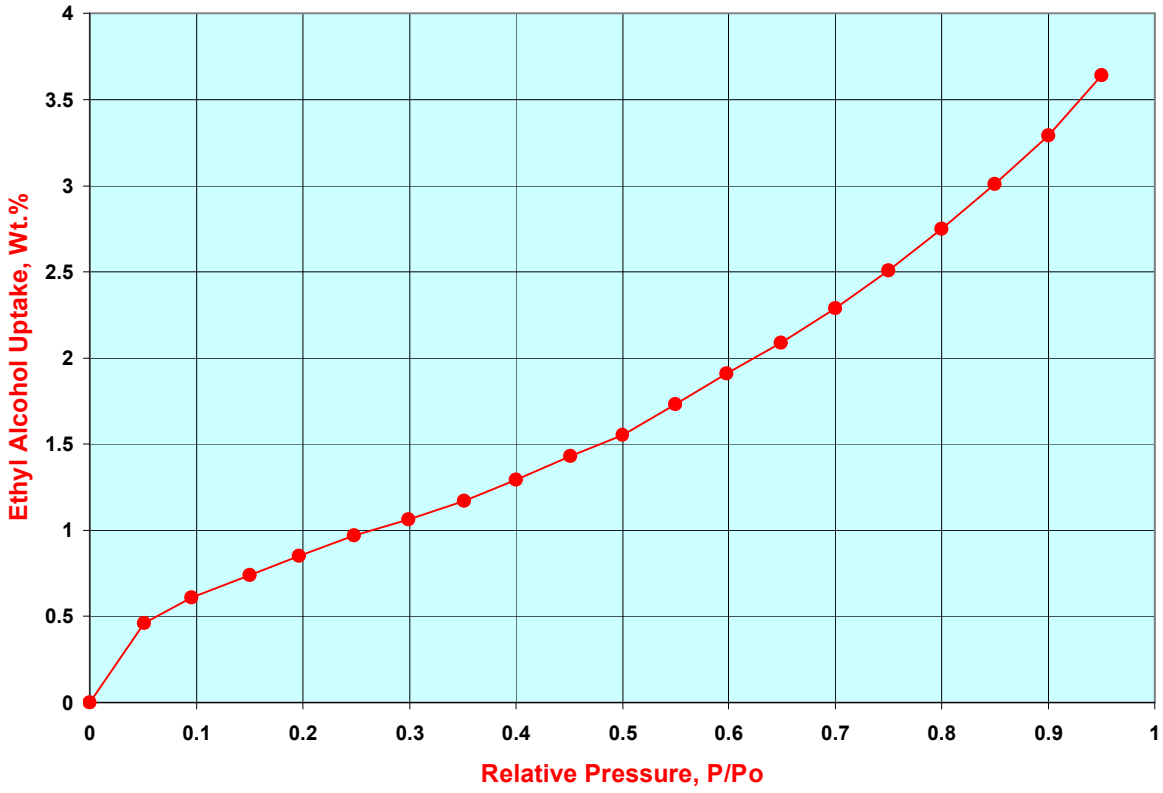
Example #7 - Organic Vapor Sorption - With the organic vapor sorption option, the Models SGA-100 and SGA-CX can obtain not only water sorption isotherms, but can also be used to generate organic vapor isotherms. In Example 7 we show the sorption isotherm for alpha-amylase with ethanol at 25°C.

Example 7. Ethyl Alcohol Sorption Isotherm for alpha-Amylase



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