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Pseudoempirical Modeling Ensures Effective Drug Packaging

Pharmaceutical stability and sorbent technology can be calculated in advance.

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Formulation chemists put a great deal of ingenuity into today's pharmaceutical products. Even so, drug product formulations today are often less stable than their predecessors, and longevity can be compromised by inadequate protection.

Packaging conditions are an important factor in ensuring the safety and potency of a product throughout its shelf life. However, performing tests to identify the ideal packaging requirements can be complex. Without a strategic approach to drug packaging and testing, there can be delays in bringing a new product to market.

Fortunately, there are proven, streamlined techniques to predict how a particular drug will fare in a given package. While stability testing will ultimately determine whether formulation and packaging development decisions were made correctly, pseudoempirical modeling of established drug product formulations with desired packaging presentations can help drug makers quickly determine the means by which they can maintain a drug's chemical and physical characteristics over time. Pseudoempirical modeling can be used in advance of stability testing of solid-state pharmaceutical degradation and sorbent technology in drug packaging.

CUSTOMIZING SOLUTIONS

Pharmaceuticals are subject to chemical and physical degradation through their interactions with moisture. Free moisture increases the molecular mobility within drug product formulations

that can directly affect the rate of all chemical degradation pathways. Desiccants can decrease drug degradation by aggressively reducing moisture and thereby slowing molecular mobility.

There are many desiccant formats available to maintain pharmaceutical

agement requirements for drugs, pharmaceutical manufacturers often collaborate with sorbent providers to find the optimal moisture management and packaging solutions. Experts often help customers determine the precise amount of sorbent required to combat chemical and physical degradation of sensitive drug formulations in commercial and bulk (in-process) packaging presentations.

Pseudoempirical modeling can be particularly helpful because technical engineers first define the adsorption properties of a particular drug product formulation and then simulate the effect of it in combination with the selected packaging presentation, with varying amounts and types of desiccants. This unique analytical approach takes into account the conditions during all drug processing stages, from pharmaceutical formulation to the packaging environment and throughout the distribution chain. After running this analysis, technical engineers provide clients with specifications and recommendations for the ideal drug product and packaging combinations.

Such modeling is appropriate for making moisture-management and packaging determinations for oral solid-dose drugs, oral suspensions, respiratory drug-delivery formulations or devices, and even for parenteral solutions when employing the use of oxygen absorbers. Simulations can be performed for many types of pharmaceutical packaging, in accordance with the guidelines for stability testing set by the International

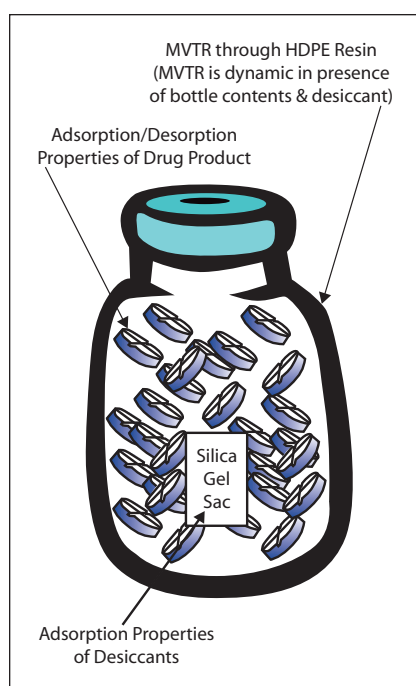


Figure 1. Depiction of a solid drug in an HDPE bottle.

integrity. It is important to choose the right desiccant type, amount, and format for each drug product. Determining the best combination requires a precise analysis that takes into account drug characteristics and packaging material properties, as well as sorbent functionality.

When evaluating the moisture man-

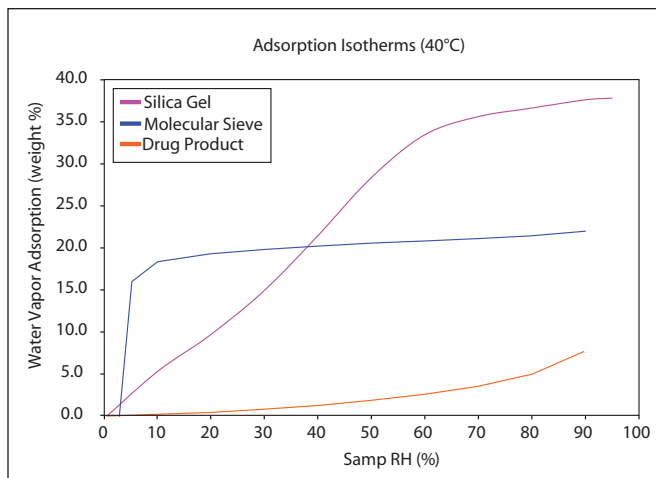


Figure 2. The adsorption isotherms for drug and desiccant.

Conference on Harmonization (ICH) for accelerated test conditions (six months at 40°C and 75% relative humidity). Real-time stability modeling (two years at 25°C and 60% relative humidity) is also available, given the effect of temperature on polymer-bottle moisture-vapor transmission rates.

Because of the ability to perform testing under accelerated conditions, simulation modeling can help pharmaceutical manufacturers find a stability solution quickly, reducing sorbent-ranging studies and related testing time by at least six months. Such modeling could speed regulatory filings, subsequent approvals, and product launches, and ultimately improve cash flow. In addition, it can result in cost savings because it enables manufacturers to purchase the precise amount of sorbent they will need for a given drug product's packaging requirements.

THE RIGHT COMBINATION

Today's sorbents are often described as active packaging components because they respond to changes in the headspace of packaging relative to outside conditions. The two goals of stability testing for drug packages are to determine what the internal conditions of a drug package will be under given inputs and to predict equilibrium relative humidity (ERH) and drug product hydration over the course of the drug product's shelf life. The calculations

take into account the humidity levels both inside and outside the package, as well as drug and desiccant affinities for moisture at varying humidity levels, and the rate of transfer of moisture and vapor through the package wall.

isotherm for the drug (Figure 2); and finally, the adsorption isotherm for the desiccant (also noted in Figure 2). The analysis would also have to calculate bottle thickness and surface area to determine approximate moisture ingress through its walls. Such calculations can be complex because they involve multiple covariates and dynamic processes. Given its performance advantages in reducing total moisture ingress, the use of a foil-laminate heat-induction seal is always assumed.

The whole package—drug product, container, and desiccant—functions as a system and will reach equilibrium relative humidity over time. When a desiccant is first dropped into a bottle, it acts on all available sources of moisture—pulling moisture out of the air as well as the drug product. In effect, the desiccant is being used as a processing tool to reduce free moisture or draw free moisture away from the drug product. The impact on the drug product is to reduce molecular mobility as well as chemical degradation. In this manner, the desiccant will reduce the relative

Modeling simulates how the interdependent variables—drug, desiccant, and package—will affect one another over time. For example, an analysis of a solid drug packaged in a high-density polyethylene bottle would take into account three interdependent parameters: the moisture-vapor transmission (or oxygen-transfer rate with the use of oxygen absorbers) through the bottle wall as illustrated in Figure 1; the adsorption

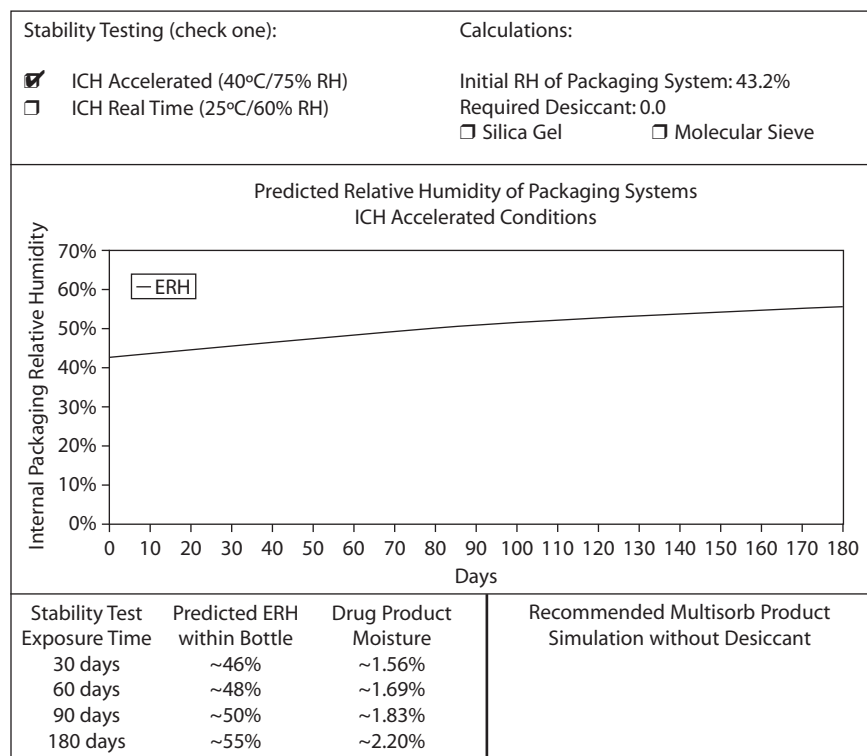


Figure 3. Simulation with no desiccant; initial drug product free moisture (LOD) = 1.40%.

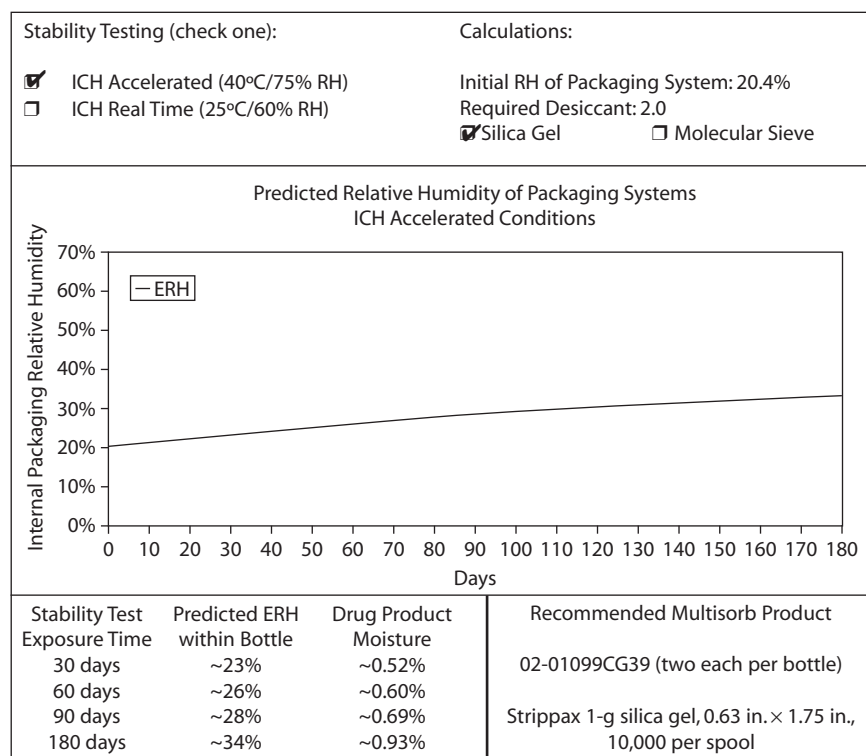


Figure 4. The modeling technique can indicate the type of desiccant to use.

humidity inside the headspace of the bottle.

For this reason, the simulation model has to calculate the required amount of desiccant to process moisture out of the drug in order to establish a protective envelope of relative humidity inside the bottle. It also has to compensate for the increased ingress of moisture—the permeation of moisture that results from the use of a desiccant itself.

Consider a scenario in which drug packaging is placed in a test chamber at 40°C and 75% relative humidity, and the bottle headspace conditions are at 40°C and 10% relative humidity. The differing humidity levels will create disequilibrium. Because the inside of the bottle wants to reach a point of equilibrium with the outside environment, it will essentially create a driving force for moisture to come into the bottle until equilibrium is achieved. Some drugs have some hygroscopic properties—they tend to absorb moisture from the

humidity in the air. Such drugs could contribute to added moisture ingress as well, although typically to a lesser degree than a sorbent. An extremely low ERH and related state of disequilibrium can be observed when molecular sieve desiccants are used.

A modeling strategy must not only measure the amount of desiccant needed to pull moisture away from the drug, but also compensate for the added ingress of moisture that builds up from the use of the desiccant in the first place.

With the example given above (Figure 4), permeation takes place relative to the adsorption properties of both the drug product and desiccant. As the products adsorb moisture, and the relative humidity comes up inside the bottle and begins to approach 75%, and the rate of permeation slows down. Carefully tracking this rate enables one to gauge the exact capacity that will be required from a desiccant. Additionally, the modeling

technique, as shown in Figure 3 can indicate the conditions of a specific drug product formulation if packaged without a desiccant.

REAPING THE BENEFITS

Pseudoempirical modeling and subsequent proof-of-concept stability testing offer valuable tools to formulation chemists and packaging engineers. The information and specifications resulting from such testing enable drug makers to customize moisture-management strategies to meet product needs. Stability tests also provide important evidence to regulators that pharmaceutical products will remain safe and effective throughout the supply chain. Stability testing is particularly valuable for commercializing today's complex drug formulations that are highly sensitive to moisture and oxygen and require careful preparation to stabilize the molecules for packaging and distribution.

Innovative modeling techniques bring precision and predictability to the process of choosing a desiccant and packaging solution. Registration stability testing can now be done on an accelerated time scale, speeding time to market. This, in turn, can help pharmaceutical manufacturers enhance product stability and ensure brand integrity.

Adrian Possumato is the global manager—pharmaceutical market for Multisorb Technologies Inc. (Buffalo, NY). He works closely with drug innovators and generic pharmaceutical manufacturers in R&D, quality, regulatory, engineering, and manufacturing departments to determine the best selection of packaged sorbents to stabilize pharmaceutical formulations. Multisorb Technologies has been an innovator in sorbent technology for more than 40 years. Founded in 1961 by John S. Cullen to protect products against the damaging effects of moisture, today Multisorb is North America's largest producer of packaged and fabricated sorbents and a world leader in active packaging components. ■