Packaging Selection: The FreeThink Technologies Process

Overview

Packaging plays a major role in many aspects of a product's overall cost, usability and quality. For some products, such as drug and medical products, packaging can play a crucial role in determining the product shelf-life. While packaging can sometimes be the source of product instability (e.g., with extractables and leachables), it is often able to protect the product from environmental factors and thereby increase its shelf-life. Traditionally, the role of packaging in setting a product shelf-life has involved labor- and time-intensive studies where products are packaged with candidate materials, and then analyzed over a period of many months. We at FreeThink Technologies have developed the science to enable packaging determinations with respect to product stability to be completed in a matter of weeks. We have broad expertise in product sensitivity to environmental factors, in analytical science to measure behavior of products, and in packaging engineering to know how specific packaging choices will impact product shelf-life. In addition, we are conscious of the cost implications for packaging selection and can recommend appropriate packaging that most cost effectively meets the critical stability needs of our customers.

Understanding the Environment Inside a Package

One consequence of packaging a product is its segregation from the external environment. The environment inside the package is what the product will actually experience, yet we define only the external environmental conditions. It is critical to understand how the external environment affects the internal environment of the package in order to determine the impact of the packaging on product shelf-life. The most important environmental factors that influence product stability are moisture, oxygen and light. Depending on the packaging materials and types, the internal environment will often change over the storage period as moisture and oxygen permeate through the packaging.

Internal Relative Humidity

The factor that is most often associated with product shelf-life is sensitivity to moisture. At FreeThink, we can quickly determine the sensitivity of a product to moisture in the form of the relative humidity (RH) that the product experiences. Determining the actual RH as a function of time inside a particular package is critical to establishing the stability of the product in that package. Fortunately, the science for this is well-developed, and can be modeled using FreeThink's commercial software package, ASAP*prime*®. The modeling requires several key pieces of data about the dosage and the package itself. The first piece of information needed is how moisture equilibrates as a function of RH. This is called the moisture sorption isotherm and will vary with the ingredients in the product.

FreeThink scientists determine moisture sorption isotherms using a Dynamic Vapor Sorption (DVS) apparatus. In many cases, the sorption isotherm can also be accurately calculated using FreeThink's database of excipient moisture sorption behavior. Figure 1 shows an example of a moisture sorption isotherm for a tablet product. The amount of water the tablet holds varies as a function of RH. For example, at 25% RH, the tablet holds 2.5% water while at 50% RH it holds 4.2% water. The water percent that a tablet can hold will not be dependent on time since tablet or capsule equilibration is fast compared to the product shelf-life. Typically, a tablet or capsule (even a film-coated tablet) will equilibrate within a few hours. Once the dosage form comes to equilibrium based on how much water it can hold at that RH, it will not pick up more water.

Case Study: Post-Approval Packaging Change
A company had been producing a relatively stable product for many years. They wanted to reduce packaging costs but did not want to do a complete stability program for product in the proposed new package configuration. An ASAP*prime*® study showed that the product's long-term behavior was well-modeled. The modeling also showed that there was very low risk of product failing with the proposed packaging. This change was approved by the US FDA without a new stability study (continued annual commitment).

The second key component of determining the internal RH as a function of time is the moisture permeability of the packaging. This can be expressed in terms of the moisture vapor transmission rate (MVTR) at a particular condition. The MVTR of a package varies with the packaging material, thickness, size, temperature and the RH at which the value is measured. We at FreeThink have generated a large database of packaging material MVTR values that allow most packaging to be accurately estimated. In addition, we can determine the MVTR of any specific packaging.

This is done using the actual package rather than on unformed sheets of material. This is important because the permeability to moisture of different materials will often be impacted by the forming process used.

Using the moisture sorption isotherm of the internal components as well as the packaging MVTR enables us to accurately calculate the RH as a function of time inside any package. For example, tablets having the moisture sorption isotherm shown in Figure 1 stored in the indicated bottle configuration will have an internal RH as a function of time that varies with tablet count and external storage conditions as shown in Figure 2. It should be noted that the tablet count impact is not very dependent on headspace but rather on the fact that each tablet can sorb a significant amount of moisture such that more tablets provide a better buffer to the rate of RH increase.

Case Study: Packaging for a Generic Product
A company that produces generic drug products had always defaulted to using the packaging of the originator product. A specific product was originally packaged in cold-form aluminum blisters. The generics company wanted to determine if the product stability would still be adequate with a less expensive thermoformed blister packaging. We conducted an ASAP*prime*® study simultaneously on both the generic and originator products. From the packaging modeling, we were able to show that a PVDC blister package provided adequate stability for the product.

Figure 1 Moisture sorption isotherm for a tablet

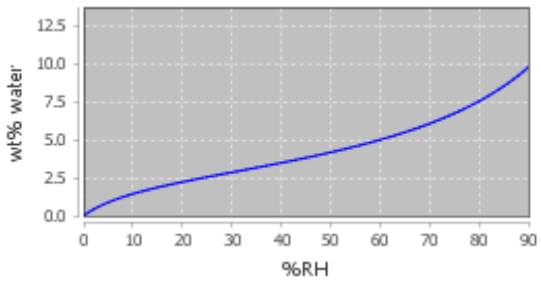
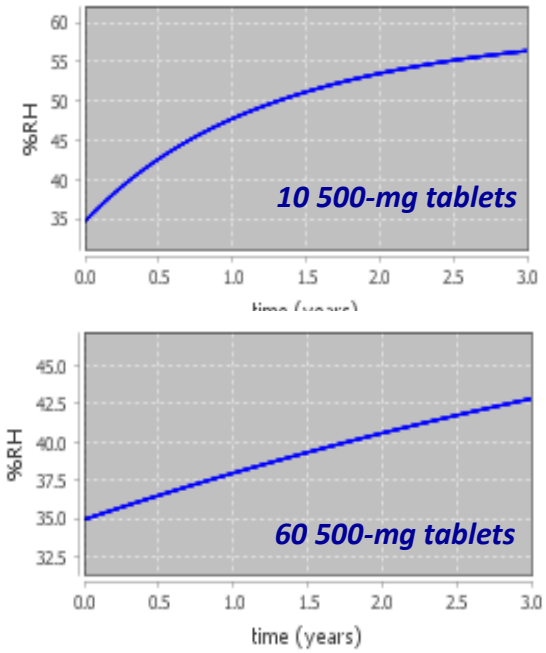


Figure 2 Internal relative humidity (% RH) as a function of storage time in a 120-cc HDPE bottle (heat induction sealed)



Internal Oxygen

Oxygen can be a critical factor in determining a product's stability. As the oxygen level decreases, oxidation rates will drop accordingly. We at FreeThink have extensive experience modeling which packaging option is best to control oxidation. The oxygen level inside a package will depend on a number of factors. The initial headspace oxygen level is an important factor. This can be reduced by flushing with an inert gas (nitrogen or argon); however, we have experience with the practical limitations of how much the oxygen level can be reduced in commercial processes.

Case Study: Blisters Global Supply

A consumer product company had a blister-packaged tablet product for which it wanted to optimize packaging costs. Working with FreeThink, the key factors in this determination were the number of different packaging options (SKUs) needed globally, the cost of the packaging materials, and the shelf-life itself (number of batches). We used ASAP*prime*® to build a stability model of the drug product from which we were able to work closely with the company to determine that the optimum was a blister material that was slightly more expensive than required for zone II (25°C/60% RH) to have a three-year shelf-life, but still gave a two-year shelf-life in zone IVb (30°C/75% RH), and enabled a single global SKU.

A liquid product will have some amount of oxygen dissolved in the liquid. This level can be reduced with degassing. The rate of oxygen transmission will be a function of the oxygen transmission rate (OTR) of the packaging. At FreeThink, we have developed unique capabilities to determine OTRs using formed packaging as a function of temperature and RH. Any oxidative degradation process occurring will consume oxygen. We can determine the oxygen consumption level as a function of temperature and RH.

Case Study: Oxidation of a Liquid

A pharmaceutical company came to FreeThink with a pediatric drug product formulated in an oil. The company wanted to avoid adding antioxidants but needed to maintain levels of peroxides below specification limits. They wanted FreeThink to determine the packaging needed to keep oxygen levels low enough to satisfy these peroxide requirements. FreeThink's scientists were able to determine that even with zero oxygen permeability and complete flushing of the headspace, there was enough oxygen dissolved in the oil to cause the product to exceed its specification limits. Because the manufacturer was unable to degas the oil, we recommended using an oxygen-permeable bottle placed in a foil blister containing an oxygen absorber. We specified the materials needed (including an improved oil) and helped the company to implement this option.

The presence of oxygen absorbers will have a significant impact on product stability when oxidation occurs. We also have extensive experience with all the commercial options for use of oxygen absorbers.

Light Transmission

At FreeThink we have the capability to measure the light transmission of different packaging options. Importantly, this transmission can be coupled with an understanding of the product's light sensitivity (action spectrum) to determine how best to protect a product from photodegradation. In some cases, protection from moisture or oxygen also provides stabilization against photodegradation.

Using ASAP*prime*® to Determine Product Stability

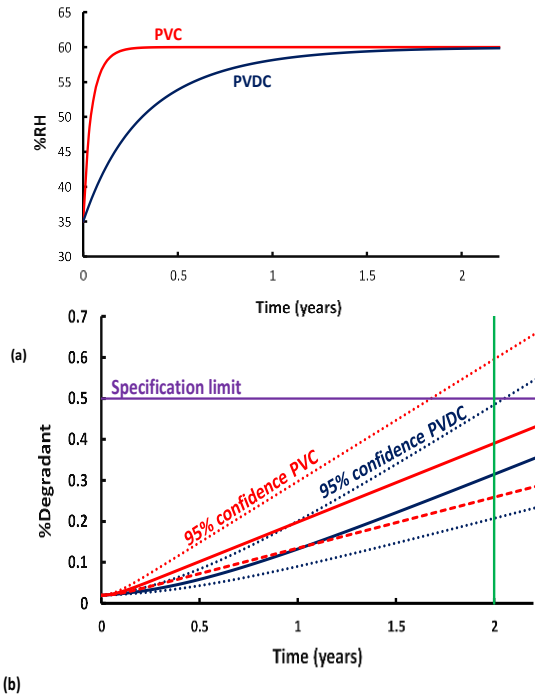
Traditional methods for determining product shelf-life use long test periods (typically months or even years) with **products protected in packaging** during the studies. FreeThink's Accelerated Stability Assessment Program (ASAP*prime*®) works very differently. The product, stored open to environmental factors, is subject to a wide range of temperature, RH and oxygen level conditions designed to highly accelerate the aging process. The degradation is measured for each sample and the data are modeled in the ASAP*prime*® software to provide shelf-life determinations in under six weeks.

Using ASAP*prime*® to Determine Packaging

Among the things that such a study determines is an explicit product sensitivity to temperature, RH and oxygen. These sensitivities can be translated into determinations of packaging requirements based on MVTR and OTR values. To couple the calculation of internal RH or oxygen level as a function of time with the measured sensitivities to these factors, we model a small unit of time where we first determine the internal RH and oxygen level. These levels of internal RH and oxygen are used to determine how much degradation will occur during the unit of time. This progresses in steps with another short time interval. From these steps, a continuous curve is built.

This allows us to determine how much degradation will occur as a function of time for each packaging configuration. In the example in Figure 3, a tablet product that has completed an ASAP*prime*® study is calculated to have the relative humidity as a function of time in two different thermoformed blister packages. In PVC (red curve), the RH rises quickly. In contrast, the product in PVDC blister packaging has a slower RH rise with time. The resulting curves show that the probabilities for still being below the specification limit at the end of a two-year shelf-life increase from 83% to 96% with the change in blister material (normally companies use a 95% probability of passing as a threshold for selecting packaging options).

Figure 3 In (a), the RH inside thermoform blister packaging for a tablet product are compared (storage at 25°C/60% RH). In (b), the resulting differences in degradant growth in the two packaging options are shown. In this case, the PVDC blister option provides a probability of passing over 95% while the PVC option does not.



Many companies work with FreeThink to determine the best packaging options for their product. Often this involves a balance between providing adequate stability at a reasonable price. Using our science helps companies to make better decisions faster.