Viewpoint

Is Accelerated Testing Reliable for Oxygen-Sensitive Drugs?

For drugs susceptible to oxidative degradation, pseudo-empirical modeling can often provide a better indication of long-term stability compared to ICH accelerated testing.

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Pharmaceutical companies undoubtedly all share a common and intense focus on drug stability. Each drug candidate will be evaluated at very early stages of the development process to determine its inherent stability and susceptibility to degradation caused by exposure to temperature, humidity, oxygen, and light.

Formal stability studies are required to ensure that a drug product will maintain its safety, quality, efficacy, and physical and chemical characteristics throughout a given timeframe, typically termed the expiry date or shelf life. Although "alternative approaches can be used when there are scientifically justifiable reasons," many companies refer to the International Conference on Harmonization (ICH) and FDA guidance document, Q1A(R2).[1]

"The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use."[1] Common storage conditions for nonrefrigerated, solid oral-dose products (e.g., tablets, capsules) in climatic zones I and II, include long-term studies (25°C ± 2°C/60% RH ± 5% RH), intermediate studies (30°C ± 2°C/65% RH ± 5% RH), and accelerated studies (40°C ± 2°C/75% RH ± 5% RH). For purposes of this document, the accelerated and long-term study conditions will be discussed.

Accelerated testing is designed to increase the rate of chemical degradation or physical change of a drug product by using exaggerated storage conditions. These studies can be used to support the long-term stability studies, sometimes referred to as real-time studies, which ultimately determine the drug product shelf life or expiry date in its commercial package.

The accelerated stability study data, typically conducted for 6 months, can be extrapolated to propose a real-time shelf life.[2] However, it is important to beware of a one-size-fits-all mentality. Typically, six months of acceptable accelerated testing data are needed as proof that this same system will pass the battery of stability tests for two years of long-term (expiry date) testing at 25°C/60% RH. Caution should especially be exercised when dealing with drug products with primary degradation pathways that are oxidative.

MOISTURE TRANSMISSION—REASONABLE COMPARISON

Relative humidity (RH) is defined as the partial vapor pressure of water in air divided by the saturated vapor pressure of water in air, p/p_0. The saturated vapor pressure is temperature dependant and is defined as the maximum amount of water vapor air can hold at said temperature. Therefore, for accelerated stability studies conducted at 40°C and 75% RH, there is a higher water vapor content than long-term studies conducted at 25°C and 60% RH. This fact, coupled with polymer changes that typically occur at higher temperatures, results in an increased rate of permeation.

Consider a standard, 75-cm³ round, high-density polyethylene (HDPE) bottle with a foil induction seal selected as the container closure system proposed for marketing of a drug product (e.g., solid oral-dose tablet or capsule). For demonstration purposes, assume there is enough desiccant (e.g., molecular sieve) within the bottle to maintain a 0% or near 0% equilibrium relative humidity (ERH) within the bottle. These conditions allow for a constant ΔRH between the external and internal conditions, 75% and 60% for accelerated and long-term stability conditions, respectively. Additionally, assume the bottle has an approximate surface area of 18.2 in.² and an average wall thickness of 30 mil.

The moisture vapor transmission rate (MVTR) for a typical HDPE resin, Marlex HHM 5502BN, is 0.381 g-mil/100 in.²/day and 0.085 g-mil/100 in.²/day at test conditions of 38°C/90% RH and 25°C/60% RH, respectively.[3] Since the MVTR for HDPE is fairly linear at constant temperature, the aforementioned MVTR at 38°C/90% RH can be adjusted to match ICH-recommended conditions of 75% RH as follows: 0.381 g-mil/100 in.²/day × (75/90) = 0.318 g-mil/100 in.²/day.
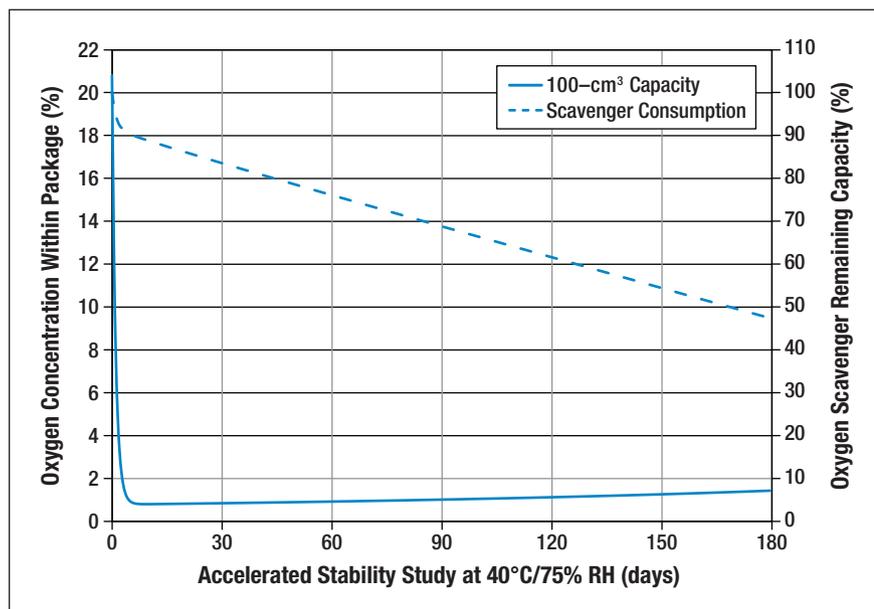
Figure 1. Accelerated stability simulation of a 75-cm³ bottle with drug product and SimulOx Oxygen Scavenger.

Using simple mathematics, the ingress can be calculated at accelerated and long-term conditions as expressed in the shaded box at the bottom right.

The total amount of moisture vapor ingress is relatively comparable at accelerated storage conditions for 180 days and long-term storage conditions for 730 days. If the drug product and sorbent weights, initial moisture contents, and sorption isotherms are known, a pseudo-empirical simulation can be generated to more closely model the moisture vapor ingress and equilibrium relative humidity conditions within the bottle over the duration of the testing periods.[4]

OXYGEN TRANSMISSION—A DECEPTIVE COMPARISON

Although hydrolytic reactions are among the most common processes for drug degradation, some pharmaceuticals are also subject to oxidation, either by reaction with molecular oxygen or reaction with other oxidizing agents present in the formulation.[5] Some oxidative degradation is moisture mediated, in which case a very aggressive desiccant can sometimes be used to mitigate the degradation reactions. However, in cases in which desiccants are not a viable solution for stabilizing oxygen-sensitive compounds, oxygen scavengers or specialty bottles (e.g., EVOH, multilayered) are considered as solutions.

With speed to market being crucial, it's clear that there is value in ICH accelerated stability testing. As previously mentioned, the increased temperature and RH will typically have some effect on the permeability of the drug package polymer. However, whereas overall moisture transmission is relatively comparable at accelerated and long-term storage conditions and durations due to changes in the polymer properties and total

moisture content in the air of the stability chamber, the oxygen concentration in the environment outside of the bottle is constant (~20.8%) at accelerated and long-term testing conditions. Although there are polymer changes that typically occur at elevated temperatures, which increase the oxygen permeability of the bottle, these changes do not compensate for the lack of a differential external oxygen concentration. Thus, for packages incorporating an oxygen scavenger, the headspace oxygen concentration after 180 days of accelerated testing is not necessarily equivalent to 730 days of long-term testing. This can result in a false sense of security and potential long-term stability failure.

Pseudo-empirical modeling is especially valuable to oxygen-sensitive drug products requiring oxygen scavengers. A good mathematical model will incorporate the oxygen transmission rate (OTR) of the polymer, the surface area and thickness of the package walls, the void volume within the package, and the absorption kinetics of the appropriately formulated oxygen scavenger. This model can then produce a complete picture of the internal oxygen environment of the package throughout the specified shelf life and can assist drug formulators and packaging engineers with evaluating the effects of the package selection.[6]

Consider the same bottle choice mentioned in the previous section. Assume the overflow volume for this bottle is 84 cm³ and is packaged with a drug product and a known quantity of appropriately formulated oxygen scavenger such that there is a total of 40% void volume. The oxygen transmission rate (OTR) for the HDPE resin is 111 cm³-mil/100 in.²/day-atmosphere and, based upon supporting data, 205 cm³-mil/100 in.²/day-atmosphere at test temperatures of 25°C and 40°C, respectively.[7] HDPE is a relatively hydrophobic polymer, and any moisture dissolving in the polymer itself is minimal. Therefore, varying humidity levels do not significantly affect the ingress of oxygen.

If an individual calculated the total amount of headspace oxygen at the time of packaging as well as the amount of oxygen

Accelerated: 40°C/75%RH:

$$\frac{0.318 \text{ g-mil} \times 18.2 \text{ in.}^2 \times 180 \text{ days}}{100 \text{ in.}^2 \times 30 \text{ mil.}} = 0.3473 \text{ grams}$$

Long-term: 25°C/60%RH:

$$\frac{0.085 \text{ g-mil} \times 18.2 \text{ in.}^2 \times 730 \text{ days}}{100 \text{ in.}^2 \times 30 \text{ mil.}} = 0.3764 \text{ grams}$$

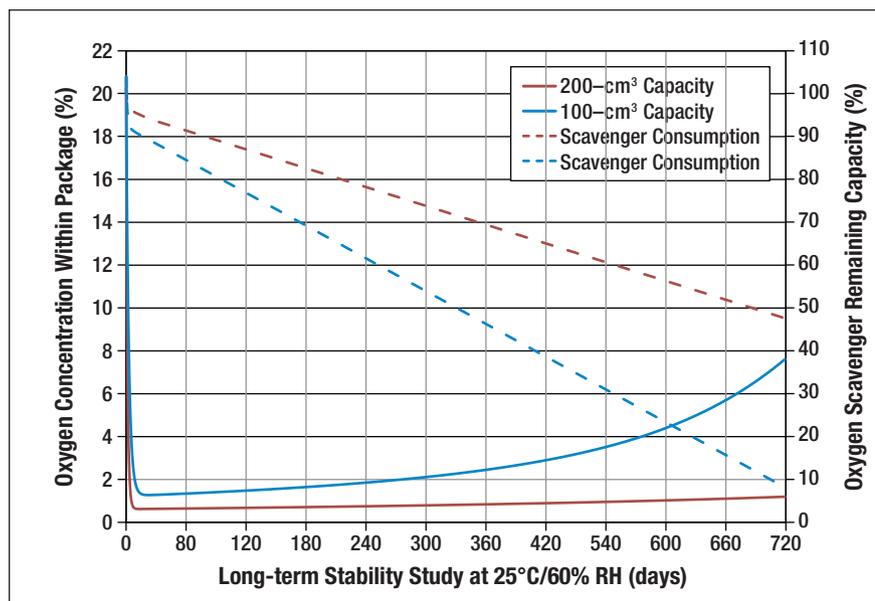**Moisture ingress into an HDPE bottle can be calculated at accelerated and long-term conditions using these equations.**

Figure 2. Long-term stability simulation of a 75-cm³ bottle with drug product and SimulOx Oxygen Scavenger.

oxygen when compared to standard high-density polyethylene bottles. These specialty bottles are typically more expensive than standard bottles and add another inventory item for pharmaceutical companies to manage. Also, unless a company decides to potentially invest capital for inert-gas flushing on their packaging lines, there will be oxygen present in the void volume of the bottle. An oxygen scavenger will most likely still be required to manage this oxygen and the ingress over time.

It has already been shown that an appropriate modeling program can be utilized to optimize the sorbent selection. The choice of a standard HDPE bottle with a larger amount of oxygen scavenger, or a specialty bottle with a reduced amount of oxygen scavenger, typically leads to a cost-benefit analysis—performance versus cost (materials, capital, and resources).

The unique properties and needs of each drug product in combination with the variety of active and static packaging options available in the market today point to the importance of an accurate modeling program to potentially save pharmaceutical companies great sums of time and money in getting their product to market successfully.

ingress over 180 days of exposure to accelerated stability conditions, they would most likely suggest using a scavenger with an approximate minimum capacity of 50 cm³ of oxygen, as shown below in the shaded box at center.

Accounting for a safety factor and exposure and handling of the scavenger, the simulated model of an oxygen scavenger with 100 cm³ of O_2 capacity is presented in Figure 1.

This same sorbent selection, 100-cm³ O_2 capacity oxygen scavenger, is simulated at long-term stability conditions. As can be seen in Figure 2, the resultant oxygen concentration within the bottle would be much higher than anticipated based upon the accelerated testing. In actuality, it would have been more prudent to use an oxygen scavenger with 200 cm³ of O_2 capacity to achieve a comparable oxygen concentration within the headspace of the bottle after 730 days of long-term testing.

$$(84 \text{ cm}^3 \times 0.40 \times 0.208) + \left(\frac{205 \text{ cm}^3\text{–mil} \times 18.2 \text{ in.}^2 \times 180 \text{ days}}{100 \text{ in.}^2 \times 30 \text{ mil.}} \times 0.208 \right) = 54 \text{ cm}^3 \text{ O}_2$$

Calculating the amount of residual oxygen in an HDPE bottle and the oxygen ingress into that bottle over 180 days could lead one to the use of a scavenger with a given oxygen capacity.

Figures 1 and 2 illustrate that insufficient sorbent quantity or packaging may be selected based upon 6 months of accelerated testing data. Selections based on simulations or models of 730 days storage (or other desired shelf life) at long-term stability conditions can result in more accurate packaging decisions and avoid the unpleasant surprise of drug product failure due to drug product degradation prior to the anticipated shelf life.

BOTTLE SELECTION FOR OXYGEN-SENSITIVE DRUG PRODUCTS

Specialty bottles (e.g., EVOH, multilayered) are sometimes considered because of their enhanced barrier properties to

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5. Modeling and simulations are intended as references and are not substitutes for empirical testing.

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