Blisters

Determining Drug Stability and Selecting Packaging

Using rapid forced degradation studies may allow you to predict the conditions under which products will fail and to select blister materials accordingly.

By Remco van Weeren, PhD, Senior Vice President, Marketing and Technology, Bilcare Inc., and Ajith Sashidharan PhD, Vice President, Global Research Services, Bilcare Ltd.

Medicinal products need protection from moisture, oxygen, light, and chemicals. In 1999, the International Conference on Harmonization (ICH) implemented guidelines that are now well established for the stability testing of new drug substances. The actual conditions used for the ICH guidelines were based on many years of development work using forced-degradation studies or stress testing. These guidelines have standardized stability testing and package determination. However, there are some limitations to current ICH testing. These guidelines were primarily developed for climatic zones I and II, and therefore they do not cover the requirements of other climatic zones.

Pharmaceutical customers often rely on ICH stability studies of the packed product as their only method to select packaging. Some, though, fail to select the optimum package, as the stability becomes only a confirmatory test for the selected packaging material.

Moreover, the stability study often does not lead to a quantitative understanding of why and when a tablet fails. In addition, there is little account for interactions between parameters.

Bilcare has worked for more than 10 years to develop a 30- to 45-day protocol that aids in quantifying the stability nature of drugs.

**FORCED DEGRADATION**

There are no detailed regulatory guidelines that describe how to carry out stress testing, as was recently mentioned in a book serving as a practical and scientific guide for the pharmaceutical scientist. As one of the authors highlights, stress testing is often used synonymously with accelerated testing. However, the two are distinctly different. The ICH defines accelerated testing as the following:

Studies designed to increase the rate of chemical degradation or physical change of an active substance or drug product using exaggerated storage conditions as part of the formal, definitive storage program. These data, in addition to long-term stability studies, may also be used to assess long-term chemical effects at nonaccelerated conditions and to evaluate the impact of short-term excursions outside label-storage conditions such as might occur during shipping.

Stress testing is defined as the following:

Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the

<table>
<thead>
<tr>
<th>Exposure conditions</th>
<th>Observed result</th>
<th>Notation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 25 °C and 75% RH</td>
<td>Nominal change</td>
<td>NA</td>
</tr>
<tr>
<td>2 25 °C and 90% RH</td>
<td>Severe change</td>
<td>Tablet breaks and becomes wet and sticky</td>
</tr>
<tr>
<td>3 40 °C and 75% RH</td>
<td>Severe change</td>
<td>Tablet breaks and becomes wet and sticky</td>
</tr>
<tr>
<td>4 40 °C and 90% RH</td>
<td>Severe change</td>
<td>Tablet breaks and becomes wet and sticky</td>
</tr>
</tbody>
</table>

Table I. Testing matrix from a case study describing visual observations after exposure.

Figure 1. Peak absorption rate of case-study products at various conditions, with temperatures shown in Celsius at left and relative humidities at right.
development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

From a regulatory perspective, stress testing or forced-degradation studies are a scientific tool to understand stability issues and are inherently predictive in nature. Accelerated testing, on the other hand, is purely focused on whether or not stability is maintained at a preset condition.

Bilcare has developed a testing protocol called Bilcare-Optima that helps users gain a detailed and precise understanding of the nature of their applications and failure modes. It is intended to identify the conditions under which the failure happens and to identify the moisture-, gas-, and light-barrier properties in the protective packaging.

Rather than evaluating the solid oral dose as part of a set of packaging materials, this protocol evaluates the actual dosage form in an open-dish environment. The dosage form is tested under a range of different conditions, aimed at determining the critical characteristics that determine the shelf life of the product. An evaluation of the test data, in conjunction with a blister cavity model, results in a recom-

Table II. Hygroscopicity grading (0 is lowest, 10 is highest).

<table>
<thead>
<tr>
<th>Exposure conditions</th>
<th>Average grading, 3 batches</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 °C and 75% RH</td>
</tr>
<tr>
<td>2</td>
<td>25 °C and 90% RH</td>
</tr>
<tr>
<td>3</td>
<td>40 °C and 75% RH</td>
</tr>
<tr>
<td>4</td>
<td>40 °C and 90% RH</td>
</tr>
</tbody>
</table>

Figure 2. Maximum moisture gains of case-study products at various conditions, with temperatures shown in Celsius at left and relative humidities at right.

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amendment for the best material specific to that dosage form.

Three batches of dosage forms are studied under various environmental conditions for a more precise understanding of the following:

- Hygroscopic tendency.
- Dehydration tendency (if needed).
- Degradation tendency (physical and chemical).
- Effect on drug release properties.
- Effect on hardness.
- Photosensitivity as a function of RH and temperature.
- Gas liberation tendency.
- Dimensional aspects.

After evaluating these properties, an exact determination is made as to which oral-dose characteristic is the most sensitive to the environment. Based on that determination, the blister configuration for the solid oral dose is modeled, and the maximum amount of moisture transmission is determined, resulting in the appropriate material selection. Because all polymers thin upon thermoforming, a critical understanding of the thinning characteristics of the various polymers in relation to the

**Figure 3.** Moisture absorption capacity of case-study products at various conditions, with temperatures shown in Celsius at left and relative humidities at right.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Moisture Threshold Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Real time mild climatic condition</td>
<td>3.30</td>
</tr>
<tr>
<td>2 Real time tropical condition</td>
<td>4.36</td>
</tr>
<tr>
<td>3 ICH accelerated condition</td>
<td>3.78</td>
</tr>
<tr>
<td>4 Tropical accelerated condition</td>
<td>3.44</td>
</tr>
</tbody>
</table>

Table III. The moisture threshold value that is used to determine the packaging material.

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cavity design through a software package using cavity-forming parameters is critical to optimize the barrier properties of the blister structure for the specific application.

Based upon the test data and the blister cavity design work, a recommendation is made regarding the appropriate moisture-vapor transmission rate (MVTR) and packaging material.

**CASE STUDY**

A customer approached us with a specific packaging problem. One of its current applications was on the market in a foil strip pack. There was a desire to move to a transparent blister pack, but all earlier stability trials had failed.

The product was studied under the BilcareOptima process to identify the critical parameters and to be able to convert the product to a blister pack with certain additional requirements. Certain important findings from the study are correlated to find the barrier requirements for the product.

When the testing was initially performed under four conditions, the resultant visual observations give enough clues for the product's sensitivity towards moisture. The results are in Table I.

One of the most important observations detailed in Table I is that the product’s physical degradation is as severe under the low-temperature, high-humidity condition as it is under the accelerated conditions. This low-temperature, high-humidity condition is a realistic condition for most tropical areas and was heretofore not evaluated. Normally, moisture sensitivity of the product is defined based on moisture and absorption isotherms and equilibrium moisture content (EMC).

However, it has been our experience that measuring the hygroscopic tendencies of the product cannot be complete using only the EMC. Absorption rate as well as absorption capacity play important roles, especially when a product is packaged in semipermeable packaging like a blister pack. In real-world packaged conditions, most products within their shelf-life period do not approach the EMC. The absorption rate thus becomes an important parameter that defines the moisture absorption in the packaged condition. Peak absorption rate (PAR) as well as the maximum absorption capacity (MAC) are dependent on the exposure condition, and in many cases show different behavior than the EMC given the presence of a secondary phenomena, such as desorption. Figures 1, 2, and 3 show the results for the EMC, MAC, and PAR, clearly indicating in the results of the PAR and EMC that the maxima are happening at
the lower-temperature conditions. A striking observation is that under the standard accelerated conditions (40°C and 75% RH), the product does not exhibit the full severity of the product’s moisture sensitivity. Hence, even if the product exhibits stability at standard accelerated conditions, it could degrade beyond acceptable limits under realistic conditions prevailing in tropical areas.

Based on the overall hygroscopic nature of the product, we have developed a grading scale that allows us to rank different products as a function of their hygroscopicity on an absolute scale. It is shown in Table II.

One of the key physical characteristics to study in this case is the hardness variation as a function of the exposure conditions. The hardness requirement of the tablet for a strip pack (or even a bottle) is very different for a blister pack. The push-through force can break the tablet if the tablet has become too weak. We have developed a testing apparatus to understand the hardness requirement for push-through of a solid oral dose and use the required force as a key characteristic during testing. Figure 4 shows the drastic drop in hardness during exposure at all conditions.

A similar approach is used to study and quantify the sensitivity of the product with respect to other parameters like chemical stability, drug release pattern, dehydration effect, photosensitivity, gas liberation tendency, and various other environmental parameters. The study shows that the moisture had very little effect on the chemical assay, drug release

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pattern, or gas liberation, nor were there any photosensitivity effects for this product. Based on these results, it was concluded that physical degradation is the critical parameter for this product and that the influencing environmental parameter was humidity.

A further detailed study was conducted to estimate the moisture threshold values at various storage conditions and the package barrier properties needed to ensure the moisture level stays below a critical moisture threshold value to ensure that parameter does not fail. Table III shows the moisture threshold value (MTV) that is used to determine the packaging material. Recommendations for the optimum packaging material were made based on these MTVs and a design model of the blister cavity evaluating the expected thinning of the packaging material as a function of the blister size, shape, and design, using a simulation mathematical model. Table IV shows the recommendations as a function of the exposure condition. These data give a clear picture why earlier stability studies failed. The packaging material selected earlier was not able to give the required barrier, especially in the real-time conditions.

From this study, it became clear that even if the product passes accelerated stability studies, it may not pass real-time studies. It was evident that the product needed to be packaged in PVC/Aclar or alu/alu to give the required stability for the stipulated period. However, there was a strong desire to minimize the packaging costs. A suitable alternative was selected to satisfy cost and stability requirements: Bilcare’s aluminum-coated, PVC-based material, Ultra, with a flat film WVTR of 0.18, was selected as the primary packaging material. Because the actual barrier requirements are higher than 0.18 for long-term stability, a secondary pack of an aluminum composite, which provides a complete barrier to moisture, was selected to give the required protection for the period of shipping, transit, and storage, exposing the primary pack for a limited period only.

Table IV. The case-study recommendations as a function of the exposure condition.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Moisture Threshold Value (%)</th>
<th>Time period</th>
<th>Max. WVTR of package (g/day)</th>
<th>Flat Film WVTR (g/m²/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Real-time mild climatic condition</td>
<td>3.30</td>
<td>24 months</td>
<td>0.00007</td>
<td>0.11</td>
</tr>
<tr>
<td>2 Real-time tropical condition</td>
<td>4.36</td>
<td>12 months</td>
<td>0.000025</td>
<td>0.04</td>
</tr>
<tr>
<td>3 ICH accelerated condition</td>
<td>3.78</td>
<td>6 months</td>
<td>0.00016</td>
<td>0.26</td>
</tr>
<tr>
<td>4 Tropical accelerated condition</td>
<td>3.44</td>
<td>3 months</td>
<td>0.0008</td>
<td>0.11</td>
</tr>
</tbody>
</table>
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21st Century Solutions

Chuck Reed

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Weiler has enjoyed more than 30 years in its leadership position, serving the marketplace with the latest in advanced, sterile, aseptic liquid packaging technology. Approximately 100 people are involved in the design and construction of these machines, providing 21st Century Solutions packaging for parenterals, ophthalmics, respiratory drugs, biologicals, nutraceuticals, and other complex solutions.

Weiler began manufacturing BFS machines under the Bottlepack brand, continued with the ALP trademark, and is now building the latest generation of ASEP-TECH blow–fill–seal systems. The Weiler design incorporates the three-step process of blow molding, aseptic filling, and hermetic sealing of liquid products in one sequential operation on a compact machine frame.

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