Honeywell Aclar® Films

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Avoid Delays from Failed Stabilities due to Package Integrity - How to Ensure Your Blister Package Passes Stability

Honeywell

Abstract

Pharmaceutical companies all share the same goal: Delivering safe and effective drugs to patients. One aspect of achieving this objective is conducting stability studies that demonstrate to regulatory organizations that a drug's formulation is safe and effective. Stability studies are conducted on each drug and its package to assure that the drug will meet this goal for the shelf life indicated. Too often, pharmaceutical companies focus on stability studies with minimal consideration for package performance, not realizing that a stability test failure may have nothing to do with the drug itself, rather the failure can be attributed to its packaging.

To avoid stability failure and gain understanding of the sensitivity of your dosage, the performance of the drug's package should be studied at the same time the performance of the drug itself is being evaluated. Package integrity can be determined very early in the stability test's timeline. In doing so, a potential cause for failure can be identified and corrected, allowing Pharma to prevent delays in the launch process due to package failures. This ensures that the drug's packaging is performing as intended and will pass stability.

This white paper covers three guiding principles relevant to barrier films that pharmaceutical companies can employ to reduce the risk of failure, understand the barrier required to pass stability, avoid over-packaging and potential delay.

Is Your Package Design Suitable?

To optimize the barrier of the blister, pharmaceutical engineers should prepare and plan upfront, taking into consideration the drug's sensitivity, the choice of materials available, and the type of machinery available. Not all machines are capable of processing every material optimally – especially barrier materials – so be sure to discuss compatibility of machines and materials with your machinery and material suppliers respectively.

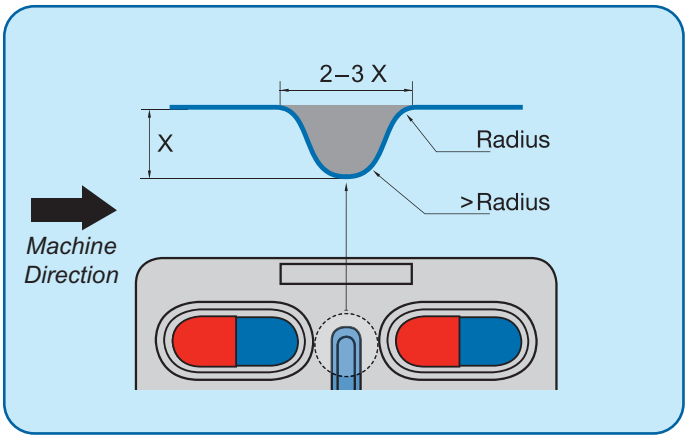
The packaging engineer should also pay close attention to package design and tooling. A successful package design and subsequent tooling design can improve barrier performance dramatically. Shown next are several guidelines for successful tooling design:

- For maximum flexibility, all thermoforming molds should be designed as dedicated molds with features recommended for high-barrier materials. Dedicated molds provide more uniform thickness distribution than universal molds which result in improved barrier performance.
- Use a dedicated cavity dimension for each pill size and pill shape. When standard cavities are used for multiple sizes or shapes, the large cavity design will increase the surface area of the cavity which in turn increases moisture permeation of the cavity when packaging smaller pills.
- Calculate the theoretical barrier of the package. (See additional information on barrier prediction methods in the "Weight Gain Test" section).

To optimize package permeation rates, packaging engineers should also consider the following design recommendations:

- Cavity dimensions must allow for proper clearance between the dosage and the lid stock to enable efficient product feeding and proper sealing of the lid stock to the blister.

- For cavities deeper than 6 mm or with a deep draw ratio greater than 3:1, pre-forming with plug assist is recommended.
- Design reinforcing or strengthening ribs perpendicular to the machine direction. The ribs should have a width-to-depth ratio between 2:1 and 3:1 to avoid under-forming. Sufficient air evacuation ports must be included in the rib design to achieve full forming.



Is Your Thermoform Process Correct?

The next consideration is establishing the thermoforming conditions. This ensures that the package achieves the expected barrier performance and is not vulnerable to compromise. Following are some thermoforming and sealing guidelines to assure a high-quality blister:

- Use the proper forming temperature for your material. Forming temperatures vary with material type, thickness and manufacturer, thermoformer, speed, timing and mold temperature. For additional information on proper Aclar® laminate forming, Honeywell developed the "*Aclar® Films Thermoforming Guideline*" for your reference.
- To achieve fully formed blister cavities, avoid cooling the laminate before forming and ensure you have sufficient force to form the parts. For cavities deeper than 6mm or with a deep draw ratio greater than 3:1, use plug assist in combination with air pressure to improve thickness distribution and barrier performance.
- Different lid stocks require different sealing conditions. For example, when the lid stock is sealed to the Aclar side of a laminate, companies must use proper lid stock seal lacquers designed for this purpose. If you seal against the PVC side of the laminate, use standard PVC films sealing station set-up.

Good sealing is a critical aspect in attaining package integrity. Consult with your lid stock supplier for sealing recommendations as sealing conditions will vary with pack layout, foil type and manufacturer, line speed and machine type. The selection of sealant is dependent upon the polymer that is in contact with the foil coating. If the contact layer is consistent, no change in conditions is required. For example, PVC mono film, PVdC coated PVC and Aclar film laminated to PVC can be sealed using the same foil and conditions providing the foil is sealed to the PVC side in all cases.

Are Your Testing Methods Sufficient?

In addition to using the correct design and thermoforming techniques, pharmaceutical companies must examine their blister packages in a variety of ways to ensure that the performance of the package matches the theoretical barrier expectations.

Leak Detection Test

One of the most common methods used to test blister packages for leakage is the methylene blue test. The package is placed into a vacuum chamber that is partially filled with a mixture of water and methylene blue dye. The packages are submerged in the liquid and held in place while a vacuum is drawn on the chamber. The package is held at a specified vacuum level for a specified time period. The chamber is vented to atmospheric pressure and each card is inspected to determine if there is evidence of blue dye in the cavities and/or seal areas. One limitation of this method is that the actual samples tested cannot be used for subsequent weight gain testing. A statistical sampling is used to verify that the process is producing acceptable blister cards.

There are also new testing techniques based on over-pressurizing or under-pressurizing the blister cavity that do not use methylene blue dye. They too can reveal whether or not your blister package has open channels. These methods are non-destructive and can be used to inspect 100 percent of the samples to be evaluated in the stability test.

If no leaks or open channels are found during leak detection testing, be advised that micro channels or stress cracks in the lid stock may be present which go undetected. As a result, additional tests are needed to verify seal integrity as well as ensure proper thickness distribution of the film.

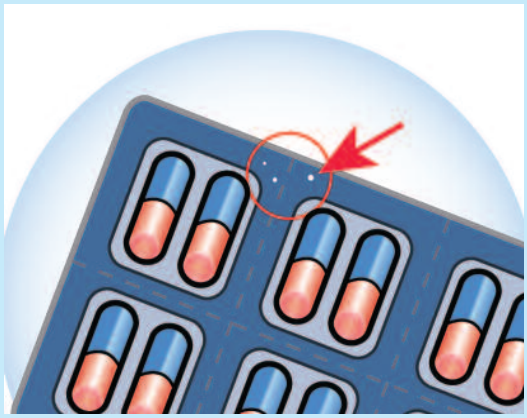
Polarized Film Sheet

Polarized Film Test

This test examines the blister for stress in the sealing flange area. The blister must be made of transparent film and be backed with a reflective background, such as foil lid stock or a second piece of polarized film. Hold the blister card under the polarized film at a 45 degree angle to the film. If there is stress in the sealed area, there will be a color differential. If there is stress in the formed blister cavity, for Aclar laminates, the color will change from brown to blue and then to more brilliant colors as the stress increases. For PVdC materials, shades of gray will indicate stress.

High Intensity Light Test

This simple test will check for cracks in the foil and should be done every time you run a stability test. Take the sealed blister card to a dark room and shine a flashlight through one side of the card. Look for any light coming through the foil and plastic. If blister packages are made out of opaque film that prevents light from penetrating the blister card, run a few packages with clear material and conduct the test to ensure there are no pinholes in the seal.



High Intensity Light Test

Magna-Mike® Test[1]

This test measures the thickness distribution of the blister cavity. The Magna-Mike is a handheld thickness gauge that uses magnetism to perform reliable and repeatable measurements. These measurements are performed by holding the gauge's magnetic probe to one surface of the test material and placing a small steel target ball on the opposite surface. A Hall-effect sensor built into the probe measures the distance between the probe tip and target ball. Due to the nature of this test, only certain points of the blister can be measured, rather than the entire blister cavity.

Microtome Test

This is another test to measure thickness distribution. A laser microtome is used to cut an epoxy mold of the blister cavity for microscopic examination. The test is more time-consuming and expensive than the Magna-Mike and is not appropriate for machine setup or trial. The test measures a continual line around the parameter of the cavity and assumes that if the cavity is round, it will have the same thickness distribution throughout. For capsules, two cuts are required: one running lengthwise and one running the width of the cavity. Although this test will not measure the thickness distribution of the entire blister cavity, it does measure more points than the Magna-Mike test, thereby giving the packaging engineer a greater understanding of the blister's barrier thickness.

Weight Gain Test

The single most important test for a blister pack is the weight gain test with desiccant. This test, which takes approximately 40 days, is similar to USP <671>, a test that gauges the moisture permeability for multiple unit containers used for capsules and tablets. By conducting weight gain testing on packages filled with desiccant, the permeation of the package can be studied independently from the drug dosage. A summary for the procedure follows.

- First, the sample size must be statistically significant. Typically, six to 10 blister cards with desiccants in each card is sufficient for each International Committee for Harmonization (ICH) condition. (The ICH has set up four conditions for stability studies: 40°C/75% RH; 30°C/65% RH; 30°C/75% RH; and 25°C/60% RH).
- Each blister pack is placed into a properly marked package holder and weighed to determine its initial weight (day zero). Next, the samples are placed into the humidity chamber with the desirable ICH conditions.
- Samples should be weighed preferably every day for 10 days (at least every other day). More frequent weighing early in the study allows for more rapid assessment of the performance of the cards under test. After 10 days, the test frequency can be reduced to one weighing per week.
- The first 10 days are important when measuring low barrier materials such 40g PVdC at high ICH conditions as desiccant tablets will become saturated quickly and plotted data will not be linear.

- Weight gain results are reported as weight gain (WG_{dayX}) in g/package and plotted on a graph. When interpreting the results, the packaging engineer should check the graph for linearity. Nonlinearity may indicate a problem with the samples, saturated desiccant tablets or the data collection method. Similarly, packaging engineers should also check the variation between samples to determine whether or not their design, package, and process are robust.

Assuming the weight gain results are linear, the next step is to use this data to calculate the moisture permeation rate per day for each cavity. These weight gain results are then compared to the theoretical results determined during the design phase using a barrier prediction method such as Finite Element Analysis (FEA).

In addition to FEA, Honeywell has also developed a simple method to calculate the expected barrier for a given cavity when Aclar/PVC laminate is the material of choice. Because the model doesn't take into account any layers in the laminate except the Aclar film, the model works well only when the Aclar is laminated to PVC as PVC does not provide any barrier properties to the overall structure. This simple method calculates the thickness distribution in the formed cavity and provides a prediction for the WVTR. For more information on this method of theoretical barrier prediction, contact Honeywell at **www.aclar.com**.

The results of the weight gain test compared to the theoretical barrier prediction method used should not show a difference greater than 10 to 20%. If the final numbers are within this percentage, the packaging engineer will have documentation that his package successfully passed stability at the end of the 40-day weight gain study. If the comparison results are greater than 20%, the packaging engineer can stop the stability study early recognizing that the package has failed. The weight gain test provides the information needed to determine what packaging changes are required and a new stability test can begin, thereby saving costs and avoiding potential lengthy launch delays.

If after several months, the stability test is not producing favorable or as expected results, the packaging engineer will have enough information to determine that the package is not the reason for failure and alternate causes should be investigated.

Furthermore, the weight gain test provides a wealth of information that has significant benefits for research and development. To help determine the best barrier protection for a drug, the packaging engineer can reference the catalog of weight gain data for different cavity shapes and materials and gain an understanding of design limitations or the forming process. The test is also beneficial for package transfer activities, such as site transfers, because it allows the company to evaluate the other site's standards and compare them to its own standards. This helps to ensure consistency of packaging performance across packaging sites.

Conclusion

The three principles: Suitable design, correct thermoforming, and sufficient examination will produce quality blister packages which will perform as predicted. While the stability study with the dosage focuses on testing the drug for efficacy and safety, the weight gain test with desiccant separates the performance of the drug from the performance of the package by testing the package directly without the drug's influence.

Combining this information assists in identifying issues with package integrity rapidly, and helps the pharmaceutical industry bring drugs to market without delays attributed to packaging.

About the Author

Ms. Zuzana Sabova-Kepic is the manager of Honeywell's Barrier Packaging Analytic Lab in Morristown, N.J., and is the lead technical specialist for Honeywell's Health Care and Packaging business.

Zuzana provides technical support for Honeywell Aclar films, working with pharmaceutical companies on packaging design, pre-stability and registration stability studies, and new product launches. She helped develop Honeywell modeling systems for barrier calculations, weight gain analysis and value calculators.

Zuzana holds a bachelor's degree in chemical engineering and a master's degree in analytical and physical chemistry from Slovak Technical University in Bratislava, Slovakia. She is a Six Sigma Black Belt and has participated in the leadership program developed by the Society for Women Engineers, as well as Smith College's executive education program, "From Specialist to Strategist: Business Excellence for Women in Science, Technology and Engineering."

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1. Magna-Mike® is a registered trademark of Olympus Corporation

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