Leak-testing blister packages: The limitations of the blue dye method

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Blister packages are a convenient format for consumers and a practical approach to preserving the quality of tablets and capsules. Most blister package applications are considered low risk, and do a very good job of protecting drug products from the ingress of moisture, which may lead to product degradation. Tablets of a hydrophilic nature—a tendency to absorb moisture—are especially in need of such protection.

New medicines require new tests

In recent years, however, concerns about the integrity of blister packaging have increased as the number of hormone-based and steroidal treatments has grown. Packaging these and other classes of drug products is considered a high-risk application given their potential to deteriorate and affect treatment results. To counter that, manufacturers typically opt for a fully aluminum, cold-formed package, which provides the best protection against the ingress of oxygen, although some companies have packaged highly sensitive steroidal treatments in thermoformed blister packaging. Whatever the packaging used in this high-risk application, it’s very important that you check for microscopic leaks, as these products are more sensitive to environmental conditions than most other tablets and capsules.

The amount of environmental contamination (moisture) that can enter a blister package and degrade its contents usually depends on the size of the leak. With blister packaging, even tiny leaks can be a problem. Given the relatively little headspace—about 0.25 cubic centimeters—in most blister cavities, oxygen and moisture can reach critical levels within hours. For example, a foil defect equivalent to a 10-micron pinhole can allow a flow rate of 0.84 cubic centimeters per minute. Depending on the pressure, temperature, and duration of exposure, it doesn’t take long for contaminants to find a path through a channel leak in the seal and/or through a series of many microscopic flex cracks.

Several methods are available to leak-test blister packs, and each has its advantages and drawbacks. The ideal method is simple, reliable, and line-ready. Unfortunately, the most common method remains the blue dye test, which has been in use for decades. I call it unfortunate because a dye may fail to identify tiny leaks in packages of critical products, a fact recognized by the US Pharmacopeia, which revamped USP General Chapter <1207>: Container Closure Integrity Testing [1]. The chapter now encourages manufacturers to use tests that are more quantitative and reliable, which reflects the need to address the requirements of today’s higher-risk products, as well as the availability of better technologies.

Subjectivity and variability mar results

To conduct the blue dye test, one or more blister packs is submerged in a chamber containing the blue liquid and a vacuum is drawn. The chamber is then brought back to atmospheric pressure, and the packages are retrieved and inspected to see whether any dye has entered them. If no dye is present in the blister package, no defect is detected.

The method’s major fault is its reliance, in most cases, on a timer during the vacuum phase, even though the blue dye only enters the package after the vacuum phase. Thus, when operators return the chamber to atmospheric pressure, nothing restrains them from immediately removing the packages from the dye during this critical final stage.

The blue dye test is also subject to other variables that are not easy to control, including package headspace and dye surfactant concentration. In fact, the test really only tells you how easily or rapidly the dye can enter the blister cavity. It gives you no information about the ingress of oxygen or vapor. That’s a major drawback because these gaseous contaminants can penetrate foil and film through a small leak or a series of micron-scale leaks more easily than the liquid dye, which is subject to surface tension and requires a relatively large single passage to enter the package. The subjective nature of the operator’s inspection is another major disadvantage and difficult to monitor. Although a comprehensive standard operating procedure, coupled with training, can mitigate subjectivity, there is no way to eliminate it.

Furthermore, most dye-based leak tests are validated by using a needle to prick a hole, and most test apparatuses
are not validated to detect leaks smaller than 50 microns and, as noted above, an even smaller leak can have a big impact on the package contents. How big an impact and how fast it occurs depend on how sensitive the active ingredient(s) is/are to ambient conditions. Once you determine that, scrutinize your test method's reliability and validate it according to leak size. If you find that ambient moisture and oxygen conditions don't affect the tablet or capsule, maybe the blue dye method is appropriate, at least for that application.

**Seek better methods**

Fortunately, superior technologies are available, including nondestructive methods such as volumetric imaging under vacuum [2]. With this method, you enter the number of blister cavities, place the blister package on the inspection plate, and press "Start." In less than 15 seconds, the equipment passes or fails the package and identifies the defective cavity (photo). It finds defects as small as 10 microns and requires no tools or changes to test parameters.

With any inspection method or protocol, the reliability of the test results is key. If the results aren't reliable, it's not really a test method. As drug products become more sensitive to environmental conditions, it's important to be vigilant and to re-evaluate your test methodology for its ability to provide reliable detection of critical defects.

**References**

1. The revised standards took effect in August 2016. See the first supplement to USP 39-NF 34, US Pharmacopeia, Rockville, MD.

2. VeriPac UBV from PTI, Tuckahoe, NY.

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