Deconstructing The Blue Dye Leak Test Method

Answering the right questions and challenging the effectiveness of the method may actually improve detection capability and resolve quality issues many are experiencing today.

Blistex packaging manufacturing for tablets and capsules has process and material parameters that are unique to each product. Barrier properties of blister packaging are primarily designed to eliminate moisture ingress, a result of $H_2O$ molecules passing through micro leaks over extended periods of time.

Moisture ingress into blister packaging is best measured and evaluated by conducting a desiccant weight gain study. Past desiccant weight gain studies have shown that significant moisture ingress begins to occur with pin hole defects of 15μm and greater. However, results vary based on a variety of package, product, and environmental variables, including:

- Differences in pressure from inside the package cavity to the outside;
- Differences in relative humidity from inside the package cavity to the outside;
- Air temperature;
- Defect dimensions and characteristics;
- Package cavity dimensions and head space;
- Hydrophilic properties of tablet/capsules.

The dye ingress leak test is currently the most common method for leak testing blister packaging. It has variable leak testing capabilities depending on package characteristics, and is one of the most misunderstood and misused leak tests in the industry. A variety of factors impact the effectiveness of the dye ingress leak test, including:

- Package characteristics;
- Surfactant concentration;
- Vacuum level;
- Vacuum dwell time;
- Ambient pressure dwell time.

To determine if the dye ingress method can be successfully deployed for a certain package, a simple four-step procedure can be followed using a few measurements and basic gas laws ($P_1V_1=P_2V_2$). This article aims to codify the blue dye leak test, deconstructing common assumptions and misconceptions of one of the most widely used and highly subjective methods in the market.

In tablet and capsule manufacturing, why has the blue dye test traditionally been the go-to method? It is perceived as simple, relatively effective, and has low capital cost. Despite its wide acceptance, this method is often applied under circumstances in which the package or the test variables render the method ineffective for many package formats with certain attributes.

In its most common form, a package is placed in a bath of methylene blue dye within a test chamber and a set vacuum is drawn on the package, which we will call Phase 1. During Phase 1, the method attempts to draw air out of the package cavity. Following Phase 1, the vacuum is released from the test chamber and Phase 2 begins. If the package cavity leaks air during Phase 1, the package cavity will have a negative pressure, drawing blue dye inside the package cavity. After this stage of the test, the lab operator must inspect the package for any blue dye ingress. The test has three main test inputs: the test vacuum level (Phase 1), the dwell time at the test vacuum level (Phase 1), and the dwell time at atmospheric pressure (Phase 2).

We can begin by making a very broad sweeping and potentially controversial statement. The blue dye ingress test as described above is ineffective in testing flexible packaging. A flexible bag will expand...
in Phase 1, contract in Phase 2, and the constant compensation by the package during the test cycle generates little driver to force blue dye through leaks. Perhaps blue dye can leak through a 500 micrometer pinhole, but testing flexible packaging using this method will not reliably detect critical leaks in flexible pharmaceutical packages.

This leaves rigid and semi-rigid packaging, most notably the tablet and capsule blister pack. Determining if the blue dye method will be effective for a blister package format can be boiled down to four steps. Going through these steps with one of your blister package formats with low head space is highly recommended. You may discover something about your current method, and you may be able to implement simple adjustments to improve the effectiveness of your blue dye leak test method. More on these adjustments later. Open up an Excel spreadsheet to work your way through the calculation. This exercise will be using metric measurements in centimeter, milliliter, and millibar.

The Four-Step Approach To Determine Blue Dye Ingress Capability:

**Step One**
*Measure the head space within the package cavity (with tablet or capsule inside).*

Use a syringe that provides fill measurement accuracy down to 0.01mL. Fill the syringe with water to a fixed volume (ex. 2mL). Puncture a small air vent (0.5mm) on one end of the blister pack’s foil lidding, then inject the water through the foil lidding on other end of the cavity until there is no more air inside the blister cavity. Subtract the ending volume in the syringe from the starting volume to produce the first piece of critical data, head space volume ($V_1$). For example, the beginning volume of water in the syringe was 2mL, and the ending volume is 1.9mL. The cavity head space volume is 0.1mL.

**Step Two**
*Determine the blister package maximum expansion volume.*

This step aims to measure how much the blister package will expand under vacuum, and is probably the most difficult aspect to measure. For this step we will estimate the height that the blister package lidding will deflect outward. Measure the surface area of the lidding covering the cavity. Multiply this surface area by the lidding height deflection to calculate the added volume of the expanded blister cavity.

**For example:**
Circular cavity with a diameter of 0.8cm and a deflection of 0.3cm:

\[
circle surface area: (0.8/2)^2 \times 3.141 = 0.5cm^2
\]
\[
exansion volume: 0.5cm^2 \times 0.3cm = 0.15cm^3
\]

Add the expansion volume to the head space volume from step one to get the blister package head space at maximum expansion ($V_2$):

\[
0.15cm^3 + 0.1cm^3 = 0.25cm^3
\]

**Step Three**
*Calculate at what pressure the blister package will reach maximum expansion under vacuum.*

Using inert gas laws, one can calculate at what pressure the blister package cavity will reach maximum expansion. For the purpose of this study, convert all of your measurements to metric values (millibar and milliliter).
Using the law $P_1V_1 = P_2V_2$:

$P_1$ atmospheric pressure at which the cavity volume was measured; typically 1000mb, but check your local weather station.

$V_1$ head space volume (step one)

$V_2$ head space at maximum expansion (step two)

$P_2$ the unknown variable

$P_1V_1 = P_2V_2$  \((0.1 \times 1000)/0.25 = 400mb\)

$$(P_1V_1)/V_2 = P_2 \quad P_2 = 400mb$$

$P_2$ is the internal pressure inside the blister package during Phase 1 of the blue dye ingress leak test.

**Step Four**

**What is the difference in pressure from the inside of the blister package to the outside under test vacuum conditions?**

The USP blue dye ingress leak test calls for a test vacuum level of 22 in Hg. Converted into millibar, the test vacuum is 250mb of pressure. Determine the $\Delta P$, which is the internal pressure from step three ($P_2$) and your test vacuum. $P_2$ should be greater than $\Delta P$, otherwise there is no driving force to draw air from the blister package cavity.

$$\Delta P = 400mb - 250mb = 150mb$$

A solid baseline for $\Delta P$ is 250mb. Above 250mb $\Delta P$, the initial driving force achieved during the vacuum cycle of the blue dye test is still significant enough to drive air out of the package fast enough for the blue dye test to be effective. Below 250mb $\Delta P$, air flow begins to see dramatic reductions through critical leak sizes, and the generally low $\Delta P$ is an indicator that the initial low package head space will inhibit leak detection using the blue dye leak test. A simple adjustment to this method may improve the effectiveness of this method. Increase the test vacuum to a point at which the $\Delta P$ calculated in step four exceeds 250mb.

When operating the blue dye test, there are three main variables that all manufacturing lines will have in their standard operating procedure; the test vacuum reached during Phase 1, the dwell time under vacuum during Phase 1, and the dwell time at atmospheric pressure in Phase 2. These steps are suitable for an operating procedure, and yet there are more factors to consider when establishing methodology. If a standard operating procedure has these three inputs standardized across different package formats, it can be assumed there is a different test method capability across the different package formats.

There is also a strong possibility that the dye test may not be effective for some of your package formats due to variable characteristics between package formats. The principle behind this statement is straight forward. A blister package that has more head space will generally create a greater driving force for air to bubble out of the package. This in-turn would create a greater vacuum inside a blister package cavity in Phase 2, increasing the likelihood that dye is drawn through a leak. A package with low head space will work against detection capability.

It is vital that these aspects of the leak test methodology are established to ensure uniform test sensitivity from batch to batch. These variables associated with this method are low-hanging fruit, and more critical to the method is the sheer physics of the package during the leak test.

This analysis of the blue dye ingress leak test can dig layers deeper, into the dynamic flow rates of air out of the package, surface tension of the dye bath, and operator detection capability. The main takeaway is that even some package formats that would seem to be suitable for leak detection using the blue dye ingress method may be immune to this type of test.

Validating the blue dye ingress method requires
locking down variables that may be taken for granted. Once you have completed steps one through four, and determined that your package does in fact have the adequate headspace characteristics to test using the blue dye ingress method, begin to develop a standard operating procedure that captures all inputs of your test method:

- When preparing the blue dye bath, is the methylene blue concentration standardized? Is surfactant added to the mixture? If so, to what concentration?
- What amount of dye is an operator actually able to visually see? Using a micropipette, inject microliters of blue dye into the blister package to validate operator detection capability. Will the lab operators actually see the dye leak into the package? This is not a cut and dried response, and it’s important to test different operators as you may receive different results.
- The final challenge would be to make positive controls (calibrated laser drilled leaks) and challenge the entire standard operating procedure to determine what leak rate operators can provide.
- Challenge the method regularly and its ability to achieve reliable and repeatable detection of defects.

The blue dye ingress test is more complicated than one may think and may not be an all-around solution for leak testing all types of packaging (flexible, semi-rigid, and rigid). Answering the right questions and challenging the effectiveness of the method may actually improve detection capability and resolve quality issues many are experiencing today.

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