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Closure Moisture Analyzer (CMA)

Basic Theory of Operation

One of the unique properties of water is that it has a permanent dipole which results in an unusually high dielectric constant of 78.5 when compared, for example, to the dielectric constant of butyl rubber which is just about 2.4. As a result small amounts of moisture in an elastomer material can result in significant changes in the observed dialectic properties. The CMA (1) is custom designed for measuring the dielectric properties of elastomer closures used in sealing vials containing lyophilized products.

Sources of Moisture in Closures

The first source of moisture in the closure stems from the closure manufacturing process. The basic formulation of the elastomer will contain a certain amount of moisture. Some but not all of this moisture is removed during the curing process. Therefore the closure supplied by the manufacturer will already contain various amounts of residual moisture depending on the nature of the curing process.

In those cases where the lyophilization will be performed in an aseptic environment, the closure must undergo a sterilization process either by irradiation or steam sterilization. For those closures that are steam sterilized at 121 ^{o}C at 15 psi for some period of time, additional moisture is absorbed by the closure.

Effect of Closure Moisture on Product Stability

Depending on the composition of the closure, temperature and relative humidity on the sealed vial containing the lyophilized product, the closure can increase the relative humidity in the vial and thus increase the residual moisture in the product that will adversely affect its stability. The process whereby moisture is released from the

closure is generally referred to as “outgassing”. For some products outgassing can be so severe that the dried product will go back into solution.

Frequency Distribution of the Dielectric Properties of Closures

The manufacture of elastomer closures is a very complicated and complex process with a host of variables. While the dimensions of the closure can be carefully maintained within close tolerances, there will be changes in such parameters as mass and composition. For that reason there will be a frequency distribution in the dielectric properties of the closures even in the absence of any moisture in the closure. Increasing the moisture content in the closures will not only increase the mean value but will also cause an increase in the standard deviation.

The CMA is designed to rapidly and nondestructively determine the frequency distribution of the dielectric properties of a large number of closures and therefore ensure that all the closures in a batch of processed closures will not have residual moisture values that will result in the loss of stability of a lyophilized product during storage.

Using the CMA

Using the CMA is extremely simple and safe. Just press the open button on the Touch Screen monitor and the door in the base of the instrument will open. Place a closure on the specially designed holder and give the door a gentle push and it will automatically close, the closure is rapidly measured and the door will automatically open again. The closure is removed and another closure is positioned in its place and the process is repeated.

After each individual measurement the measured dielectric value is shown on a histogram plot, a frequency distribution plot and on a tabular data file. In addition to recording the dielectric value the system also records the ambient temperature and relative humidity under which the test was conducted. With such a rapid and simple to use the frequency distribution of the dielectric properties can be determined in a few hours. IT would take a year or more with other methods such as the Karl Fischer or Loss on Drying.

To ascertain just what dielectric frequency distribution you would need to ensure that the closure drying process is producing closures with moisture values that will not affect the stability of a lyophilized product is quite simple.

- First of all take a batch of closures and determine the frequency distribution of the dielectric properties of the closures.

- Place these closures in a drying oven and dry the closures at an elevated temperature for some period of time.
- Determine the frequency distribution of these oven dried closures.
- Again place these closures in a drying oven and dry the closures at an elevated temperature for some period of time.

Determine the frequency distribution of these oven dried closures.

- Repeat the last two steps until there is no significant change in the mean dielectric property and the standard deviation.
- Use these closures to make a test batch of the lyophilized product and place the samples on an accelerated stability test at elevated temperatures to verify that there is no loss in stability as a result of an increase in the moisture in the product.

Use the established frequency distribution of the dried closure as a standard to which you can adjust the closure drying process used in the manufacturing process to obtain the same results.

The CMA is now used to quickly check each batch of dried closures to validate that the closures are dried and safe to use in producing a lyophilized product.

The CMA statistically removes the "guess work" out of drying closures

For more technical information concerning the CMA contact Phase Technologies, Inc. by e-mail jennings@phase-technologies.com or phone 610-660-9665

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(1) Patent Pending