

Interaction between lyophilised products and elastomeric closures

In this issue of *The Source*, we'll examine moisture ingress by way of the stopper. We'll consider the effect of residual moisture in the elastomer and the impact of the stopper drying cycle after steam sterilisation.

Because of their sensitivity and often poor solubility, many biopharmaceutical drug products are brought to market in lyophilised form. Lyophilisation extends the shelf-life of the drug, which may be unstable as a liquid.

Pharmaceutical manufacturers need to consider the optimal moisture content of the lyophilised product and maintain that level over the product's shelf life. Moisture can be introduced into a lyophilised cake from the elastomeric stopper and from the atmospheric headspace; it can also permeate the stopper, a process known as moisture vapour transmission.

Because lyophilisation is a costly and complicated process, selecting the appropriate vial and stopper for packaging the drug is essential to market success. The packaging components must assure seal integrity and maintain the purity of the packaged drug product.

Residual moisture in elastomeric closures can cause degradation of a lyophilised drug product. Pharmaceutical manufacturers typically wash, steam sterilise and dry the closures. This process drives moisture into the closure. If the drying conditions for the closure are not optimised, residual moisture can transfer into the lyophilised drug product over time.

Protecting Against Moisture Absorption

West Pharmaceutical Services is conducting a study of elastomeric stoppers to determine their effectiveness in protecting a lyophilised drug product from moisture absorption. The study uses vials filled with lyophilised lactose, a compound chosen because of its hygroscopic properties.

To provide a comparison for the impact of the drying cycle after sterilisation, stoppers were autoclaved and then dried at three durations. The study will monitor the moisture content of the stopper after initial autoclave sterilisation and drying, and at each time point over a three-year period. West will also evaluate the moisture levels in the lactose over the same time.

This study evaluates closures subjected to a pharmaceutical-grade wash process, a typical steam sterilisation cycle and three

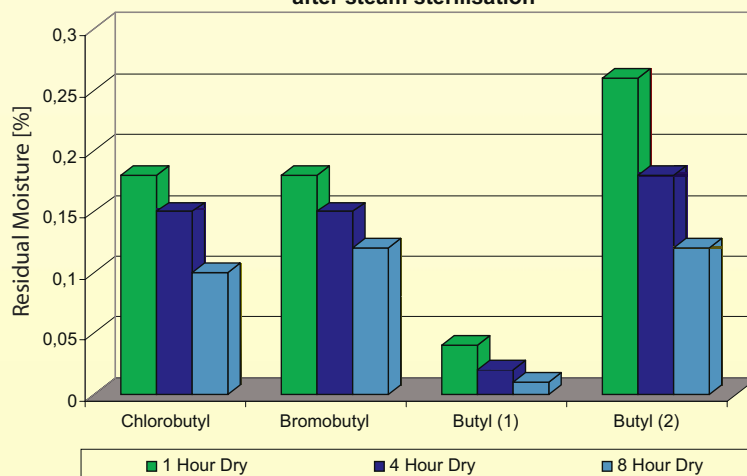
drying cycles. Closures were placed on a vial containing a 5% lactose solution; the filled vials were then lyophilised. The amount of moisture in the closure and in the lactose was measured over one year, using a coulometric Karl Fischer titrator with a drying oven.

Test Observations

Because this study is ongoing, the assumptions need to be confirmed by test results.

As shown in table 1, the residual moisture content of an elastomer is specific to its formulation and could be significantly reduced by a proper drying process. Table 2 shows that the longest drying time (8 hours) provides the lowest cake moisture increase. Additional studies have shown that longer drying times do not affect the residual moisture content because residual

Table 1 Impact of drying times on residual moisture after steam sterilisation



moisture follows an asymptotic behaviour. Time and energy spent on further drying has an insignificant effect on lowering residual moisture content.

Table 3 shows that the dryness of a stopper may not limit the impact on the moisture content of the lyo cake. While butyl shows much lower residual moisture content after drying compared to bromobutyl, this is not reflected in the respective cake residual moisture content. After 3 months, cake moisture content is even higher for vials closed with a butyl stopper. An explanation for this may be found in looking at the different moisture vapour transmission rates for both elastomer formulations.

Test Summary

For all samples, it is evident that there is moisture transmission from the environment to the closure. It was thought that after drying a closure there would be only residual moisture retained in the closure but the moisture would not increase over time; however, this study shows that moisture will migrate from the environment to the closure and consequently to the lyophilised cake over time. The amount of residual moisture is dependent on the formulation as well as the drying time. This study also indicates that while it is very important to optimise the drying time of closures to reduce residual moisture, it is also important to choose a closure formulation that will reduce the transfer of retained moisture to the lyophilised cake.

Table 2 Residual moisture in lyo cake over one year after different drying times

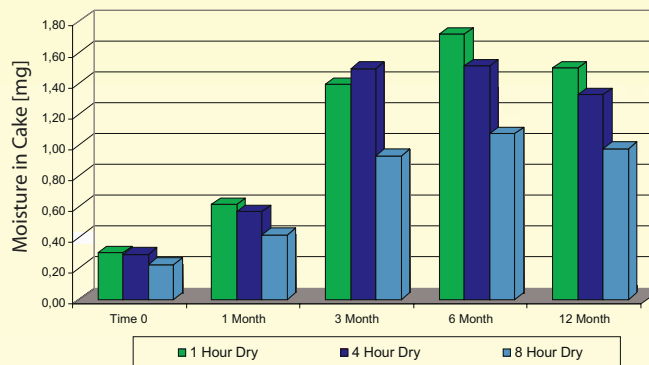
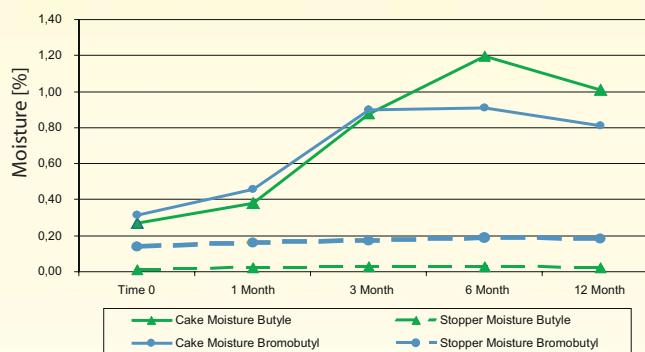


Table 3 Moisture comparison Butyl(1) and Bromobutyl



West to Present at the PDA's PFS Conference

Visitors to the Parenteral Drug Association's conference, The Universe of Pre-filled Syringes and Injection Devices, at the Hilton Hotel, Berlin, can attend two presentations by Dr. Mike Schäfers, Vice President, Marketing, Europe.

On Tuesday, November 27 at 11:15 a.m., Dr. Schäfers will present *Daikyo Crystal Zenith® – A Ready-to-Use Prefillable Syringe System for High Demanding Biopharmaceuticals*. On November 28 at 7:30 a.m., he will present *Elastomeric Components for Prefillable Syringe Systems*.

While at the conference, stop by table 10 where you can meet West's technical experts who will answer your questions and demonstrate how West's innovative products can provide solutions to your product development challenges. West will also be at table 9 with its subsidiary, Medimop Medical Products, Ltd., to showcase safety and administration systems for drug reconstitution, transfer and mixing.

**For further information, please contact Sascha Karhoefer,
Biotechnology Technical Service Engineer.**

Tel +49 (0) 2403-796-358, Sascha.Karhoefer@westpharma.com.

In Asia Pacific, please contact Koh.Sok.Tiang@westpharma.com.