CASE STUDY

Microclimate Control for DPIs Using a 3-Phase Activ-Polymer™ System: Investigation of the Equilibrium Relative Humidity for Capsule-Based Dry Powder Inhaler Products

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Introduction

The physicochemical stability of capsule-based dry powder inhalers (DPI) is related to the moisture present in the hard-capsule shells. Intrinsic moisture from the capsule shell can transfer to the formulation contents in the capsule on storage, causing lower drug product stability.[1] The equilibrium between the captured air inside the packaging, the capsule and capsule contents will generate a relative humidity inside the blister package that is fundamental to control in order to maintain shelf-life stability of the drug product. This is known as the equilibrium relative humidity (ERH). To limit the transfer of water vapor and condensation between components during storage, materials and formulations need to be equilibrated prior to individual capsule packaging. For example, tiotropium in Spiriva HandiHaler has been reported to have a very short in-use stability profile due to sensitivity to moisture.[2]

Objectives

The aim of this study was to determine the ERH of the blistering cavity headspace of a number of commercial capsule-based DPI drug products to better understand their packaging and equilibration requirements. The study also explored the ability of Aptar CSP Technologies' proprietary 3-Phase Activ-Polymer™ system to control the microclimate of a container closure system containing capsules from the Spiriva® HandiHaler product.

PRODUCT	CAPSULE MATERIAL	COMPANY
Onbrez®	Gelatin	Novartis
Foradil®	Gelatin	Novartis
Seebri®	HPMC	Novartis
Spiriva®	Gelatin + PEG	Boehringer Ingelheim
Tobi® Podhaler	HPMC	Novartis

Table 1: Commercial capsules-based dry powder inhaler drug products with reference to type of capsule material employed in the drug product.

Methods

Using a Novasina LabMaster AW CM3, the ERH of a number of commercial capsule-based inhaled products in blister packs were measured. Ten DPI capsules from commercial products (Table 1) were used in the measurement, creating a monolyer of the capsules to be tested. The total transfer time from package to measurement was no more than 30 seconds. A stabilization time of two hours was allowed per measurement of product, and the final ERH was recorded.

The ability of Aptar CSP Technologies' 3-Phase Activ-Polymer™ system to control the ERH of Spiriva capsules was also determined. Five Spiriva capsules were enclosed in 55 mL flip-top vials, which were loaded into five pre-loaded 3-Phase Activ-Polymer™ M-3003-398 components to achieve ERH microclimate conditions of 0, 10, 20 and 40% RH. The vials had a temperature and humidity data logger placed into the vial with the capsules and the 3-Phase Activ-Polymer™ (Figure 1). The vials loaded with capsules were allowed to equilibriate at room temperature before being placed into stability cabinets set at 40ºC/75%RH for 7 days.

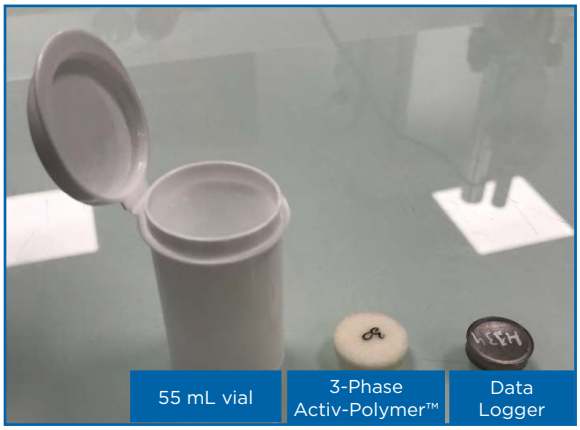

Figure 1: Experimental setup of container closer system for 3-Phase Activ-Polymer™ systems.

Results and Discussion

The ERH of various commercial capsule-based DPI drug products is shown in Figure 2. All of the commercial capsule DPI drug products investigated showed differences in their respective ERH, and followed the rank order below:

Onbrez > Foradil > Seebri > Spiriva > Tobi

It is possible to infer that the processing conditions for these drug products are different and may be dependent on physicochemical properties of the active present in the drug products. The measured ERH of these drug products will be related to the conditioning of the filled capsules and the environmental conditions upon packaging. For example, patent literature reports Spiriva HandiHaler capsules are conditioned between 10–16% RH.[1] The Tobi Podhaler had the lowest measured ERH, which may have been in order to maintain the shelf-life stability of the product.[3]

The ability of a 3-Phase Activ-Polymer™ system to stabilize and control the ERH of a container closure system containing Spiriva capsules was determined. The 3-Phase Activ-Polymer™ system was employed to create different ERH conditions, and the capsules were then placed at 40°C/75% RH for seven days to determine if the 3-Phase Activ-Polymer™ material enabled the control of the ERH at elevated temperature and humidity conditions. Figure 2 shows that without the Activ-Polymer™ technology, the relative humidity in the vial stored at 40°C/75%RH was 72.5%RH. For system controlling the RH at 0, 10, 20 and 40% RH, the measured relative humidity in the vial was 4.1, 13.9 and 38.9%RH. These data show that the 3-Phase Activ-Polymer™ system was able to control the microclimate in the container closure system, which may help to maintain the shelf-life stability of capsule-based DPI formulations.

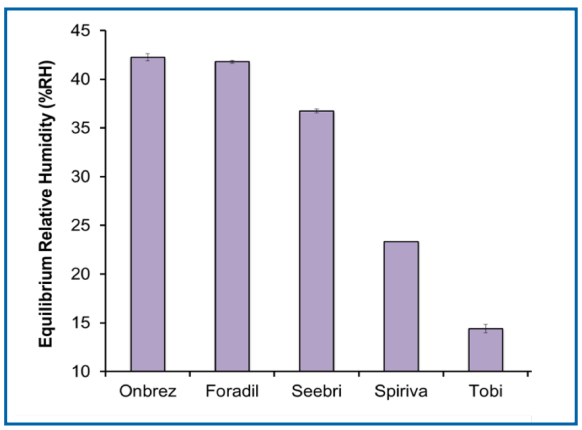

Figure 2: Equilibrium relative humidity measured at 25°C of commercial capsule-based DPI drug products.

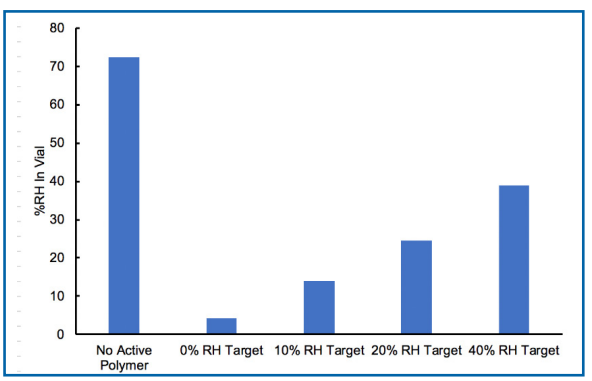

Figure 3: Equilibrium relative humidity measured after storing Spiriva Capsules at 40°C/75%RH in flip-top vials containing 3-Phase Activ-Polymer™ material to generate ERH of 0, 10, 20, and 40% RH.

Conclusions

Packaging individual components after their equilibration proves to overcome end product stability and shelf-life. If the capsules that hold formulations have not been acclimatized at the right conditions, they can cause large fluctuations in humidity inside a sealed blister. Temperature fluctuations outside the sealed cavity or humidity destabilization within the sealed cavity can have a profound effect on the physical chemical product characteristics and performance. Stability, shelf-life and usability will ultimately change during transit and storage. Controlling the temperature and packaged ERH is vital in developing a robust inhalation product.

References

1 Lehto VP. A desiccant system for the regulation of humidity in inhalation powders. 2008.
2 Hochrainer D, Bechtold-Peters K, Walz M, and Trunk M. Inhalation capsules. 2004.
3 Miller DP, Tan T, Tarara, TE, Nakamura J, Malcomson RJ, and Weers JG. Physical Characterization of Tobramycin Inhalation Powder: I. Rational Design of a Stable Engineered-Particle Formulation for Delivery to the Lungs. *Molecular pharmaceutics*. 2015.