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Investigation of the Equilibrium Relative Humidity for Capsule Based Dry Powder Inhaler Products: Control of Microclimate Using a Three-Phase Active Polymer System

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Introduction

- The physicochemical stability of capsule-based dry powder inhalers (DPI) is related to the moisture present in the shells. Intrinsic moisture from the capsule shell can transfer to the formulation 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 which is fundamental to keep under control. This is known as the equilibrium relative humidity (ERH).
- There are requirements to equilibrate materials and formulations prior to individual capsule packaging. For example, tiotropium in Spiriva HandiHaler has been reported to have short in-use stability profile due to sensitivity to moisture [2].

The aim of this study:

1. **To determine the ERH of the blistering cavity headspace of commercial capsule-based DPI drugs.**
2. **To study the ability of a three-phase active polymer system to control the capsule microclimate.**

Methods

- Using a Novasina LabMaster AW CM3, the ERH of a number of commercial capsule-based inhaled products in blister packs were measured.
- 5 Spiriva capsules were enclosed into 55 mL Flip-top vials, which were loaded with 5 3-Phase Active Polymer M-3003-398 (Aptar CSP, USA) to achieve ERH microclimate conditions of 0, 10, 20 and 40% RH.
- The vials had a temperature and humidity data logger placed together with the capsules and the 3-Phase Active Polymer (Figure 1). The vials loaded were then placed into stability cabinets set at 40ºC/75%RH for 7 days.

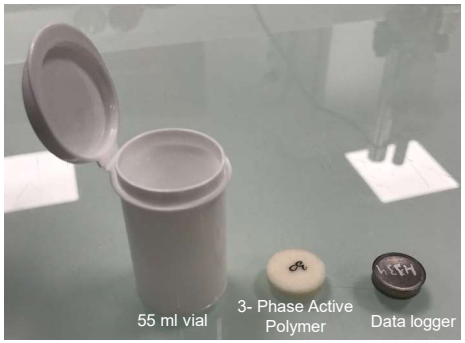

Figure 1. Experimental setup of container closure system for 3- Phase Active Polymer systems.

Results

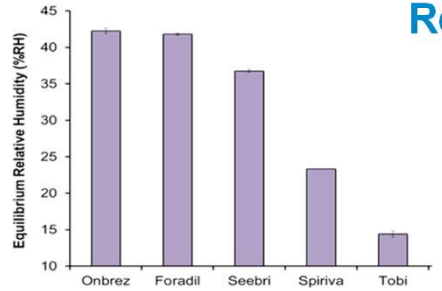

Figure 2. Equilibrium relative humidity measured at 25°C of commercial capsule-based DPI drug products.

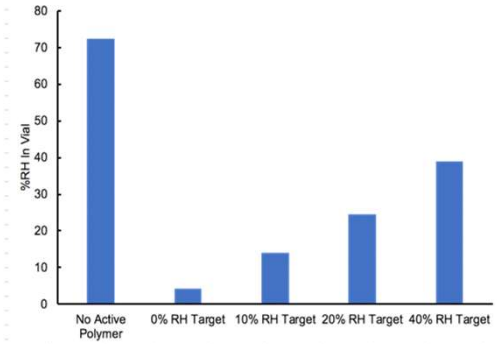

Figure 3. Equilibrium relative humidity measured after storing Spiriva Capsules at 40ºC/75%RH in Flip-top bottles containing 3-Phase Active Polymers to generate ERH of 0, 10, 20 and 40% RH.

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

  Onbrez > Foradil > Seebri > Spiriva > Tobi

- The measured ERH of these drug products will be related to the conditioning of the filled capsules and the environmental conditions upon packaging. Patent literature reports Spiriva HandiHaler capsules conditioning 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].
- Figure 3 shows that in the reference vial, without the Activ-Polymer technology, the relative humidity (stored at 40ºC/75%RH) was 72.5%RH. For the systems controlling the RH at 0, 10, 20 and 40% RH, the measured relative humidity in the vials was 4.1, 13.9 and 38.9%RH. The data shows that the 3-Phase Active 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.

Conclusions

- Temperature fluctuations outside the sealed cavity or humidity destabilisation within the sealed cavity can have a profound effect on the stability, shelf-life and usability of the drug during transit and storage. Controlling the temperature and packaged ERH is vital in developing a robust inhalation product.
- 3-Phase Active Polymer M-3003-398 (Aptar CSP, USA) contributes to the stabilization of the microclimate inside the capsule, keeping the ERH low independently of the conditions outside the blister pack.

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, Malcolmson 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.