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THE KAITEKI COMPANY
Mitsubishi Chemical Holdings Group

Quali-V®-I Inhalation

TWO-PIECE HARD CAPSULES FOR DRY POWDER INHALERS

Inhalation delivery offers significant and unique benefits in the treatment of a variety of illnesses. The lungs may be used as a portal of entry to the body that enables administration of a drug via the airways into the blood stream, and as such can present an advantageous alternative to oral delivery. Inhaled formulations for systemic delivery are an attractive proposition, one that takes advantage of the permeability of macromolecules within the lungs, and thus presents opportunities for conditions requiring rapid response.

PUNCTURING CAPSULES IN DRY POWDER INHALERS

Figure 1 shows how capsules are punctured in a DPI. The pin, after contact with the capsule dome, forms a depression in the surface of the shell before perforation. When a patient inhales using the DPI, the powder emerges through the puncture hole and flows up with the airstream, delivering the active ingredient in the powder deep into the lungs.

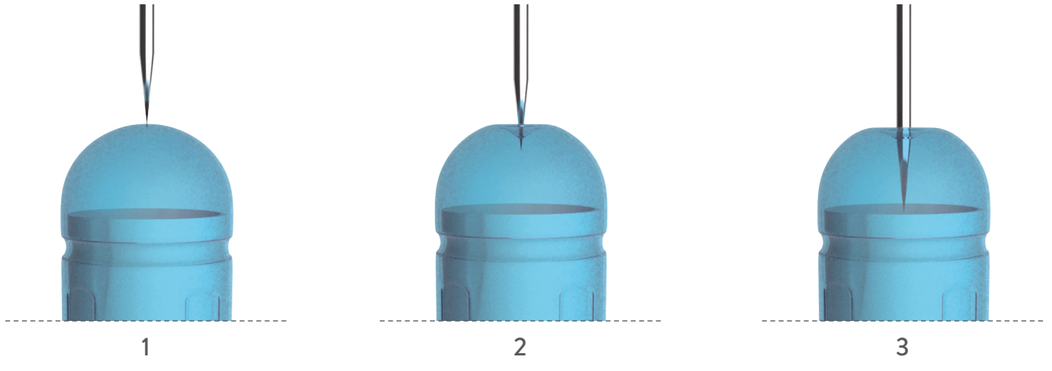

Figure 1: *Puncturing process of a capsule in a DPI.*

1. Pin comes into contact with capsule, cap or body.
2. Depression forms in dome of capsule.
3. Pin penetrates shell.

Qualicaps® Engineered to perform

Qualicaps® has developed a capsule specifically designed for inhalation with outstanding properties in terms of moisture content, puncturing, and powder aerosolization.

LOW MOISTURE CONTENT

As the active ingredient in inhalation formulations is moisture sensitive, then the use of a capsule with a low moisture content is required. The specification for moisture content in Quali-V®-I capsules is 4.5% – 6.5%, significantly less than the 13.0% – 16.0% in gelatin capsules used for this application.

Water does not act as a plasticizer in Quali-V®-I capsules, unlike in gelatin capsules, which become brittle when they lose moisture. Quali-V®-I capsules can even be dried to less than 1.0% without losing their physical properties nor suffering brittleness.

As the active ingredient is moisture labile, then it can be further protected by using desiccants in the packaging, a solution that is not viable for gelatin capsules, which would become brittle on storage.

Figure 2 displays the testing device used to obtain the results in **Figure 3**, which shows the relationship between capsule moisture content and brittleness for gelatin and Quali-V®-I capsules. The brittleness in gelatin capsules increases as the moisture content lessens, whereas Quali-V®-I capsules remain unchanged in low moisture conditions between 6.5% and 1.0%.

BRITTLENESS TESTER (QUALICAPS®)

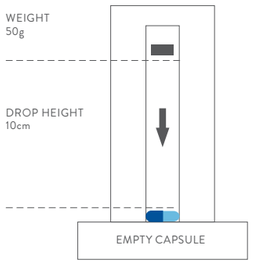

Figure 2: *Test device for measuring capsule brittleness.*

BRITTLENESS AND MOISTURE CONTENT

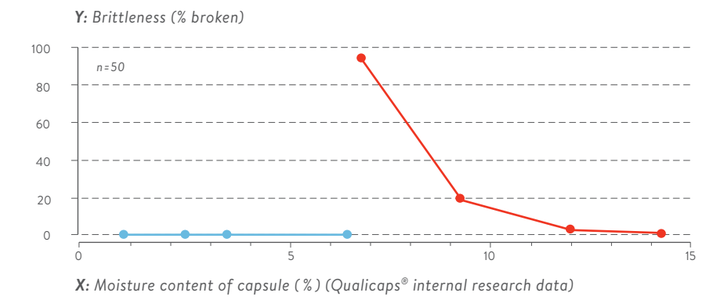

Figure 3: *Relationship between moisture content and capsule brittleness.*

PUNCTURING

Figure 4 shows the traces obtained when testing a sample of ten Quali-V®-I capsules. Each was preconditioned by storing over a saturated solution of lithium chloride (RH 13%), with a moisture content of 1.0%.

Qualicaps®, with the aid of the School of Pharmacy and Pharmaceutical Sciences, Cardiff University, UK, developed a robust methodology to determine puncture characteristics of different types of capsules in order to assist in inhalation capsule formulation. This methodology allows for measuring the movements of the DPI pin when a capsule is punctured, as well as the corresponding forces generated. The results are reproducible and can rapidly characterize the process of capsule penetration to determine whether changes in capsule materials and/or conditions have an impact on their potential performance in DPIs.

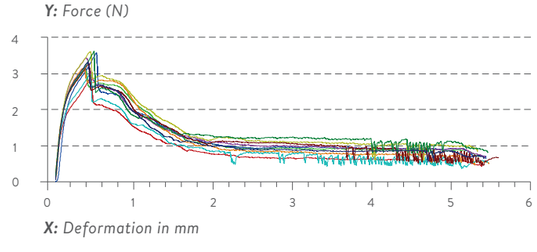

Figure 4: *Traces produced by a Zwick® materials testing device, showing the relationship between the force on the DPI pin with the distance moved from the initial contact with the pin and the surface of the capsule. The capsules were preconditioned by storage at 13% RH.*

AEROSOLIZATION

For powders to penetrate deep into the lungs, they must have a particle size less than 5 microns. Capsule moisture content plays an important role in this property, as the increase of water vapor in a system promotes the formation of bridges between particles, thus increasing their particle size (capillary condensation). Another important factor in powder aerosolization is the quantity of internal lubricant in the capsule, as it influences the quantity and consistency of powder delivery from the DPI. Since the use of an internal lubricant is essential for the capsule manufacturing process, the quantity applied to the stainless steel pins on which the capsule shells are formed is carefully controlled during the manufacturing process for the optimum quantity that ensures positive powder aerosolization. Quali-V®-I capsules are made with an internal lubricant specially designed for this application.

Figures 5, 6, and **7** show images taken with an Atomic Force Microscope (AFM) of the internal surface of capsules at different lubricant concentrations. They demonstrate that the capsules with lower internal content appear to have a high surface roughness, which could cause a greater amount of powder adherence, and thus a worse performance in aerosolization properties in the studied cases.

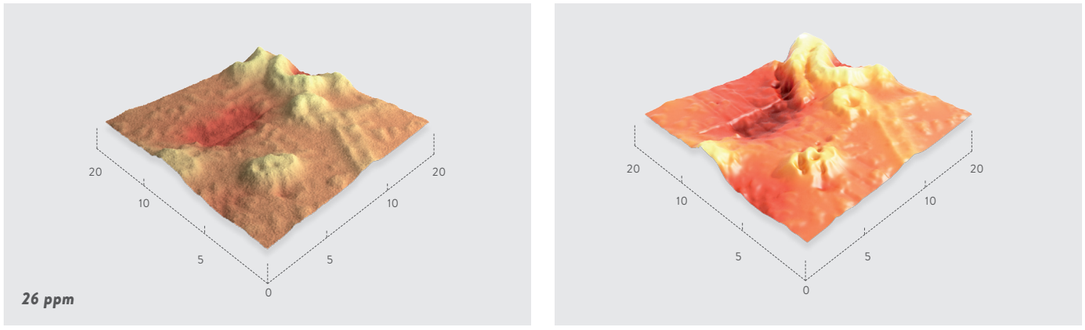

Figure 5: *Topographical image of Quali-V®-I capsules' inner surface with a low level of internal lubricant.*

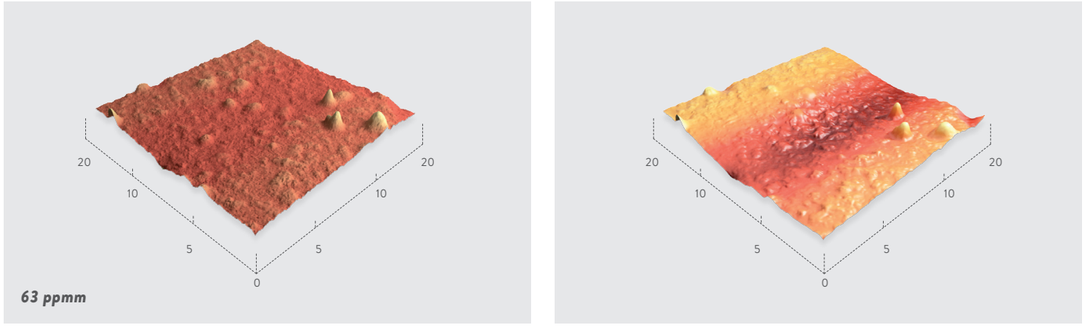

Figure 6: *Topographical image of Quali-V®-I capsules' inner surface with a medium level of internal lubricant.*

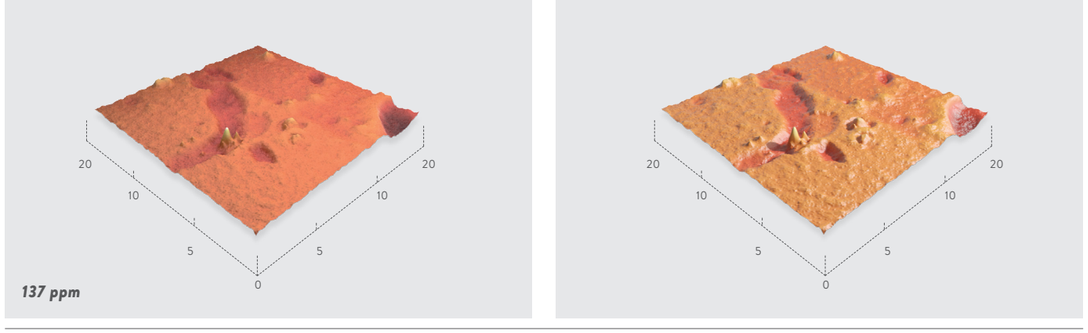

Figure 7: *Topographical image of Quali-V®-I capsules' inner surface with a high level of internal lubricant.*