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Hard Capsules for Dry Powder Inhalers: Performance on Puncturing

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Key words: Dry powder inhaler, DPI, Hypromellose capsule, puncturing, moisture

PURPOSE

The study presented describes the behavior of various dry powder inhaler (DPI) hard capsules under puncture, at different relative humidities (RH).

Hard gelatin-based capsules have been used for pulmonary applications for several decades now. More recently, capsules from hypromellose (HPMC) were developed and became available for use in DPI devices. These capsules have lower moisture content, and their mechanical properties are less sensitive to changes in relative humidity. Especially, hypromellose capsules do not become brittle when losing moisture.

When a capsule shell is punctured in a DPI device, the holes should be regular in shape. The material should not be too brittle to produce detached particles which could be inhaled, and it should not be so elastic that it returns and recloses the hole once the needle withdrawn.

Our objective was to study the puncturing force and holes morphology of gelatin, gelatin/PEG and hypromellose hard capsules when equilibrated at low RH and subjected to puncturing with a pin from commercial DPI device.

METHOD

Storage and Conditioning

- Three types of Capsugel hard capsules size 3 manufactured for inhalation were used: gelatin, gelatin/PEG and HPMC shells.
- They were stored over saturated salt solutions in desiccators at 13%, 23% and 33% RH for two weeks.
- Moisture content was determined as loss on drying (LOD) by the oven method.

Puncture Force

- A single pin from Spiriva® Handihaler® was used, mounted on a Texture Analyzer from Stable Micro Systems.
- As the location of the puncture varies according to the devices, the dome of a cap and the side wall of a body were punctured for this study (fig.1).
- The capsules to be tested were fixed vertically in a metal holder when the cap dome was punctured, and horizontally on the plate when the body side was punctured.
- The pin was moved downwards and into the capsule shell at a constant

speed of 0.5mm/s. The displacement of the pin and the resulting force were automatically recorded on the puncturing curve.

Scanning Electron Microscopy (SEM)

Representative samples from the punctured capsules were cut off and sputter-layered with gold under partial vacuum. Scanning electron micrographs were taken using FEI Quanta 400 scanning electron microscope.

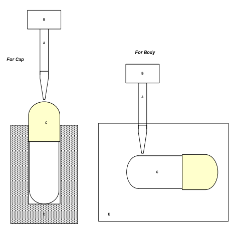

Fig. 1: Setup for measuring capsules penetration

Figure 2 shows the moisture content of the capsules after conditioning at relatively low humidities. Such conditions are regularly requested by the customers as inhalation formulations are often based on highly hygroscopic powders. HPMC shells have much lower moisture content compared to gelatin and gelatin/PEG ones.

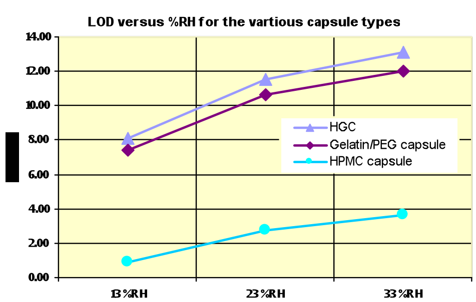

Fig. 2: Moisture content of capsule samples

On Figure 3, the maximum force generated during capsules penetration is shown. Gelatin and gelatin/PEG capsules are harder giving higher puncture forces. Moreover, their mechanical properties are more affected by moisture content. HPMC capsules are softer and require lower penetration force for puncture. More important, they retain their puncturing properties stable over large range of moisture

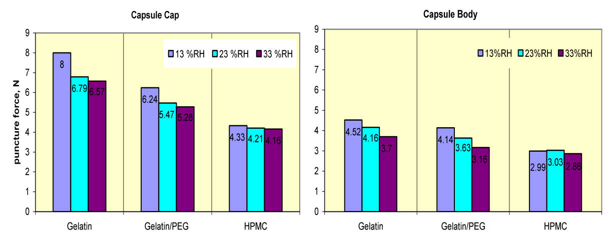

Fig. 3: Forces generated during capsules shell puncture

The nature of the puncture is different between gelatin and HPMC capsules, and can be deduced from the different stages of the penetration curves (Figure 4).

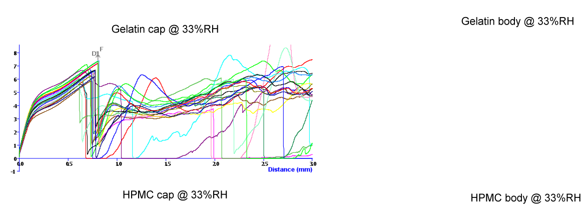

Fig. 4: Penetration curves: Force recorder versus the displacement of the pin.

At the point of maximum force the pin punctures the shell of the capsule and the penetration force starts going down. For gelatin, the recorded force drops to zero indicating that pieces of the shell had broken off. For HPMC, the force never reaches zero, indicating that the material remains in contact with the pin and that the deformation is more plastic. These observations are confirmed by the exact morphology of the holes on the SEM pictures (Figure 5).

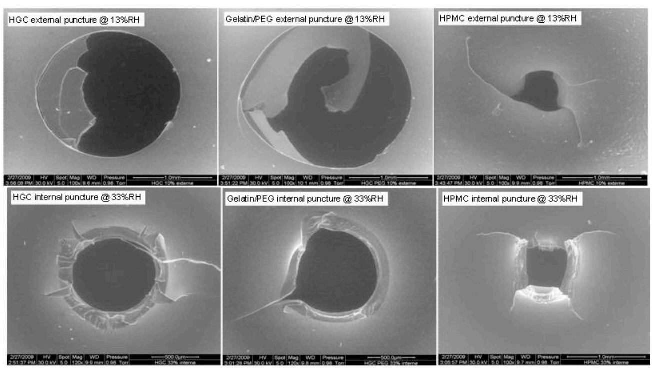

Fig. 5: Scanning electron micrographs showing the external and internal morphology of puncture holes

Gelatin and gelatin/PEG holes are larger, with broken pieces at 13%RH, HPMC holes are smaller with no pieces detached but flaps formed by splitting the shell.

CONCLUSION

This study reports on forces and types of deformation involved in puncturing hard capsules for DPI. The relative humidities used in the tests simulate storage in stress conditions. The results show that the puncturing properties of hypromellose capsule are more robust than gelatin ones over large range of RH.

REFERENCES

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