**METHODS**, continued

**PURPOSE**

- Capsule-based dry powder inhalers (DPIs) are an increasing popular dosage form. To date, published studies have focused on the influence of capsule moisture content on the puncture performance of both gelatin and hypromellose capsules at ambient temperature, 20º-25ºC.1,2
- DPIs are stored and used at locations that are significantly below ambient temperature.
- The aim of this work was to determine if low temperatures influence the capsule puncturing performance by a DPI.

**METHODS**

- Two grades of inhalation capsules were tested: size 3, gelatin and hypromellose (Quali-VII-I).
- Capsules were conditioned by storage in desiccators for at least one week over saturated solutions of calcium chloride (RH 33%) or magnesium nitrate (54%), to produce capsule moisture contents in the lower and upper half of the moisture specification respectively. These conditions were replicated at both 4.8ºC and 19.0ºC. The moisture content was determined by a loss on drying test.
- A steel conical tipped pin from a commercial DPI device (Plastiape S.p.a., Monodose Mod.7, 2 x 1 pin), see Fig. 1, was mounted in a bespoke miniaturised materials testing machine (Zwick® Testing Machines Ltd, UK), attached to an XForce P 500N load cell, see Fig. 1. The equipment is designed to measure small changes in force (accuracy ±1% of the measured value) during a measurable displacement.
- A stainless steel bushing from a capsule-filling machine (Qualicaps), held a size 3 capsule at a fixed position directly below the steel pin.

**RESULTS**

- All tests took place in an air conditioned laboratory at 19.0ºC or in a cold room at 4.8ºC.
- A force-displacement curve was captured for each puncturing event and the maximum force (force required for puncture) and shape of the profile were used to provide quantitative comparison between capsule types.
- Capsules were imaged within 30 minutes of puncture using an AmScope® light microscope. Images were recorded and the puncture area (cross section from the 2D image) was calculated with ImageJ® software.
- Capsule punctures were also categorized into 2 shapes, regular or irregular, see Fig. 2.
- Statistical analysis to compare the puncture forces and the area of the puncture at both temperatures was performed using Prism® 5 for Mac OS X (GraphPad Software Inc. USA).

**CONCLUSIONS**

- The moisture contents of capsules after conditioning are shown in Table 1, and gave results as expected.
- The shape of force displacement puncture profiles recorded during puncture of the capsules was comparable between capsules stored at 4.8ºC and 19.0ºC at both moisture contents.
- When stored over CaCl₂ there was no statistical difference in the mean puncture force recorded for hypromellose or gelatin capsules at each of the studied temperatures.
- When stored over Mg(NO₃)₂ there was a statistical difference (independent sample two-tailed t-test; p<0.05; N=20) in the mean puncture force required to puncture both hypromellose capsules (2.62 ± 0.31 N at 19.0ºC and 2.87 ± 0.83 N at 4.8ºC) stored at the two studied temperatures.
- All hypromellose capsules produced 'regular' puncture shapes at both 4.8ºC and 19.0ºC. However, for gelatin capsules at 19.0ºC only 40% (low moisture) and 80% (high moisture) produced regular puncture shapes and at 4.8ºC it was 40% and 90% respectively.
- There was a statistically significant decrease, using an independent sample two-tailed t-test, in the size of punctures created at 4.8ºC compared to 19.0ºC for all capsule samples, except for low moisture gelatin capsules, which were not affected.

**BIBLIOGRAPHY**