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INFLUENCE OF TEMPERATURE ON CAPSULE PUNCTURING PERFORMANCE

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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, 20°-25°C[1,2].
- DPIs are stored and used by patients in variety of settings. In some locations, such as Northern Europe, low winter temperatures mean that devices may be stored and/or used at temperatures that are significantly below ambient temperature.
- The aim of this work was to determine if low temperatures influence the capsule puncturing process by a DPI.

METHODS

- Two grades of inhalation capsules were tested: size 3, gelatin and hypromellose (Quali-V®-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 4.8°C and 19.0°C. 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 in a fixed position directly below the steel pin.

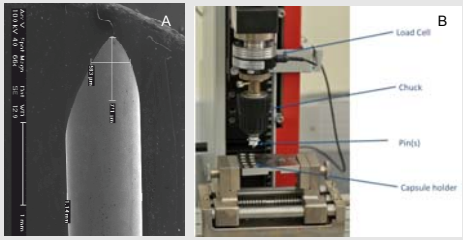

Figure 1. (A) The tip of the pin, obtained from a Plastiape Monodose Mod.7 inhaler and (B) the materials testing machine set-up used in this study

METHODS, continued

- All tests took place in an air conditioned laboratory at 19.0°C or in a cold room at 4.8°C.
- A force-displacement curve was captured for each puncturing event and the maximum force (force required for puncture) and the shape of the profile were used to provide quantitative comparison between capsule types.
- Capsules were imaged within 30minutes 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).

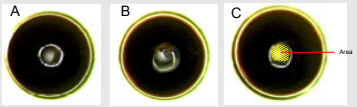

Figure 2. Examples of the puncture images recorded and their categorization as (A) 'Regular' or (B) 'Irregular'. The area of the puncture was measured, as exemplified in (C).

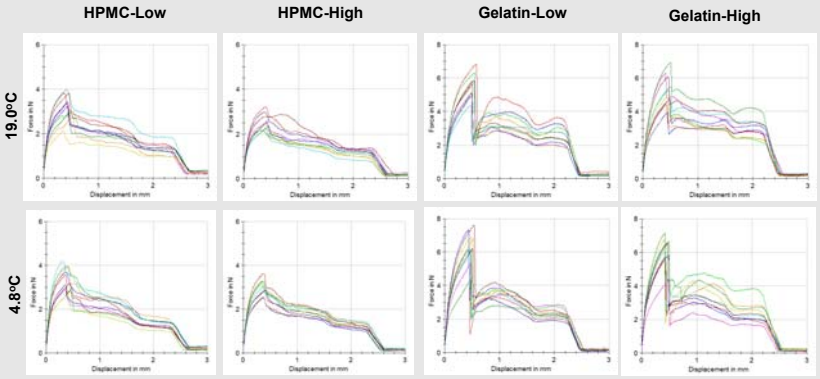

Figure 4. Illustrative examples of force displacement curves recorded by the Zwick Materials Testing Machine, showing the effect of temperature and capsule moisture on the puncturing process. Key: HPMC = hypromellose capsules, Gelatin = gelatin capsules; Low = lower moisture, High = higher moisture.

- We would like to thank José Luis Encinas of Qualicaps Europe, S.A.U. for supplying the capsule holder.

RESULTS

- 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 4.8°C and 19.0°C at both moisture contents.
- When stored over $CaCl_2$ 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 $Mg(NO_3)_2$ 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 ± 0.31N at 19.0°C and 2.87 ± 0.42N at 4.8°C) and gelatin capsules (5.85 ± 0.83N at 19°C and 5.98 ± 0.83N at 4.8°C) stored at the the two studied temperatures.
- All hypromellose capsules produced 'regular' puncture shapes at both 4.8°C and 19.0°C. However, for gelatin capsules at 19.0°C only 40% (low moisture) and 80% (high moisture) produced regular puncture shapes and at 4.8°C it was 40% and 60% respectively.
- There was a statistically significant decrease, using an independent sample two-tailed t-test, in the size of punctures created at 4.8°C compared to 19.0°C for all capsule samples, except for low moisture gelatin capsules, which were not affected.

Table 1. The effect of temperature and moisture content on the area of the puncture created in gelatin and hypromellose capsules

Conditions/Capsules		Gelatin		Hypromellose	
Temp.	Salt solution	Moisture %	Puncture area mm²	Moisture %	Puncture area mm²
19.0°C	$CaCl_2$	13.22 ± 0.37	0.82 ± 0.18	4.38 ± 0.39	0.63 ± 0.08
	$Mg(NO_3)_2$	14.58 ± 0.32	1.01 ± 0.10	6.64 ± 0.23	0.79 ± 0.08
4.8°C	$CaCl_2$	14.60 ± 0.10	0.88 ± 0.08	6.07 ± 0.43	0.39 ± 0.10
	$Mg(NO_3)_2$	14.80 ± 0.01	0.76 ± 0.18	7.16 ± 0.54	0.60 ± 0.08

CONCLUSIONS

- At one of the tested humidities greater force was needed to puncture capsules at the lower temperature.
- Temperature also had an impact on the geometry and size of punctures created in capsules by a DPI pin. The area of puncture was reduced in the hypromellose capsules at the lower temperature tested.
- More extensive studies are required to better characterize the impact of these observations on performance within a DPI.

BIBLIOGRAPHY

1. Birchall, J.C., Jones, B.E., Morrissey, A. at al., **Drug Dev. Ind. Pharm.**, 2008, **34**, 870-876, "A comparison of the puncturing properties of gelatin and hypromellose capsules for use in dry powder inhalers"
2. Torrisi, B.M., Birchall, J.C., Jones, B.E., Diez, F., **Int. J. Pharm.**, 2013, **456,** 545-552, "The development of a sensitive methodology to characterise hard capsule shell puncture by dry powder inhaler pins"
3. Renswouw, D.C., van Laarhoven, A.C.M. et al., **J. Pharm. Pract.**, 2010, **23**, 548-552, "Storage conditions for inhalation capsules: consequences of incorrect storage and adherence in daily practice"