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The development of a robust methodology to evaluate inhalation capsule puncture performance

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PURPOSE

- Two-piece gelatin capsules have been used traditionally as an oral dosage form and as unit dose containers for a powdered drug for use in dry powder inhalers (DPI).
- Hypromellose is an alternative capsule material that has been shown to possess better functional properties than gelatin when used in DPI[1,2].
- Both materials are currently used in DPI but a standardised methodology to evaluate capsule puncture performance, which is an essential property, does not exist.
- This study aimed to develop a robust methodology to determine potential differences in the puncture characteristics of different capsule materials, to assist in the development of hard capsules for this application.

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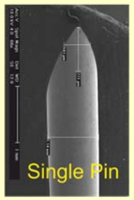

Figure 1. Puncture pin from Plastiape Monodose Mod.7 inhaler

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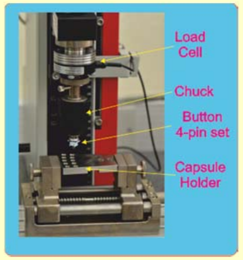

Figure 2. Zwitter Tester showing capsule holding device

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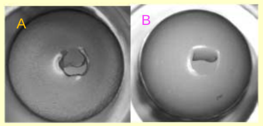

Figure 3. Example of puncture holes in capsule caps conditioned at 33% RH: A, hypromellose: B, gelatin

METHODS

- 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. 2**. 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.
- Hypromellose and gelatin capsules (n=10 per each test), conditioned over saturated solutions of Calcium chloride (33% RH) and Lithium Chloride (11%RH) at 22ºC for 1 week, to simulate poor storage conditions[3].
- Capsules were punctured by the pin at a speed of 10 mm/s and the displacement of the pin and the resulting forces were recorded on a force-displacement curve[4,5].
- Punctured capsules were subsequently removed from the bush for visual inspection, see **Fig. 3**.

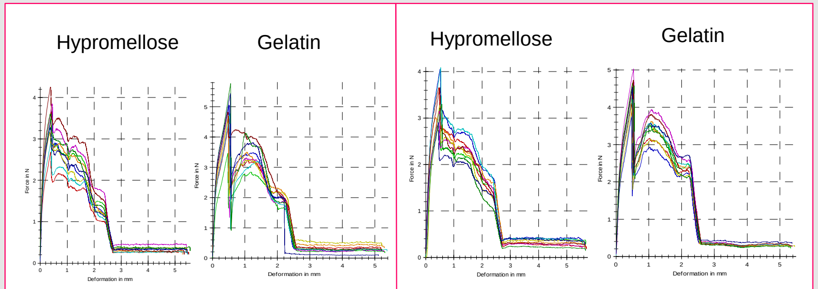

Figure 4. Force(N)-Displacement(mm) curves for Hypromellose & Gelatin capsules conditioned at 11% and 33% RH

Table 1. Force/ deformation values for Hypromellose and Gelatin capsules

Capsule	Hypromellose		Gelatin	
	11% RH	33% RH	11% RH	33% RH
Maximum force (N)	3.36 ± 0.35	3.43 ± 0.41	4.76 ±0.62	4.45 ±0.39
dL at F_{max} (mm)	0.45 ± 0.07	0.49 ± 0.06	0.51 ±0.03	0.51 ± 0.03

RESULTS

- Repeated force-displacement profiles were highly reproducible for each of the capsule materials. However, HPMC and gelatin capsules possessed different signature profiles, characterised by differences in the penetration event, see **Figure 4**.
- Gelatin capsules: showed a rapid drop in force after puncture indicating that the pin had lost contact with the shell wall; the force then increased as the flap regained contact. This was more marked after lower RH conditioning indicating particles of the shell wall had become detached
- Hypromellose capsules: compared to gelatin the drop in force after puncture was less rapid and declined less; there was a much reduced second peak compared to gelatin. The difference probably being due to a lower elasticity of these puncture flaps compared to the gelatin ones.
- The force required to puncture hypromellose capsules was lower than for gelatin and occurred at a shorter deformation distance, see **Table 1.**

CONCLUSIONS

- A rapid and robust methodology has been developed that is able to characterise penetration of a hard shell capsule by the pins that are employed in DPI.
- The sensitivity and reproducibility of the methodology enables users to describe differences in the capsule materials. This could have a significant impact on the design, development and quality assurance of hard shell capsules for use in DPI[5].

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