

# Characterising capsule puncture of different capsule types following patient actuation of a dry powder inhaler

B.E. Jones<sup>1,2</sup>, Z. Atrah<sup>1</sup>, S.A. Coulman<sup>1</sup>, J.C. Birchall<sup>1</sup>, F. Díez<sup>2</sup>

<sup>1</sup> School of Pharmacy & Pharmaceutical Sciences, Cardiff University, Cardiff, CF10 3NB, UK, <sup>2</sup> Qualicaps Europe S.A.U., 28108 Alcobendas (Madrid), Spain

## PURPOSE

- Gelatin capsules have been used in dry powder inhalers (DPI) since 1971<sup>1</sup>.
- More recently hypromellose capsules have also been used. Laboratory studies have compared the puncture properties of these two capsules and have shown that hypromellose capsules have superior puncturing properties in terms of the better uniformity of the holes and less shell particles shed in the process<sup>2,3</sup>.
- No work has been published on their in-use performance. The aim of this study is to characterise the puncture performance of HPMC and gelatin capsules when perforated by a two-pin DPI operated by a member of the public to determine the inter- and intra- individual variability.

## METHODS

- Appropriate ethical approval was obtained.
- Participants were recruited by convenience sampling. Each potential participant was provided with an information sheet (IS), and consent form. The IS explained the purpose of the study, which was to better understand how capsule DPI are used to help in improving their design, why they would be chosen to participate and to explain the experimental process.
- Participants were given an opportunity to ask questions and were provided with a brief questionnaire to determine demographic characteristics, age, gender, occupation (medical or non-medical) and previous experience of inhaler use to ensure that they were not familiar with this usage
- All participants included in the study provided informed consent.

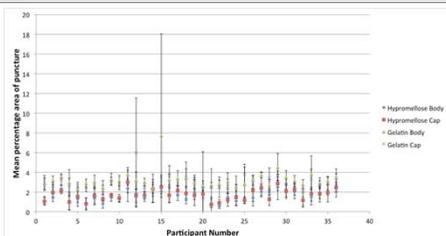


Figure 1. Mean puncture area for each participant for both capsules

## METHODS, continued

- Capsule DPI naïve participants (n=36) selected were in the following categories:
  - Gender; 23 female and 13 male: Age Range, 18 to 65: Employment, Medical Related 12, Non-Medical Related 24: Previous experience with Inhalers, None 24, with MDI 11 and with a non-capsule DPI 1: Witnessed inhalers in use, 17 had and 19 never.
- Test equipment:
  - Plastiape® Monodose Dry Powder Inhaler Mod. 7, 2-pin
  - Inhalation grade empty hard capsules, Qualicaps Europe, size 3, gelatin and HPMC (Quali-V®-I). Before use capsules were conditioned in desiccators over a saturated solution of calcium chloride (33% RH) for at least a week. This RH was chosen to represent sub-optimal storage conditions<sup>4</sup>. Their moisture content was determined by a loss on drying tests<sup>5</sup>.
- Capsules were packed, 5 at a time, in screw-cap plastic bottles labelled with a code.
- Each participant was supplied with an inhaler and an illustrated instruction sheet, which was prepared to show them how to use the DPI. They were given time to read this before being handed five HPMC and five gelatin size 3 capsules. The researchers did not intervene or give any advice on how to use the inhaler during the study in order to reproduce the experience of a naïve patient using one for the first time. A computer generated randomisation sequence was employed to further blind the study because the first participant observed that gelatin capsules made a louder noise than the HPMC capsules when punctured.
- After puncturing the researcher removed the capsule from the DPI, placed it in a bottle and stored this in another desiccator over saturated calcium chloride solution until analysis.
- Participants were then provided with a tick-box questionnaire to obtain their opinions on the loading and puncturing of the capsule using the DPI and with a space to make comments.
- Punctured capsules were placed in a bespoke holder to ensure the capsule was orientated vertically. The dome of the cap and body of each one was imaged using a light microscope (Amscope®, USA).
- Total areas of the capsule ends and puncture holes were measured by Image J analysis of the micrographs. The puncture area was defined as the puncture hole and excluded the area where the flap was visible and partly blocking the opening. The puncture area was expressed as a percentage of the dome area.
- The location of the puncture and the degree it deviated from the centre of the dome was quantified by the researcher as either 'central' or 'not central', without measuring the amount of deviation of the latter.
- Three categories of puncture flap were allocated: flap present (FP), part flap (PF) and no flap (NF).

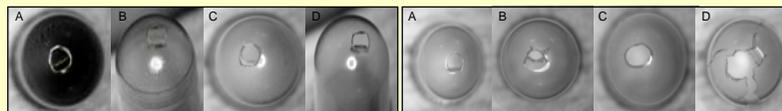


Figure 2. HPMC capsules: A, central hole, B, C & D, non-central holes. A & C flaps partly closed

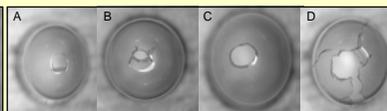


Figure 3. Gelatin capsules: A, central hole, B, C & D, non-central holes. B flap partly closed. C flap missing. D broken cap

## RESULTS

- Punctures in HPMC capsules (cap 1.58% ± 0.80%, body 1.72% ± 0.79%) were smaller and less variable than gelatin capsules (cap 3.21% ± 1.98%, body 2.89% ± 1.34%), see **Figure 1**.
- Results for gelatin were influenced by their brittleness; 2 capsules (1cap & 1 body) had large holes where pieces of shell wall had broken off.
- The punctures were not all central in the capsule domes. The deviation was greater for the bodies, 50% for HPMC and 35% for caps, probably being caused by the body having a smaller diameter than the caps, allowing this end to move more in the capsule chamber, see **Figures 2 & 3**.
- For HPMC capsules, all flaps were undamaged and remained attached, though many showed signs of elastic recovery and visually occluded the hole. Gelatin capsules, flaps were missing or damaged on 23% of the bodies and 27% of the caps that contributed to larger size puncture holes
- Four caps and 3 bodies were unpunctured the reason for which was unclear.
- Participants observations:
  - On DPI usage: Inhaler loading was very easy (19/36), easy (16/36) and difficult (1/36); Pressing buttons was very easy (30/36) and easy (6/36).
  - Six found them 'fiddly' to use or commented that people with dexterity problems may find them difficult to use. Four noticed a difference in puncture noise and one of these felt that the 'click' made them feel confident.

## CONCLUSIONS

- Both the size and shape of punctures created in a capsule when people used a two-pin DPI were more reproducible for hypromellose than for gelatin capsules.
- Patient factors such as age, gender and previous experiences with an inhaler appear to have little influence on the puncture characteristics of capsules.
- This preliminary study shows the need for further studies using larger groups of participants or the use of narrower age ranges to obtain sufficient results to differentiate the performance of groups.

## BIBLIOGRAPHY

1. Jones, B.E., *Drug Deliv. Tech.*, 2003, **3**(6), 52-57, "Quali-V®-I: A new key for dry powder inhalers"
2. 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"
3. Torrini, B.M., Birchall, J.C., Jones, B.E., Díez, 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"
4. Rensouw, D.C., van Laarhoven, A.G.M. et al., *J. Pharm. Pract.*, 2010, **23**, 548-552, "Storage conditions for inhalation capsules: consequences of incorrect storage and adherence in daily practice"