

Understanding intra- and inter-individual differences in capsule puncture following actuation of a dry powder inhaler

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PURPOSE

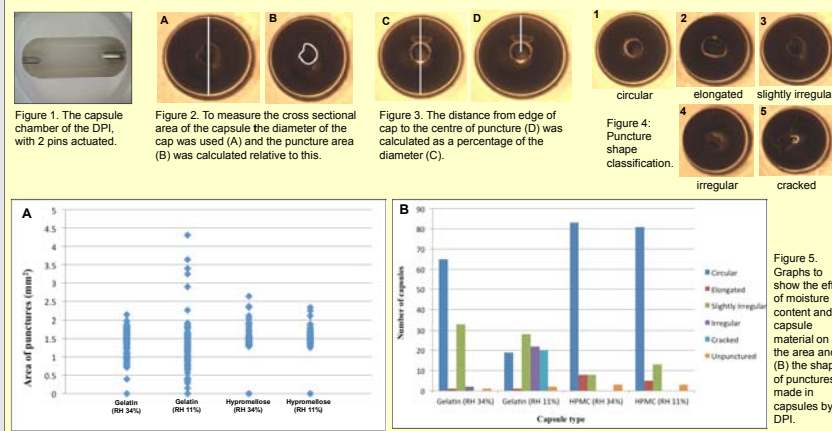
- Inhalation grade capsules formulated using gelatin and hypromellose, for use in dry powder inhalers (DPI), have different puncturing properties.
- Previous studies, conducted in the laboratory environment, have used materials testing devices to characterize the puncture holes produced in a capsule by controlled insertion of a DPI pin^{1,2}.
- Patients do not always follow instructions regarding either the correct use of medical devices or the appropriate storage conditions.
- Incorrect storage has been shown to cause gelatin capsules to become brittle³.
- The aim of this study is to better understand capsule puncture upon actuation of a capsule loaded DPI by a user.
- To achieve this the study will:
 - Develop a simple method for characterising capsule punctures
 - Assess the impact of moisture content on the characteristics of a DPI capsule puncture
 - Assess intra- and inter-individual variability on capsule puncture by a DPI

METHODS

- Approval for a study using volunteers was obtained from Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.
- Participants were recruited by convenience sampling and data was collected from each volunteer on their age, gender, occupation and experience of using a DPI.
- Sampling aimed to recruit equal numbers of men and women across five different age groups between 18 and 65. Exclusion criteria included previous experience of using or witnessing a DPI being used.
- An information sheet was provided to volunteers and consent was obtained before the study.
- A standard script was used to provide a brief description of study and an instruction sheet was provided to explain how to use the DPI. No additional verbal information was given. Standardised answers to questions that participants could ask were prepared in advance.
- A questionnaire was given to each participant to rate how easy or difficult it was to load capsule and press the buttons.
- DPI naïve participants (n=34) were selected: gender; 18 female and 16 male; ages, 7 in groups 18-24, 25-34, 35-44, 45-54, and 6 in 55-64
- A two-pin Monodose DPI supplied by Plastiapi S.p.A. (Milan, Italy) was used in the study, **see Fig.1**.

METHODS, continued

- Inhalation grade hard capsules size 3, clear/clear, gelatin and hypromellose (Quali-V®-I) were supplied by Qualicaps Europe.
- Before use capsules, closed manually to the locked position, were conditioned in desiccators over a saturated solution of lithium chloride (c. 11% RH) and calcium chloride (c. 34% RH) for 10 days at room temperature. The RH were chosen to represent sub-optimal storage conditions and give moisture contents below and at the lower end of the moisture specification limit. Their moisture content was determined by loss on drying tests⁴.
- Four types of capsules were tested; gelatin & hypromellose (at the lower end of moisture specification) and gelatin & hypromellose (below the moisture specification).
- Each participant punctured 12 capsules, 3 of each type, in a randomised order and were blinded to the capsule type.
- Participants were then given a questionnaire to comment on their experiences.
- Punctured capsules were positioned in steel holder, cap facing up, and were imaged using an AmScope stereo-microscope before being analysed using ImageJ® software.
- The puncture hole was outlined and the puncture area was expressed as a % of the total cap area, **see Fig. 2**.
- The puncture position was expressed as the location of the puncture along a diameter line that passed through the centre of the puncture. Five zones from 47.5%-50.0% to 37.5% to 39.9% were established, **see Fig. 3**.
- The puncture shape was defined as circular, elongated, slightly irregular, irregular or cracked, **see Fig. 4**.



RESULTS & DISCUSSION

- A small number of capsules failed to be punctured by the DPI user; hypromellose (n=6) and gelatin (n=3). The difference was not statistically significant (Z-test for comparing proportions, $p=0.3124$). Hesitancy, observed in some participants at the beginning of the experiment, may account for some non-punctures.
- Results indicate that the greatest variability in the area of the puncture was in gelatin capsules with a moisture content below the specification range **see Fig. 5A**.
- Statistical analysis indicates that the inter-individual variability in the puncture area was not different between hypromellose capsules stored at the two different moisture levels or between gelatin and hypromellose capsules with normal moisture specification. However the inter-individual variability in puncture area was significantly different between gelatin capsules stored at normal or low moisture ($p = 0.001$).
- The intra-individual variability was also greater for gelatin capsules than hypromellose capsules at both moisture levels.
- The shape of the punctures in hypromellose capsules at both moisture contents were predominately circular (>80%).
- Puncture shapes in gelatin capsules were more variable, particularly at low moisture content, **see Fig. 5B**, and flaps were also detached (74.5%), compared to the gelatin capsules with normal moisture content (99.1%).
- The majority of participants rated the process of loading the capsules and pressing the buttons as very easy (27/34) and the remainder as easy.

CONCLUSIONS

- Within the normal moisture specification hypromellose and gelatin capsules produced regular sized punctures on DPI actuation.
- The punctures created in gelatin capsules had a more variable area and shape at low moisture levels, which results in significant intra- and inter-individual variability.
- Changes in moisture content have less impact on the characteristics of the punctures created in hypromellose capsules.
- Care is therefore required to prevent gelatin capsules from losing moisture during storage to
- The use of light microscopy to characterise capsule punctures is limited by the 2-dimensional images that are created. Future studies need to utilise systems that give 3-dimensional images to better understand the flap position and to provide a more accurate measure of the puncture aperture.
- Future studies aim to determine how differences in the capsule puncture characteristics impact on delivery of a dry powder formulation from a DPI.

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 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".
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