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Evaluating the sensitivity, reproducibility and flexibility of a method to test hard shell capsules intended for use in dry powder inhalers

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ABSTRACT

Pharmaceutical tests for hard shell capsules are designed for orally administered capsules. The use of capsules in dry powder inhalers is widespread and increasing and therefore more appropriate tests are required to ensure quality and determine if these capsules are fit for purpose. This study aims to determine the flexibility, reproducibility and sensitivity of a quantitative method that is designed to evaluate the puncture characteristics of different capsule shell formulations under different climatic conditions. A puncture testing method was used to generate force displacement curves for five capsule formulations that were stored and tested at two different temperatures (5 °C and 19 °C). Force-displacement puncture profiles were reproducible for individual capsule shell formulations. The methodology was able to discriminate between capsules produced using different primary materials i.e. gelatin versus hypromellose, as well as more minor changes to capsule formulation i.e. different material grades and excipients. Reduced temperature increased the forces required for capsule puncture however further work is required to confirm its significance. Results indicate the method provides a reproducible and sensitive means of evaluating capsule puncture. Future studies should validate the methodology at different test sites, using different operators and with different capsule shell formulations.

1. Introduction

Dry powder inhalers (DPIs) are used to deliver micronized drugs to the lungs, typically to treat pulmonary disease (Atkins 2005; Pavkov et al., 2010). In some DPIs hard shell capsules are used as a single-dose container for the drug in association with a carrier excipient. To facilitate pulmonary drug delivery from such devices the capsule wall is either punctured with a set of sharpened pins or cut by a blade. The powdered drug is then released from the capsule and entrained into the airflow upon inspiration by the user (Jones 2003). DPIs are established delivery systems that have formed the basis of many highly successful drug products for the treatment of asthma and COPD. In recent years there has also been an increase in new capsule products for use in DPIs.

A hard shell capsule consists of two open-ended cylinders, a cap and body, that fit one inside the other (Jones, 2004). The capsule manufacturing process typically involves sourcing raw materials, preparing a solution of the capsule shell formulation, dipping standard rod-shaped-moulds into this solution, drying the films formed, removing them from the moulds and cutting the dried capsule shells to the correct length before joining the capsule body and cap together. Pharmaceutical materials used to manufacture DPI capsules are typically based on either gelatin or hydroxypropyl methylcellulose (HPMC). Gelatin, which is commonly derived from collagen that has been extracted from bovine bone and skin, has been used by the pharmaceutical industry to manufacture hard shell capsules for more than a century. The properties of this biological material are governed, in part, by the source of the raw material and the processing steps that are used. Under 'normal' storage conditions gelatin capsules have a water content of 13.0–16.0%. This water acts as a plasticiser in gelatin films and therefore in low humidity conditions gelatin capsules become brittle and prone to breakage on transport or during use (Jones 2003; Nagata 2002). HPMC capsules are used as an alternative to gelatin as they offer particular advantages: they are made from a plant-derived material, the capsule shells have a significantly lower moisture content, 4.0–6.0%, maintain appropriate physical properties when

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exposed to low humidities and provide a suitable container for moisture-labile compounds (Nagata 2002; Ogura et al., 1998).

Hard shell capsules were originally developed for oral dosage forms and the Pharmacopoeial tests are for filled capsules and not for empty ones. None are designed to evaluate the mechanical properties of capsule shells, a key parameter when the aim is to introduce an inhaler pin into the capsule to create a hole for powder emission. There is therefore a need to establish more predictive tests for capsule performance in DPIs that are robust enough to be used for quality assurance purposes and yet sensitive enough to detect minor changes in capsule properties. Our group have recently developed a methodology that can be used to evaluate the puncture performance of capsules that are to be used in DPIs (Torrisi et al., 2013), however, further work is required to determine the reproducibility, sensitivity and flexibility of the method.

Patients do not always appreciate the importance of correct storage (Renswoow et al., 2010) or are unable to adhere to storage instructions. However, DPIs are used in countries and regions, with very different climatic conditions, and therefore filled capsules, for use in DPIs, are often packaged in blisters. Blister packing ensures that under adverse storage conditions capsules are offered some protection from moisture gain or loss. DPIs are used by patients in many different climatic conditions, for example in northern climes during winter they will be used at lower temperatures. The potential use of biologics in DPIs may also necessitate storage in the refrigerator. However, little is known about the influence of temperature on the performance of capsules in DPIs. This study uses a previously reported method (Torrisi et al., 2013) to characterise the puncture of five different capsule formulations, using a pin from a DPI, at two different time points and at two different temperatures (5 °C and 19 °C). The aim is therefore to establish the reproducibility, sensitivity and flexibility of the method as a means to control the quality of empty capsule formulations, intended for use in DPIs, and potentially predict their performance under different climatic conditions. A secondary objective is to extend the previously described method to provide semi-quantitative characterisation of capsule punctures.

2. Materials and methods

2.1. Capsule conditioning at controlled temperature and humidity

Five different capsule shell formulations (labelled A–E; Table 1), provided by Qualicaps Europe, S.A.U. (Alcobendas, Spain), were conditioned either in a cold room (target temperature 5 °C) or in a temperature controlled room (target temperature 19 °C) for a minimum period of 7 days. All capsules were stored in desiccators over either a saturated solution of calcium chloride (Sigma–Aldrich, Poole, UK), to create a capsule moisture content in the lower part of the normal moisture specification limits (13–16% for gelatin and 4.5–6.5% for HPMC inhalation grade capsules), or magnesium nitrate (Sigma–Aldrich, Poole, UK), to create an environment that resulted in capsule formulations with moisture contents in the upper part of the normal range or slightly above. Capsules A–D consisted of a blend of HPMC, carrageenan (a gelation aid) and potassium chloride (a network promoter). Capsule D was produced from HPMC that had been sourced from a different supplier than capsules A–C. Capsules A and D were colorless, capsule B contained titanium dioxide (and was therefore white) and capsule D contained FD&C yellow. The loss of water on drying (LOD) test (Council of Europe, 2005), was used to determine the moisture content of capsules both prior to and during the testing period.

2.2. Capsule puncture force measurements

The force of capsule puncture was measured and recorded using a Zwick materials testing machine (Herefordshire, UK), as previously described (Torrisi et al., 2013). However, to enable testing to take place in different locations (a temperature controlled room and a cold room) the materials testing machine and accompanying hardware were mounted on a mobile heavy-duty trolley, which was re-positioned as necessary. Puncture tests were performed at a test speed of 10 mm/minute with an angular single metal pin from a RS01 2-pin inhaler (Plastiape S.p.A; Milan, Italy). This was attached via a chuck to the materials testing machine, which converts the force of puncture into a measurable electrical voltage. Tests were conducted multiple times ($N = 10$) at two different time points for each capsule type in order to evaluate test reproducibility.

2.3. Physical characterisation of punctured capsules

All punctured capsules from a single experimental set ($N = 10$) were mounted in a cap bushing from a capsule filling machine (Qualicaps Europe S.A.U) and inspected visually using an AmScope Stereo Inspection Microscope (CA, USA). Representative images were captured using the MU900 integrated digital camera (×3.3–×180 zoom) within 30 min of capsule puncture. The shape of the capsule puncture was recorded as regular or irregular (Fig. 1), the presence or absence of a flap at the point of puncture was recorded and the cross sectional area of the puncture (Fig. 2) was measured, relative to the capsule cross sectional area, using ImageJ (NIH, USA) software.

2.4. Data processing and statistical analysis

Figures were generated and statistical analyses (unpaired two-tailed *t*-tests) were performed using Prism 5 for Mac OS X (GraphPad Software Inc., USA).

3. Results

3.1. Capsule conditioning

The mean average daily temperature in the temperature controlled room was 19 ± 0.19 °C and in the cold room was 4.8 ± 0.23 °C. The humidity in the temperature controlled room and cold room was 44.9 ± 4.0% and 81.8 ± 5.2% respectively, however, capsules were stored in desiccators in order to control their moisture content. Table 2 provides detail of the moisture

Table 1
The denominations and descriptions of the capsule shell formulations tested in this study.

Capsule label	Description	Principal material	Other excipients
A	Quali-V®-I transparent clear	HPMC	
B	Quali-V®-I opaque white	HPMC	Titanium dioxide
C	Quali-V® grade A transparent orange	HPMC	
D	Quali-V® grade B transparent clear	HPMC	
E	Hard transparent clear	Gelatin	