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The development of a sensitive methodology to characterise hard shell capsule puncture by dry powder inhaler pins

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ABSTRACT

In order for hard-shell capsules to function effectively as drug reservoirs in dry powder inhalers, the capsule must be punctured with sharpened pins to release the powdered medicament upon inspiration. Capsule performance in this setting is poorly understood. This study aims to develop a methodology to characterise hard shell capsule penetration by needles from commercial dry powder inhalers, to determine whether changes to capsule materials impact on their performance.

Two pin types from two commercial dry powder inhalers were mounted in a material-testing machine, equipped with a 500 N load cell. A stainless steel bush was used to secure a capsule directly below the steel pin. Hypromellose ($n = 10$) and gelatin capsules ($n = 10$) were conditioned in 'normal' or low humidity conditions and were subsequently punctured with both types of pin. Each puncture event was recorded on a load–displacement curve.

The force required for puncture was 2.82 ± 0.26 N for hypromellose capsules and 4.54 ± 0.26 N for gelatin capsules, stored in normal humidity. Different capsule materials possessed distinguishable signature profiles but repeated force–displacement profiles were highly reproducible i.e. intra-individual variability was minimal. A rapid, robust yet sensitive methodology has therefore been developed that is able to characterise hard shell capsule materials based on the puncture performance.

1. Introduction

Hard-shell gelatin capsules are an established dosage form for drug delivery either via the oral route or as part of dry powder inhaler (DPI) systems, where they are used as a single-dose container for a powdered drug (Jones, 2003). DPIs are primarily used for the localised treatment of pulmonary conditions such as asthma, bronchitis and chronic obstructive pulmonary disease (Timsina et al., 1994; Pavkok, 2010), however they have also demonstrated benefit in the systemic delivery of therapeutic polypeptides and proteins including insulin (Klingler et al., 2009) and vaccines (Lin et al., 2011). Release of medicaments from a capsule that has been loaded in a DPI occurs in two distinct stages; the first is puncture of the capsule shell with sharpened pins, although blades for capsule cutting are also used (Jones, 2003), and the second is expulsion of the powdered medicament upon inspiration.

Capsule puncture within a DPI is determined by a number of factors related to the design of the device, the materials used in its component parts and how the patient uses the device. The first marketed DPI, the Spinhaler®, was produced by Fisons in the late 1960s (Jones, 2003) and used two pins to create opposing holes in the sidewall of the body of a gelatin capsule. Subsequent DPIs have used either pairs of pins, to make single holes in the sidewalls (Handihaler®, Boehringer Ingelheim) or in the domed ends (Plastiape), or two sets of four pins (Cyclohaler®, Pharmachemie and Foradil®, Novartis), to make multiple holes in both the domed body and cap. In each of these devices insertion of the needle into the capsule wall is a manual mechanical process controlled by the patient.

Two-piece hard gelatin capsules contain a significant amount of water; their moisture content specification is 13.0–16.0%. Water acts as a plasticiser in gelatin films and when their moisture drops below 11% they become brittle (Nagata, 2002; Jones, 2003). This can happen when capsules are exposed to low humidities during storage or in use. This is a major disadvantage, particularly in the case of inhalation capsules, because it can lead to large irregular shaped puncture holes and the production of shell particles that can be inhaled by the patient (Jones, 2003). There is anecdotal evidence that this can cause patients to complain of a sensation of tingling in the back of the throat, which is acknowledged in patient literature (EMEA, 2012). In the last 10 years hypromellose capsules have been introduced to the inhalation market to overcome the

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problem of brittleness. The moisture content of hypromellose capsules, 4.5–6.5%, is lower than gelatin and can be reduced to <1% without significantly affecting physical properties (Ogura et al., 1998; Nagata, 2002).

The development of hypromellose capsules for use in DPIs requires an understanding of their physical properties particularly in relationship to their puncturing and cutting. Several studies have been published comparing the type of puncture holes made in hypromellose and gelatin capsules by DPI pins. The size and shape of the punctures made manually using different DPI were quantified by measuring the geometry of the holes and by using a quality scoring system (Jones, 2003). Sakuma et al. (2004) were the first to publish work measuring their physical properties of inhalation grade hypromellose capsules. Capsule mechanical strength and puncturing properties were analysed using an Autograph AGS-J Table-top Type Universal Tester (Shimadzu, Japan), using a platen to measure crushing strength or a standard 1 mm sewing needle to measure puncturing force. Birchall et al. (2008) were the first group to use a pin from a DPI to measure capsule puncturing forces. They used an Instron tester with a single pin extracted from a set of 4 used in Foradil® inhaler. They conditioned capsules at two RHs, 11% and 34%, which gave capsules at the lower end of the normal specification and significantly below these limits. The limitations of this study were that the methodology was not sensitive enough to detect subtle changes in force and the experimental set-up only permitted penetration in the centre of the capsule domed end and did not replicate how a set of 4-pins would behave when penetrating the periphery of the capsule end domes. Currently there is no reliable and validated methodology to determine capsule puncture performance.

The present study aims to develop a simple, rapid, robust but sensitive methodology that can be used to characterise the penetration of hard shell capsules by needles that are used in commercial DPIs. This methodology should enable high throughput analysis that can rapidly characterise the process of capsule penetration and determine whether changes to materials and/or conditions have an impact on their potential performance in DPIs. As a corollary, this study will further define the behaviour of gelatin and hypromellose capsules when punctured by pins used in commercial DPI devices. Additionally this study aims to characterise penetration of hard shell capsules using a four-pin system, a process that is currently poorly understood.

2. Materials and methods

2.1. Materials

Size 3 standard opaque pink/clear gelatin and clear/clear hypromellose, Quali-V®-I, empty hard-shell capsules for inhalation products were provided by Qualicaps Europe, S.A.U. (Alcobendas, Spain). Pins used to puncture the capsules were obtained from Plastiape S.p.A. (Milan, Italy): two types of stainless steel pins from their DPIs were used in this study and are differentiated in the text by the shape of the needle tip i.e. (i) conical, which is used in an inhaler with 2 sets of 4-pins that penetrate the periphery of cap and body domes and (ii) angular, which is used in an inhaler with 2 single pins that penetrates the centre of each dome. A set of four pins mounted on their push button from an 8-pin inhaler was also evaluated. Lithium chloride and calcium chloride were purchased from Sigma Aldrich (Poole, UK).

2.2. Capsule moisture content conditioning

Gelatin and hypromellose capsule samples were stored in desiccators over saturated solutions of lithium chloride and calcium chloride at 22 °C, for a minimum period of 7 days. Calcium chloride and lithium chloride produce a relative humidity (RH) of approximately 34% and 11% respectively. Capsules stored over a saturated solution of calcium chloride were dried to a value at the lower end of their normal moisture specification limits i.e. 13.0–16.0% for gelatin capsules and 4.5–6.5% for hypromellose capsules. Conversely, capsules stored over saturated solutions of lithium chloride were dried to a value below these specifications. The moisture content of capsules was determined by the loss of water on drying method using a vacuum oven. Hypromellose capsules were dried at 100 °C for 2 h (Qualicaps standard method) and gelatin capsules were dried at 105 °C for 17 h (Council of Europe, 2005) The tests were carried out using duplicate 1gram samples. Results were expressed as the mean of duplicate samples.

2.3. Metallic DPI pin characterisation

The two single metal pins used in this study were mounted on aluminium stubs and characterised by scanning electron microscopy (SEM) (FEI XL30, Eindhoven, The Netherlands). The set of four pins, embedded in the plastic mount that is employed in a DPI, was sputter coated with gold under partial vacuum (SC500, Bio-Rad, Hemel Hempstead, UK) and analysed by SEM. The four pin set was also characterised at low magnification using a digital camera (Canon digital Ixus 82 IS, Watford, UK).

2.4. Capsule penetration tests

2.4.1. Experimental Set up

A Zwick® materials testing machine (Zwick® Testing Machines Ltd., Herefordshire, UK) was used to conduct the penetration tests (Fig. 1). The Zwick® materials testing machine consists of a single column device for tensile, compression and cyclic testing up to 5 kN. An XForce P 500 N load cell (accuracy ±1% of the measured value), which converts the force into an electrical measurable voltage, was employed in this study. The load cell was attached to the moving crosshead device of the materials testing machine, whose movements were controlled using testXpert® II software. A collet chuck (Zwick® Testing Machines Ltd., Herefordshire, UK) with a clamping range from 0 to 10 mm was positioned on the load cell through a mounting stud. A stainless steel bush (Qualicaps, Alcobendas, Spain), from a capsule filling machine, was mounted in a parallel vice (Zwick® Testing Machines Ltd., Herefordshire, UK) which itself was held in position by a T-slot base. The bush holds size 3 capsules in a fixed position, with minimal lateral movement.

2.4.2. Experimental protocol

Hypromellose and gelatin capsule samples ($n = 10$ for each test) were positioned, cap side up, into the recess of the stainless steel bushing, which was orientated appropriately and subsequently secured in a fixed position (Fig. 1). The metallic pins used in this study (the single conical pin, the single angular pin and the four conical pin arrangement) were attached to the chuck and the software was programmed to conduct a compression test at a speed of 10 mm/min and to collect data following a registered force of 0.05 N, corresponding to the initial contact between the pin and the capsule wall. The displacement of the pin and the resulting force were recorded and registered on a load–displacement curve. The test was completed at a displacement value that was pre-determined in order to ensure at least a 5 mm penetration of the pin into the capsule and thus completion of the event. At this stage the pin was returned to its original position. The punctured capsule was then removed from the bush for visual inspection (Section 2.5) and was replaced by an untreated capsule and testing was continued.