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A Comparison of the Puncturing Properties of Gelatin and Hypromellose Capsules for Use in Dry Powder Inhalers

J. C. Birchall and B. E. Jones
Gene Delivery Research Group, Welsh School of Pharmacy, Cardiff University, Cardiff, UK

A. Morrissey
Biomedical Microsystems Team, Tyndall National Institute, Cork, Ireland

B. E. Jones
Qualicaps Europe, S.A., Alcobendas, Madrid, Spain

This study investigates capsule puncture in dry powder inhalers. Gelatin and hydroxypropylmethyl cellulose (HPMC) capsules (stored at 11 and 33% relative humidities) were punctured using a pin from a Foradil® inhaler, with insertion force measurement via an Instron tester. In HPMC capsules, the force after capsule puncture reduced by half and then increased to a second maximum as the pin shaft entered the hole. In gelatin capsules, the postpuncture force reduced to zero, indicating shell flaps losing contact with the pin. At lower moisture contents, both capsules were less flexible. This provides a tool to measure the shell properties of inhalation capsules.

Keywords capsule; puncture; dry powder inhaler; gelatin; HPMC

INTRODUCTION

Hard two-piece gelatin capsules have been used as a container for unit doses of medicines to be taken by inhalation since the early 1970s (Bell, Hartley, & Cox, 1971). Originally, such inhalers were designed as a means of treating localized pulmonary conditions such as asthma. In recent years, there has been increased interest in the delivery of an extended range of active pharmaceutical ingredients (APIs) to the lungs as this delivery route is capable of transferring the active ingredients into the general circulation while avoiding the digestive processes and first-pass metabolism. It has been suggested therefore that the lung represents a useful drug delivery portal for several therapeutic applications including lung diseases, systemic diseases, vaccines, and the noninvasive delivery of peptides and proteins (Patton, 2004): the recent advance of inhaled insulin to the market being one such example. Hard capsules have traditionally been used for pulmonary application because they are relatively inert, can be filled with small quantities of powder on high-speed automatic machines, and are of a size that enables patients to handle them easily. To release the powder from the capsules the unit-dose dry powder inhalers (DPIs) are designed to puncture the capsule shells, either with a needle or a blade (Nakate et al., 2005). The powder is subsequently released from the capsule through the opening(s) made in the shell wall when the patient inhales through the DPI. The first marketed dry powder inhaler was the Spinhaler® of Fisons that used gelatin capsules filled with a mixture of lactose and sodium cromoglicate (Fisons Pharmaceuticals, 1970). The Spinhaler® was unique for its time because it was a breath-actuated inhaler and overcame the problem of patient coordination, which provided a significant limitation with other contemporary inhalers. Gelatin capsules are generally well suited for this application; however, they become brittle if they lose moisture due to exposure to low humidities (Kotny & Mulski, 1989) or due to interaction with powder fills (Bell, Stevenson, & Cox, 1971).

More recently, capsules have become available made from hypromellose that have a lower moisture content than gelatin capsules and which do not become brittle when they lose moisture (Nagata, 2002; Ogura, Furuya, & Matsuura, 1998). It has been suggested that these capsules would have better functional properties than gelatin capsules (Nakate et al., 2005). When the capsule shell is punctured in the DPI, the holes produced need to be regular in shape and size, and the material cut from the wall should remain attached as a flap, remain in an open position, and not be so elastic that it returns to its original position reclosing the hole when the needles or blades are removed. If particles of shell become detached, they will be inhaled by the patient and there is circumstantial evidence that this causes irritation in their throats. Thus these factors are used in judging the quality of puncture holes.

Address correspondence to J. C. Birchall, Welsh School of Pharmacy, Cardiff University, King Edward VII Avenue, Cardiff CF10 3NB, UK. E-mail: birchalljc@cardiff.ac.uk

Little work has been published on the mechanical properties of hard capsule shells that could be used to predict their performance in a DPI. Podczeck (2002) compared the load required to distort gelatin and hypromellose capsules over a range of humidities and found that hypromellose were less resistant to distortion than gelatin capsules but that they maintained their properties over a wider range of humidities. Two student projects in the Welsh School of Pharmacy have compared gelatin and hypromellose capsules puncturing in several types of DPI, with capsules conditioned to moisture contents in the lower part of their normal specification and to a value below this to simulate storage under adverse conditions (Jones, 2003). The hypromellose capsules produced more regular shaped holes with significantly less shedding of pieces than the gelatin capsules. Sakuma, Tochio, and Nagata (2004), measured the mechanical strength and puncturing force of capsules for inhalation with a force measuring device (Autograph, AGS-J, Shimadzu, Corporation, Kyoto, Japan) fitted with a standard 1-mm-diameter sewing needle (Sakuma et al., 2004, S. Tochio, personal communication, 2007). They compared the standard gelatin capsules with hypromellose capsules, made with different grades of raw material at standard moisture contents. They measured the caps of the capsules only and found that the force to dent the ends of capsules using a flat platen was in the range 10–30 N for hypromellose capsules and 55 N for gelatin capsules; and the force to puncture the shells was 2–3 N for hypromellose and 8 N for gelatin.

A recent paper used a time-domain ^{1}H-NMR method to monitor the state of water in gelatin and hypromellose capsules and its relationship to their mechanical properties as their moisture content was changed (Kuentz, Rothenhäusler, & Röthlisberger, 2006). They used the following instruments: a Bareiss U73 tester (Bareiss Testing Instruments Ltd., Oberdischingen, Germany) to measure the hardness and a texture analyzer, TA-Xt2i (Stable Microsystems Ltd., Godalming, Surrey, UK) to measure the stiffness of the shells. They showed that at low humidities, hence low moisture contents, both types of capsule were harder and stiffer, with gelatin shells having the higher values and that these factors decrease as the humidity was increased. They related these changes to the state of the water in the shells. They described water as being in three states: tightly bound (M3), bound (M2), and loosely bound (M1) water. At humidities between 10 and 35%, water is present in all the three forms and in similar proportions.

This study was undertaken to understand further the effect of the moisture content on the puncturing behavior of two types of hard capsule shells, gelatin and hypromellose, made for inhalation products when punctured in a DPI. Specifically, an Instron tester was used to provide a real-time sensitive determination of capsule puncturing during the insertion of a pin removed from a Foradil® inhaler. Scanning electron microscopy was used to provide a detailed architectural assessment of the punctured capsules.

MATERIALS AND METHODS

Materials

Hard capsules for inhalation products were obtained from Qualicaps Europe, S.A. (Alcobendas, Spain): size 3 standard gelatin capsules for inhalation products, opaque pink /clear, and Quali-V®-I, hypromellose capsules for inhalation products, clear/clear. A Novartis Foradil® DPI (Novartis, Basel, Switzerland) (Figure 1A) was used to obtain capsule puncture pins. This device has two sets of four pins that are used to manually puncture the domed ends of the capsule shell.

Preparation of Capsule Samples

Samples of capsules, 20–30, were stored in desiccators over saturated solutions of lithium chloride and calcium carbonate at 22°C for at least 1 week. The lithium chloride solution produces a relative humidity (RH) of about 11% and both sets of capsules were dried to below their normal lower specification limits of gelatin 13.0% and Quali-V®-I 4.5%. The calcium carbonate solution produces an RH of about 33% and the capsules were dried to a value in the lower quarter of their normal moisture specification limits: 13.0–16.0% for gelatin capsules and 4.5–6.5% for hypromellose capsules. The moisture content of the capsules after storage was determined by measuring the loss on drying in an oven at 105°C for 17 h of duplicate 1 g samples.

Capsule-Puncturing Device

A Foradil® inhaler was chosen for use in the study for two reasons. Firstly, it was a simple mechanical task to isolate a single pin for use. A single pin was used to facilitate data analysis and readily relate the data to individual pin puncturing characteristics. Other DPIs that use pins have a more complex structure that would have required cutting of the metal parts and possible damage to the puncturing part, for example, a Fisons Spinhaler®. Secondly, the domed ends of the cap and body are punctured and this makes it an easy matter to place either the cap or the body of capsule onto a platform for puncture force testing and electron microscopy. In addition, there is minimal

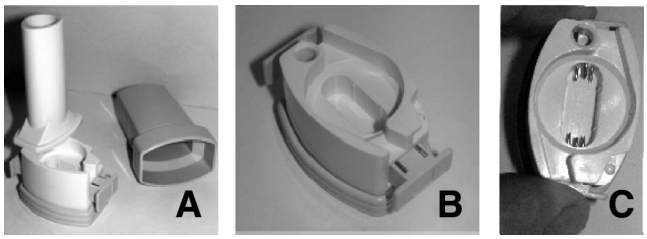

FIGURE 1. Photographs of Foradil® Dry Powder Inhaler, Novartis. (A) Complete inhaler showing constituent parts: capsule holder, mouthpiece and cover. (B) Base holder showing capsule chamber and buttons. (C) Buttons depressed showing pins in puncturing position.

flexing of the capsule part during testing unlike that which occurs if a single pin is applied to the sidewall of a cap or body because capsule parts are open-ended cylinders.

The Foradil® inhaler has two sets of four pins held in a housing at either side of a chamber in to which a capsule is placed (Figure 1B and C). When the user depresses the two buttons the pins enter into the chamber and penetrate the housed capsule. Each set of pins is arranged in a cross formation and in two opposing sets of 2, one set of which is approximately 0.4 mm longer than the other (Figure 1C). The pins themselves have sharpened ends (Figure 2). One set of four pins was removed from a Foradil® inhaler and mounted on the platform of an Instron tester 5500 (Instron, High Wycombe, UK). Three of the pins were bent out of plane so that only one pin (for ease of data interpretation) was used to measure forces generated in puncturing the end wall of a capsule. The capsules to be tested were held firmly in a metal holder placed on a platen under the pin holder (Figure 3). This was placed on a platform and the pin was lowered into the shell at a constant speed of 0.05 mm/s. The measurement accuracy of the force generated was less than 1 mN with readings taken at 10-ms intervals. The zero point was taken from the instant that the pin touches the capsule shell surface.

Scanning Electron Microscopy

Representative samples of punctured capsules were taken and the ends cut off using a scalpel. These pieces were mounted on an aluminum stub and sputter-layered with gold under partial vacuum (EMScope®: EMScope Laboratories, Ashford, UK). Representative scanning electron micrographs were taken using a Philips XL20 (Philips, Eindhoven, the Netherlands) scanning electron microscope. Additional micrographs were taken of capsule samples, which had been conditioned over calcium carbonate solution, and punctured in a standard Floradil® inhaler, and of a set of four inhaler pins.

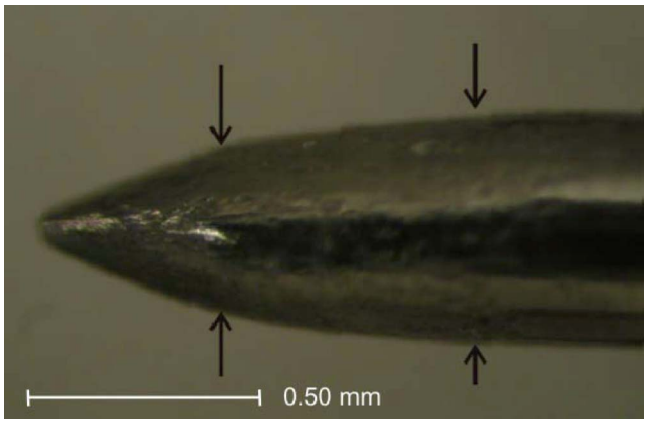

FIGURE 2. Photograph of the puncturing end of pin from a Foradil® Inhaler showing the way it has been sharpened. Left-hand arrows indicate start of incline to tip, right-hand arrows indicate end of shaft diameter.

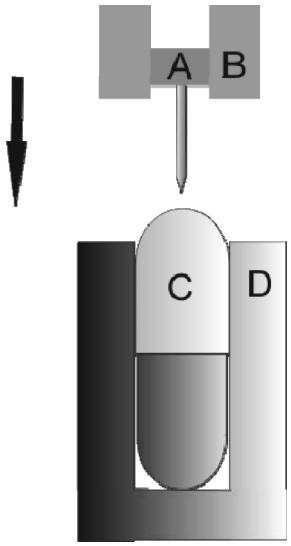

FIGURE 3. Setup for measuring capsule penetration force. A DPI pin in holder; B assembly holder; C empty hard capsule; D capsule holder.

RESULTS AND DISCUSSION

Moisture Content of Capsule Shells

Table 1 shows the moisture content of the capsules after conditioning. The samples stored over calcium carbonate solution (column B) had moisture contents just above the lower limit of the standard specification, which is 13.0% for gelatin and 4.5% for hypromellose. Those stored over lithium chloride (column A) had moisture contents about 2% below these values.

Foradil® DPI Pins

Figure 2 shows a magnified image of the tip of a single pin from a Foradil® inhaler. The picture shows that the apex of the pin comprises two distinct regions: the first region (Area 1), closest to the cylindrical pin shaft, has a shallower angle than the second region (Area 2) that terminates in a rounded point. The dimensions of a sample of 16 pins (4 sets of 4) were measured by taking photographs using a Zeiss Stemi 200-C (Carl Zeiss Ltd, Welwyn Garden City, UK) microscope fitted

TABLE 1
Moisture Content of Capsule Samples

	Storage over Saturated Solutions of	
Capsule Type	Lithium Chloride (%) (A)	Calcium Carbonate (%) (B)
Gelatin	10.4	13.1
Hypromellose	2.7	4.7

Data represented as mean of duplicate samples.

with an Olympus C-4040 (Olympus UK Ltd, Watford, UK) digital camera. The mean values, with standard deviation, of the pins were: shaft diameter = 0.50 ± 0.02 mm, length of Area = 1 0.51 ± 0.01 mm, length of Area = 2 0.36 ± 0.01 mm. The rounded point had a diameter of approximately 0.06 mm.

Penetration Force Results

The stages in the penetration of the pin into the capsule shell end walls are shown in Figure 4. When the pin first contacts the shell, a small depression is formed in the domed ends and the force increases to a maximum (Stage 1). At this point, the pin punctures the shell wall and the insertion force declines noticeably. During this process, the flaps formed by rupture of the shell wall are depressed inward. As the tapered end of the pin is lowered further into the capsule, the insertion force increases once more as the diameter of the pin entering the capsule progressively increases (Stage 2). The puncture hole reaches its maximum diameter as the pin shaft penetrates further into the capsule (Stage 3). The forces generated during puncturing are shown in Figures 5 and 6.

There was a significant difference in the behavior of the two types of capsule on puncturing (Table 2 and Figures 5 and 6). For hypromellose capsules, the mean forces to puncture each sample capsule were 4.13 N (A; low moisture content) and 3.99 N (B; normal moisture content), see Figure 5A and B, *Y*-axis, and this occurred after the pin had deflected the capsule shell wall by between 0.448 and 0.402 mm, respectively (Figure 5A and B, *X*-axis). After this peak the force reduced rapidly by about 50% in the next 0.083 mm (A) to 0.065 mm (B) of movement. As the force is not reduced to baseline, this is indicative that the flaps formed had remained in contact with the pin. The force then very gradually increased back up to a second maximum value, mean 2.0 N (A) and 1.8 N (B). Conversely, gelatin capsules required a significantly (one-way analysis of variance and Duncan's multiple range test, $p < .05$) lower puncture force to pierce the capsule wall, irrespective of moisture content, mean 3.55 N (A) and 3.21 N (B), respectively (Figure 6A and B). The amount of pin movement

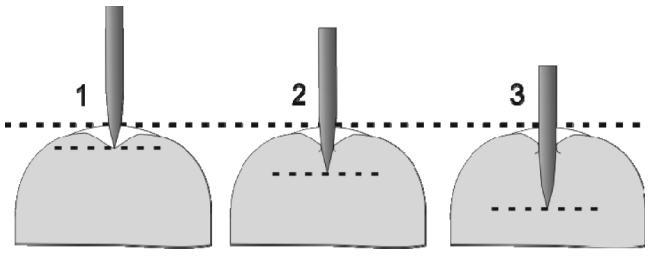

FIGURE 4. Stages in pin penetration into capsule shell: Stage 1, pin contacts shell, and depresses the shell wall; Stage 2, the pin punctures the wall; Stage 3, the pin pushes through the wall and the hole size increases to a maximum when the shaft of the pin enters the hole.

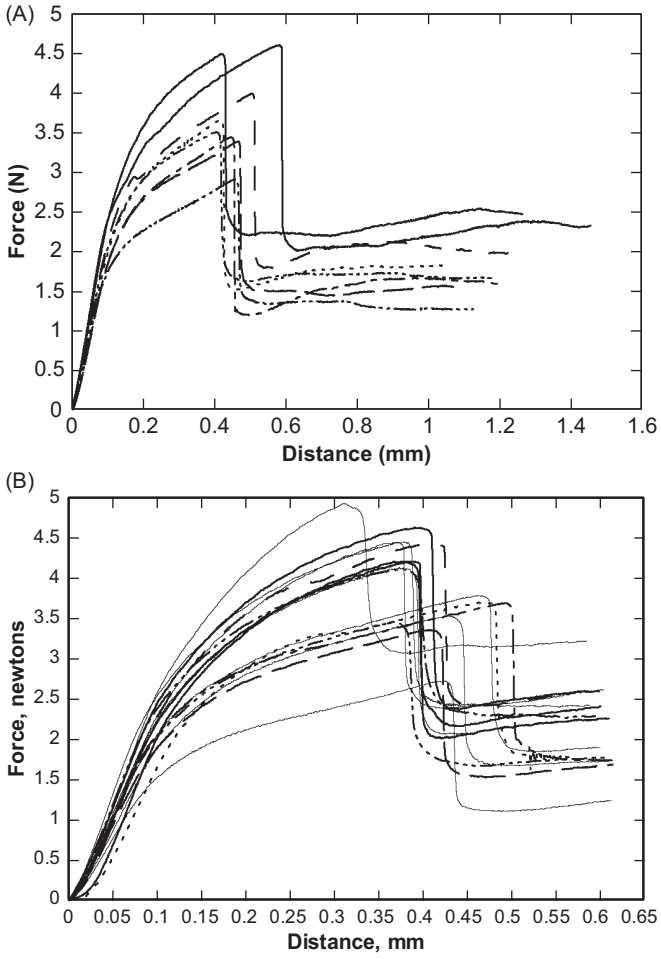

FIGURE 5. Graphs of distance moved by pin against the insertion force generated in hypromellose capsules conditioned over a saturated solution of (A) lithium chloride and (B) calcium carbonate.

required to puncture the shell wall was slightly higher than that for hypromellose capsules, 0.516 mm for (A) and 0.452 mm for (B) and this difference was significant between "low moisture content" gelatin capsules and "high-moisture content" hydroxypropylmethyl cellulose (HPMC) capsules (one-way analysis of variance and Duncan's multiple range test, $p < .05$). The force then either decreased rapidly, that is, within 0.010 mm (A) to 0.013 mm (B) of pin movement, to the baseline in 75% of the samples, or showed a similar pattern to the hypromellose capsules. As the pin moved further into the capsule, the force increased back to a second maximum value, mean 2.48 N for (A) and 2.39 N for (B), at 1.03 and 1.09 mm, respectively. This indicates that for the gelatin capsules as the pin bursts through the shell wall the flaps, which are formed, either spring open and lose contact with pin or in some cases break off. It can be seen from Figure 6A that contact with the pin is re-established quickly probably as the flaps recoil. As the pin penetrates further into the shell, its diameter increases and contact is re-established with the shell wall if the flaps have

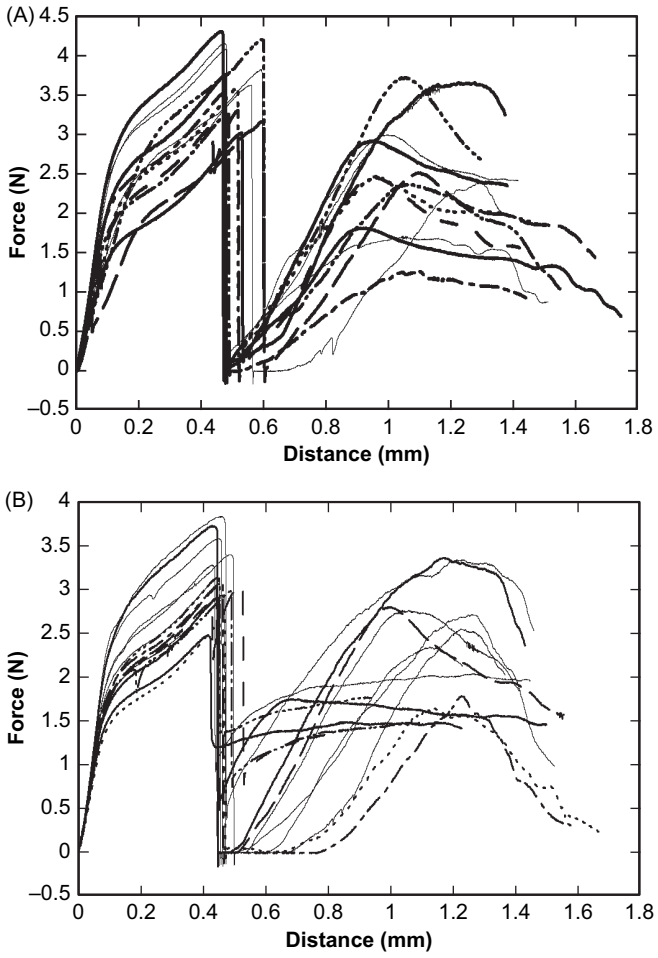

FIGURE 6. Graphs of distance moved by pin against the force generated in gelatin capsules conditioned over a saturated solution of (A) lithium chloride and (B) Calcium carbonate.

broken off. Another type of behavior is shown in Figure 6B where in some of the samples after the force reduces to zero the pin travels between 0.3 and 0.4 mm before it starts to show an increase again, whereas in others the force reduction to zero does not occur and the pattern is similar to hypromellose capsules. The capsule shell wall after puncturing will also return to something approximating its original shape, that is, the dimple depression formed will spring upward. The force for both types of capsule then increases up to a maximum when the shaft of the pin enters the puncture hole. This interpretation of the events is confirmed by the fact that this occurs at a penetration distance of between about 1.0 and 1.1 mm, which corresponds to the distance from the tip of the pin to the pin shaft plus about 0.1 to 0.2 mm, which represents the residual depth of the deflected dimple formed in the capsule end before puncturing occurs, see Figure 4. After this point, as the shaft penetrates further the force declines slowly from the maximum value.

The results show that both capsules are less elastic and more rigid at the lower moisture content. This is indicated by the increase in distance the pin moves before the shell is punctured and by the slightly higher forces observed. This is a similar observation to that seen by (Kuentz et al., 2006) obtained using a texture analyzer. These workers showed that the moisture in both hypromellose and gelatin capsules is present in three states: loosely bound, bound, and tightly bound. In the RH range 10–40%, the conditions used to condition the capsule shells in our tests, they found that all three states of water were present and as the proportion of loosely bound water increases as the RH rises, the "stiffness" of the capsules decreases. Our results are different from those reported by (Sakuma et al., 2004) because in their study they used standard capsules and not those specially manufactured for inhalation. The moisture content of the capsules was "as received," hypromellose 4% and gelatine 13%, and were not conditioned to a specific level, and the needle used was a standard sewing needle with a larger diameter, 1 mm, and not one taken from a DPI (S. Tochio, personal communication, 2007).

Morphology of the Puncture Holes

The difference in the puncturing behavior between the two types of capsule can be seen further in the images taken with the scanning electron microscope (Figures 7–9).

For gelatin capsules, Figure 7 shows that the holes when viewed from the outer capsule surface are circular with smooth

TABLE 2
Forces Generated During Capsule Shell Puncture with a Foradil® Pin

	Gelatin Capsules		Hypromellose Capsules	
Moisture Content (%)	10.4	13.1	2.7	4.7
Puncture force (N)	3.55 ± 0.52	3.21 ± 0.44	4.13 ± 0.65	3.99 ± 0.56
At distance (mm)	0.516 ± 0.054	0.452 ± 0.029	0.448 ± 0.047	0.402 ± 0.046
Minimum force* (N)	0.09 ± 0.37	0.32 ± 0.54	1.82 ± 0.36	2.02 ± 0.48
At distance (mm)	0.526 ± 0.050	0.465 ± 0.027	0.531 ± 0.066	0.467 ± 0.053

Statistical analysis by one-way analysis of variance and Duncan's multiple range test. Significance level $p < .05$.
*Post-puncturing.

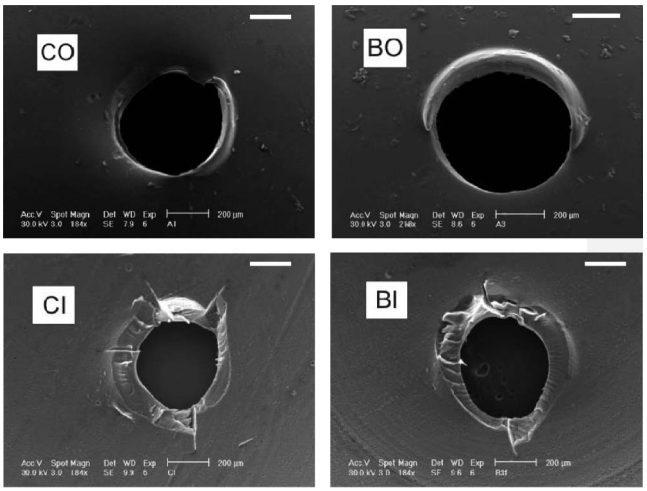

FIGURE 7. Scanning electron micrographs of the outside (O) and inside (I) surfaces of gelatin capsule showing the single puncture hole produced in the test. C = cap; B = body. Bar = 200 µm.

edges with a diameter of approximately 0.50 mm, corresponding accurately with the shaft diameter of the DPI pin. When visualized from within the capsule (inner surface), the edges of the holes are irregular and show the bases of flaps that had become detached.

Figure 8 shows that the puncture holes in hypromellose capsules are more complex in structure, being smaller because the flaps, which are formed from the shell wall, are still attached. From the inner surface view, it can be seen that the flaps have been formed by splitting or tearing of the shell wall and they have recovered from the wide open position that they would have momentarily adopted as the pin shaft entered into the capsule.

In regular use, each capsule part, that is, cap and body, is punctured by four pins at a time as shown in Figure 9. Both

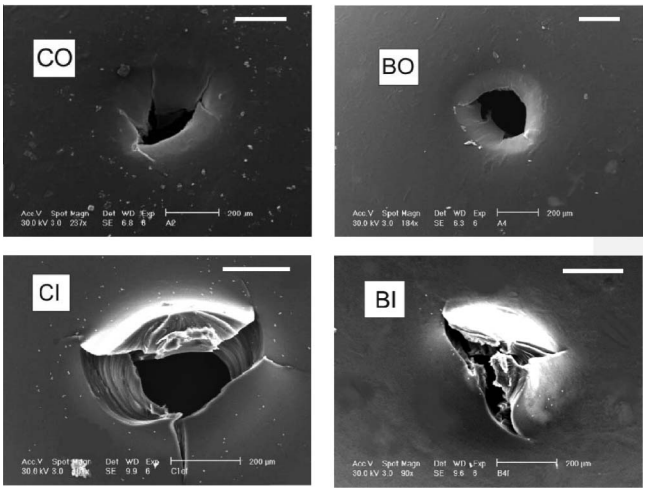

FIGURE 8. Scanning electron micrographs of the outside (O) and inside (I) surfaces of hypromellose capsules showing the single puncture holes produced in the tests. C = cap; B = body. Bar = 200 µm.

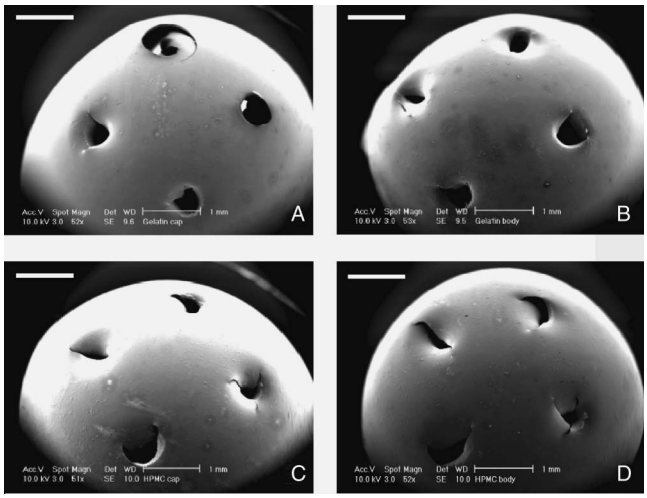

FIGURE 9. Scanning electron micrographs of the multiples holes produced by a standard Foradil® DPI in capsules conditioned by storing over a saturated solution of lithium chloride. A, gelatin cap; B, gelatin body; C, hypromellose cap; D, hypromellose body. Bar = 1 mm.

the capsules show depressions formed around the puncture hole, which vary in depth. In the case of the gelatin capsule cap, it can be seen that the shell is more brittle because in one of the holes the initial puncture can be seen in the center of a flap that has itself become partly detached from the capsule shell. This would result in a larger than standard hole being formed.

CONCLUSION

This study is the first to report on the forces involved in puncturing capsule shells in a dry powder inhaler by using an actual device pin as the measurement tool. The method is easy to perform and will be of use in the testing and manufacturing of the empty hard capsules for inhalation used in these devices. The relative humidity conditions used in the tests were chosen to simulate the storage under adverse conditions. The results show that the puncturing properties of hypromellose capsules are less affected than gelatin ones over a range of lower moisture contents. Further studies are now warranted to determine powder emission from the punctured shells and subsequent pulmonary deposition.

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