Testing and comparison of puncturing forces for gelatin and HPMC inhalation capsules

Evaluating capsule-puncturing force consistency may benefit capsule manufacturers, developers and patients

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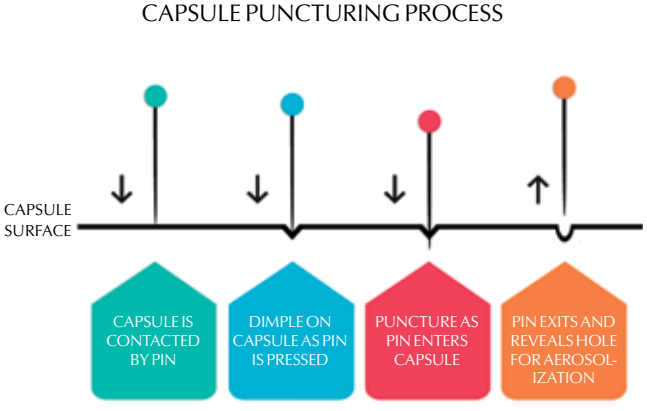
This article discusses principles of capsule puncturing then presents a comparative study of puncturing forces in gelatin and HPMC capsules. A study of this type and the data it provides about consistency in capsule puncturing could provide benefits for capsule manufacturers and developers of capsule-based inhalers (for instance, in quality control for release purposes) as well as assurances for patients.

Requirements for capsule puncturing to facilitate proper dosing

The process of drug delivery using a capsule-based dry powder inhaler (DPI) is quite simple, consisting of only two steps: puncturing and aerosolization. Capsule puncturing is diagrammed as a four-step process in Figure 1 and shown in photos in Figure 2.

Figure 1

A representation of capsule puncturing.



Each time the inhaler is used, the capsule must be punctured in a reproducible manner and fully emptied of powder to facilitate complete and consistent dosing. When the capsule is opened by pins or blades (i.e., punctured), low forces must be used. If a flap is produced, it must stay attached, remain open and not reclose or obstruct the opening. Pieces of the capsule must not shed and hindrances on the capsule must not be created, as these may negatively impact the outflow of powder during aerosolization. If powder is unable to exit the capsule due to an inconsistent puncture or being trapped on a flap, a patient may receive a dose that is lower than prescribed, which could reduce treatment efficacy.

Also, a capsule must not be crushed or broken during puncturing. Each capsule-based inhaler has a filter to capture capsule fragments to avoid their being inhaled. However, powder could stick to fragments on the filter so, again, a patient may not receive the proper dose of medication.

During inhalation and aerosolization, the flow field generated within the device rotates the capsule at high speed. Powder in the capsule is deagglomerated, impacting the internal walls of the capsule and forced to exit the capsule through the puncture holes, into the surrounding field.

Illustrating puncturing forces

Figure 3 shows puncturing force from a conical pin within an inhaler and the resulting deformation the pin causes on a hard capsule, as a 3-phase process. In phase 1, the pin contacts the capsule, which resists puncturing and begins to deform as a depression is created by the pin. The linear portion of the curve is

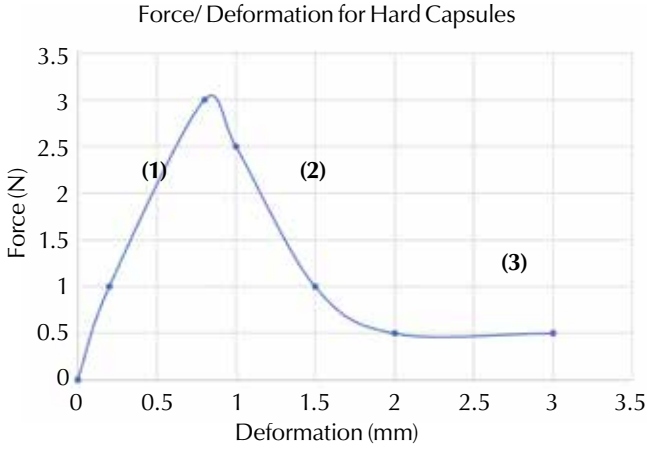
Figure 2

Various capsule-based dry powder inhalers use differing numbers of puncturing pins. Images (left to right) show one puncturing pin in the Handihaler® (Boehringer Ingelheim), eight puncturing pins in the Cyclohaler® (Cipla) and two puncturing pins in the Plastiape RS01.

the elastic region and the slope is the Young's moduli. A maximum level of force is reached immediately before the capsule is punctured. In phase 2, after puncture, there is a subsequent reduction in force, determined by the frictional forces between the pin and the perimeter of the puncture created in the capsule. This includes any flap that may be present. In phase 3, the force becomes relatively constant. This is attributed to a more constant friction force between the perimeter of the capsule puncture and the needle.[1] The profile also demonstrates there has been no shedding of capsule pieces and that the flap stayed attached during the puncturing process. If these problems were to occur, the constant force value would have been zero.

Figure 3

Puncturing force from a conical pin within an inhaler and the resulting deformation the pin causes on a hard capsule. The numbers within the graph indicate phases in the puncturing process, discussed in the text.



Gelatin versus HPMC capsules: Considerations related to puncturing

Two types of hard capsules are generally used with inhalers: gelatin capsules and hydroxypropyl methylcellulose (HPMC) capsules. Their differing chemical and physical properties can make one type or the other more appropriate for a given drug formulation. Both are currently used in commercially available, capsule-based inhalers. This article will briefly mention one notable difference between these capsule types—that of water content—which can relate to capsule puncturing.

In gelatin capsules, water plays the role of a plasticizer, maintaining the capsule's flexibility. However, when gelatin capsules are exposed to environments that have low relative humidity, water can escape the capsule shell, leaving the shell brittle and susceptible to cracking or breakage during puncture.[2] Conversely, with HPMC capsules, water does not act as a plasticizer so if water loss were to occur at low relative humidity, it would not influence capsule brittleness.

Capsule water content must also be considered when selecting a capsule for a moisture-sensitive drug formulation. If a gelatin capsule were used, the formulation could draw water from the capsule shell and—depending on the amount of moisture lost—could leave the capsule brittle and vulnerable to breakage.

However, this would not be a concern if an HPMC capsule were used.

Overall, brittleness can lead to capsule cracking and, in worst-case scenarios, capsule breakage during puncturing. These could negatively impact the drug formulation's ability to completely exit the capsule and/or the inhaler and thereby could decrease the dose to the patient.

A study of capsule puncturing forces

Materials and methods

Empty hard shell capsules have two parts: the cap and the body. The closed end of the combined cap and body is known as the dome. The necessary puncturing force depends upon the thickness of the dome and material of the capsule.

An Autograph™ Universal Tensile Tester (UTM) from Shimadzu (Kyoto, Japan), shown in Figure 4, was used to measure the puncturing compression force with high accuracy. Fixtures were developed to hold the cap and body shells within the UTM. The fixtures had a 0.5 mm hole at the end of the cavity for venting air and were specific to the capsule size cap and body.

Three batches each of size 3 gelatin and size 3 HPMC, empty, transparent, hard-shell capsules for inhalation (ACG, Mumbai, India) were evaluated. The capsules (n = 20 in each batch) were positioned in the recess of the stainless-steel bushing. The system was orientated appropriately and subsequently secured in a fixed position.

Figure 4

The Autograph™ Tensile Tester used in the study.

A common puncturing pin attached to a chuck was operated by the UTM (in compression mode) and punctured the capsules on their domes. The pin was a realistic representation of the pins in commercial dry powder inhalers. The UTM software was programmed to conduct the compression test at a speed of 25 mm per minute.

The force required for puncturing each capsule was measured in Newtons. Graphs of displacement versus load were plotted using the UTM's proprietary Trapazium-2™ software. The peak load was noted in each experiment. The displacement of the pin and the resulting force were recorded and registered on a load displacement curve at a fixed speed.[2]

Results

Puncturing forces were measured for the gelatin and HPMC capsules with dome thicknesses ranging from 110 µ to 190 µ, in 10 µ intervals. The data presented in Tables 1 and 2 highlight the midpoint of the testing range, at a thickness of 150 µ for the caps and bodies of the capsules. Maximal force values were collated and the corresponding statistical parameters are listed using the Student's distribution.

For the HPMC capsules, puncturing forces were 4.6-6.0 N with a confidence interval 0.18-0.32 N. In the gelatin capsules, the puncturing forces were 8.8-9.6 N with a confidence interval 0.22-0.33 N. Greater forces were required to puncture the gelatin capsules than the HPMC capsules. It is possible this difference was due to the larger presence of water in the gelatin capsules.

Potential applications for capsule puncture force testing

There are multiple applications in which the testing presented here could be beneficial, to capsule manufacturers for their quality control measures, to manufacturers of capsule-based inhalation products and, by extension, to patients utilizing those medications. These options all involve the concept of consistent force necessary for puncturing capsules in an inhalation device.

As product development teams seek to place new formulations into capsules other than the traditional size 3 format, consistency in all aspects of the drug/device combination are necessary. These variances could entail an increase in capsule size up to size 00 for high-dose drugs or a reduction to size 4 capsules for high-potency products.

To ensure a puncture is clean with no flap, breakage or hindrance created, the forces necessary to complete the process could be measured. Puncturing of capsule shells could be tested in a manner similar to the method described in this work. The same testing could be incorporated as a quality control release measurement for capsule manufacturers.

Consistency for patients also must be considered. From prescription to prescription, and refill to refill, patients

should feel no difference in the strength it takes to puncture the capsule within the device. If there were a difference in the way a device feels to a patient, they might believe something had changed with the medication itself. Also, if different strengths of a drug are provided in different capsule sizes, drug manufacturers could use these methods to ensure the puncturing process is reproducible and feels the same to patients across the dosage range.

Another benefit of this testing could be visual monitoring of puncturing at various strengths to ensure punctures are clean and free of capsule brittleness concerns when filled with formulations. Patients will use differing strengths to puncture capsules because their grips and hand strength will vary. Ensuring a harder puncture works adequately is important, especially if there are brittleness concerns due, for example, to a formulation's moisture sensitivity.

In general, consistency in puncturing force leads to reliability for empty capsule shells as well as capsules filled with formulations. Parameters similar to the testing in this work could provide important capabilities for capsule manufacturers and drug development teams in commercial release testing of filled capsules. In addition, such testing could benefit patients because similar, more consistent patient experiences with inhalation devices can increase patient confidence and brand loyalty.

Table 1

Average values of maximum force for three HPMC transparent capsules batches at 150 µ thickness. The confidence interval was calculated at 95% probability using the Student's distribution.

Batch	Max Force (N) Average Value	Standard Deviation	Confidence Interval
HPMC 1 Cap	5.9	0.59	± 0.22
HPMC 1 Body	5.8	0.47	± 0.18
HPMC 2 Cap	5.8	0.85	± 0.32
HPMC 2 Body	6.0	0.62	± 0.24
HPMC 3 Cap	4.6	0.71	± 0.27
HPMC 3 Body	5.0	0.74	± 0.28

Table 2

Average values of maximum force for three gelatin transparent capsule batches at 150 µ thickness. The confidence interval was calculated at 95% probability using the Student's distribution.

Batch	Max Force (N) Average Value	Standard Deviation	Confidence Interval
Gelatin 1 Cap	9.6	0.66	± 0.25
Gelatin 1 Body	8.8	0.52	± 0.20
Gelatin 2 Cap	9.4	0.87	± 0.33
Gelatin 2 Body	9.8	0.61	±0.23
Gelatin 3 Cap	9.8	0.67	± 0.25
Gelatin 3 Body	9.4	0.57	± 0.22

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