The evolution of DPI capsules

How companies have developed new types of hard capsules to overcome special challenges posed by dry powder inhalers

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Almost 40 years ago, Fisons Pharmaceutical Division introduced the Spinhaler device, making it the first company to use a hard gelatin capsule as a single dose container for inhalation powders in a dry powder inhaler (DPI). The first Spinhaler capsules contained 40 mg of an equal parts mixture of lactose and sodium cromolyn (SC) (sodium cromoglicate BP), used for the prophylactic treatment of asthma [1, 2]. This novel delivery method used the two-piece capsule in a completely new way and presented a new challenge for pharmaceutical scientists: the need to open the gelatin capsule in some way to release the powder into the patient's inspirational air stream.

Pharmaceutical companies had great incentive to overcome this challenge. For one thing, a DPI using a two-piece capsule as a unit dose carrier for an active offers the benefits of simplicity. Dry powder inhalers were the first breath activated devices to allow patients overcome coordination problems and to confirm successful dosing; the use of hard capsules as unit dose packages gives an added "green advantage" to products because the capsules are biodegradable, and the capsule DPI presents a relatively quick method of getting a product to market [3].

The use of hard capsules in DPIs has become a well established method of dosing medicines into the lungs, and their use has expanded well beyond the UK and Europe where they originated. A significant body of research on the testing and use of hard capsules in DPIs provides assurance of the viability of this method for delivering products to treat both pulmonary and systemic diseases. The number of new DPIs introduced in the last 10 years in other areas of the world, in particular the US and Japan, indicates greater acceptance, and this article traces the steps that developers have taken to adapt capsules to reach this point.

The brittleness problem

In the 1960s, manufacturers made hard gelatin capsules to match the demands of standard filling machines, and the available capsules were robust enough for this purpose. The need to puncture a shell wall for DPI applications presented a whole new set of stresses in capsule handling. Fisons, in collaboration with the Elanco Qualicaps Division of Eli Lilly, undertook initial work on capsule puncturing and found that the ideal puncture hole formed by a DPI needle inserted into a capsule shell should be roughly spherical, requiring a capsule material that would puncture smoothly.

Among the systems that use needles to puncture capsule shells, the number and location of the punctures varies, and each of the punctures needs to create a well-formed hole in order for the powder to empty properly. The Spinhaler, the first to use a needle system, makes two opposing holes in the side wall of the capsule body while the cap was retained in a holder (Fig. 1). Other inhalers make from 1 to 4 holes in both the cap and the body (Fig. 2).

Figure 1

Spinhaler use

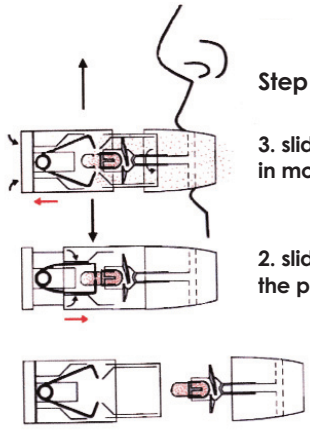
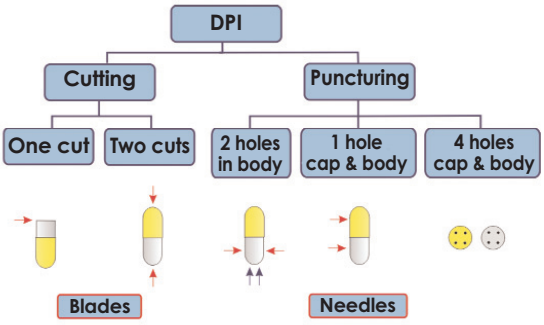


Figure 2

Hard capsule penetration devices used in DPI



The puncture needs to leave a portion of shell wall as a flap that hinges inward, stays attached to the shell wall, and remains pushed in when the needle is withdrawn; however, trials showed that the walls of the standard capsules of the time were too brittle, producing irregular holes and shedding particles of gelatin. When fragments of the shell wall break off, patients may inhale the small pieces. Typically, those fragments are too large to penetrate into the lungs and impact mostly in the throat, which patients have reported as an annoyance.

In order to overcome the brittleness challenge, Elanco needed to develop a new blend of gelatin that produced satisfactory puncturing properties yet still worked well for standard powder filling. Gelatin capsules become brittle when they lose moisture because water acts as a plasticizer for the capsule shells; so, in order to prevent brittleness, the moisture contents of the drug and the capsule shell should be at equilibrium during filling [4]. Despite following this rule, Fisons initially experienced problems.

A 1973 study of sodium cromolyn found that SC acted as a moisture sink; the SC, unlike the capsules, never returned to its starting value but slowly increased its moisture content when cycled between 20% and 65% relative humidity (RH) [5]. Maintaining a tighter limit on the empty capsule moisture content and controlling the RH in the filling areas more closely minimized the problem. However, in many parts of the world, RH falls below 30% during certain seasons of the year, drying out hard gelatin shells after the patient opens the product. The industry now uses moisture-proof packs to prevent moisture migration, but the product is exposed to environmental conditions after opening.

New types of capsules for DPIs

In the 1980s, Japan Elanco, now the Qualicaps Group, began looking for a suitable replacement for gelatin-based capsules. One of the researchers' objectives was to overcome the role of water in the film's physical properties, and they discovered two solutions suitable for the capsules used in inhalation applications. One of the new capsules was made of gelatin modified by the addition of 5% polyethylene glycol 4000 as a plasticizer. The resulting gelatin/PEG capsule resulted in a reduction, though not a total elimination, of brittleness, and testing demonstrated a significant reduction in the number of particles of shell wall shed during puncturing of the gelatin/PEG capsules compared to standard gelatin capsules [6].

Elanco also introduced a completely novel type of hard capsule made from hypromellose (hydroxypropyl methylcellulose, or HPMC). Because the properties of hypromellose capsules do not change significantly when they lose moisture [7], the new capsules retain their puncturing properties over a wider range of humidities than gelatin capsules, although the hypromellose is less resistant to deformation [8]. Compared to gelatin capsules, hypromellose capsules shed a very small number of particles from the shell walls when their moisture content falls because they do not become brittle [9] (Fig. 3).

A recent study measured the forces involved in puncturing gelatin and hypromellose capsule shells with a pin from a commercial DPI, finding values of about 3.2N for the gelatin capsule and 4.0N for the hypromellose capsule at standard moisture contents [10]. After drying the capsules to a lower RH, both types became less elastic and more rigid, and the puncture forces increased slightly.

For the gelatin capsules, the force recorded for most samples, particularly the drier ones, decreased to zero at the moment of penetration, indicating that pieces of the shell had broken off as the point of the needle punctured the capsule. During penetration of the hypromellose capsules, the force recorded fell to about half the maximum value as the point of the pin pushed through the shell and increased again as the main shaft of the pin moved into the capsule. The force never fell to zero, indicating that the shell walls remained in contact with the pin throughout the penetration.

Improvements in capsule shell manufacturing

Hard capsule manufacturing involves dipping stainless steel mold pins at ambient temperatures into warm solutions of gelatin or other suitable polymers such as hypromellose [11] (Fig. 4). The temperature drop causes the polymer to gel on the molds, forming a thin film; the molds then pass through a series of kilns to dry the film down to the required moisture content. The dried films are then stripped off of the molds.

Figure 3

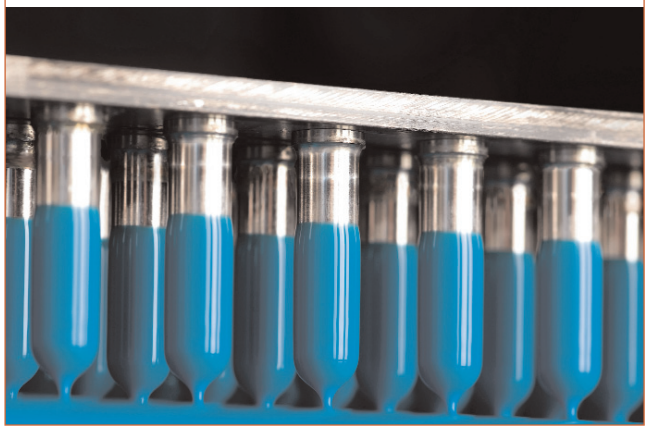
Puncture holes made in a Spinhaler

a. Quali-V(R)-I hypromellose capsule

b. Gelatin capsule

Figure 4

Mold pins dipped in polymer to form capsule shells



In order to facilitate removal of the capsules, manufacturers coat the surface of the pins with a lubricant, which is registered in each capsule manufacturer's Drug Master File (DMF). Extra care is required when producing capsule shells for inhalation products because excess lubricant on the inside wall of the capsule shell will cause powder to adhere to the capsule, reducing the inhaled dosage. The patient will see what looks like a white film on the inside of transparent capsules, the so called "snow cap" effect. On the other hand, too little lubricant makes stripping the dried shells off the mold pins difficult and results in an increase in the incidence of "splits" in the shell walls.

Recently, workers from Boehringer Ingelheim have described a method of washing gelatin capsules using supercritical CO2 to remove any residual lubricant [12]. The Boehringer Ingelheim paper reported that the process apparently removed water from the capsules since the capsules were more brittle after washing but that re-equilibrating them at a suitable RH overcame the problem. None of numerous papers on the use of standard inhalation grade hard capsules in DPIs published since then has reported problems of powder retention, indicating that the capsule shell manufacturers now have their processes under control.

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Shows	Issue	Editorial Closing A = Article P = Product	Issue Focus	Special Sections	Ad Bonus	Ad Closing
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RDD Europe Preview (May19-22)	**April**	A = January 9 P = February 13	Product Development	Contract Test Facilities	Web Review	March 13
	June	A = March 13 P = April 10	Filling/Packaging	Nasal Delivery	Lit Review	May 15
	August	A = May 15 P = June 12	Particle Characterization	Particle Engineering	READEX	July 17
AAPS Preview (Nov. 9-12)	**October**	A = July 10 P = August 14	Devices	Outsourcing Services	White Papers	September 11
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