PULMONARY DELIVERY & DRY-POWDER INHALERS:

ADVANCES IN HARD-CAPSULE TECHNOLOGY

Here, Fernando Díez, Business Development Manager at Qualicaps Europe, and Brian Jones, Scientific Advisor to the company, describe the development of capsules for dry-powder inhalers, and how the simplicity and efficacy of capsule-based dry-powder inhalers makes them an ideal delivery means for an increasing number of active pharmaceutical ingredients.

In the last decade there has been a significant change in the nature of the active pharmaceutical ingredients (APIs) that formulators have had to deal with. This has led innovator pharmaceutical companies to re-examine methods to deliver compounds other than by the standard, resulting in a renewed interest the in use of dry-powder inhalers (DPI) that use hard capsules as the dose container.

"THE MOST IMPORTANT PROPERTY FOR A CAPSULE USED IN A DPI IS ITS ABILITY TO BE CUT OR PUNCTURED IN A REPRODUCIBLE MANNER TO ENABLE THE POWDER TO BE EMPTIED FROM IT AS COMPLETELY AS POSSIBLE"

Originally this application was principally seen as a way of treating asthma and chronic obstructive pulmonary disease (COPD), but researchers have since realised that a whole range of other actives, including peptides and proteins, can be delivered by this route.

The attraction of using a capsule-based DPI is its simplicity. The powder formulation consists either of the API or a mixture of it with a carrier particle such as lactose or mannitol. A significant amount of research into particle engineering has enabled the manufacture of particles with the correct aerodynamic and carrier properties to ensure effective pulmonary delivery of the API. The small number of ingredients in the formulation reduces significantly the amount of analytical work required for the early development phases of a product compared with pressurised metered-dose inhalers.

Many types of validated DPI have been developed for delivering capsule-based products. They are reasonably cheap to manufacture, robust and effective in use. They have two roles; firstly to puncture or cut open the capsule shell so that the contents can be released; secondly to enable the patient's inspirational air flow to empty all the powder from the shell, detach the active from the carrier and guide the airstream into the patient's respiratory tract.

The first capsule DPI product, Sodium Cromolyn 20 mg (Intal Spincaps®), was developed in the late 1960s by Fisons in the UK.[1] This was a challenge for the empty gelatin capsule manufacturer because the shells in use then were not designed to be punctured by needles.

Capsules / Specification	Gelatin	Quali-V®	Quali-V®-I
Moisture Content % w/w	13.0 to 16.0	4.0 to 6.0	4.5 to 6.5
Microbial Level, cfu/g	$<10^3$	$<10^2$	$<10^1$
Triboelectrification potential	Higher	Lower	Lower

Figure 1: Table summarising specifications and properties of different hard capsules: Gelatin, Quali-V and Quali-V-I

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Qualicaps, then part of Eli Lilly, solved the problem by changing their gelatin blends to produce a capsule shell that could be punctured in such a way that the needles produced holes with flaps, which stayed open when the needles were retracted, and did not break off. This was the first breath-actuated inhalation device and it significantly improved patient treatment.

Gelatin is a very robust material and the capsules had all the correct properties for this application except for the fact that when exposed to low relative humdity they lose moisture and become brittle, because water acts as a plastizer for the shell.[2] The problem was minimised by careful control of the moisture content of the capsules and the use of suitable packaging. At that time hard capsules were only available made from gelatin.

In the late 1980s Qualicaps in Japan started a project to look for alternative shell materials whose mechanical properties were not dependent on moisture content. This resulted, in the 1990s, in a new type of capsule made from hypromellose, Quali-V®, whose mechanical properties do not change even when significant amounts of water are lost. This was the first non-gelatin hard capsule for oral use with the correct dissolution properties for pharmaceutical products.[3]

CAPSULE PROPERTIES FOR USE IN DPIS?

What are the special properties required of hard capsules for this application that standard capsules cannot supply? This is best illustrated by comparing Qualicaps special inhalation-grade hypromellose capsules, Quali-V®-I, with their standard pharmaceutical-grade gelatin and hypromellose capsules, Quali-V®. The inhalation-grade capsules differ from their standard capsules in several aspects, as shown in Figure 1.

The principal difference between the three is in the specification for the total aerobic count. The difference between gelatin and hypromellose capsules is a reflection on the manufacturing processes for the raw materials used. The lower count for the Quali-V-I capsules is achieved by a validated process for extra cleaning of the equipment used to manufacture the hypromellose solutions. This value is particularly important for inhalation capsules because unlike capsules that are swallowed the fill material from the capsule goes directly into the lungs in which there is no physiological trap like the acid environment of the stomach to prevent bacteria entering into the body.

The moisture content specification is derived from the equilibrium moisture content of the capsules between relative humidities of 35% and 55%. The hypromellose capsules both have a significantly lower moisture content than gelatin: gelatin = 13-16%, Quali-V = 4-6%; and Quali-V-I - 4.5-6.5%.

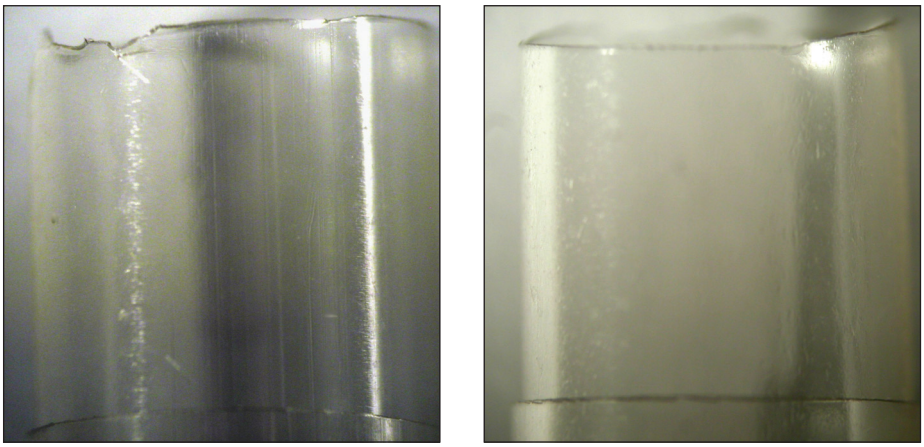

Figure 2: Capsule bodies cut open in an Aventis Eclipse® inhaler: A) Qualicaps gelatin capsule; B) Qualicaps Quali-V-I capsule. Capsules equilibrated at 35% relative humidity before testing.

The reason that the Quali-V-I capsules have a slightly higher moisture specification than the Quali-V is that they are made from a different blend of hypromellose types that are chosen for their mechanical/puncturing properties, whereas the blend used for the standard capsule is chosen for its dissolution properties. Their handling characteristics differ in that gelatin capsules are more prone to triboelectrification than hypromellose capsules.[4] This is relevant for inhalation capsules because this charge may attract powder to the shell wall and increase the amount retained in the capsule on emptying. The low moistures content of the hypromellose capsules provides a clear additional benefit with regard to moisture-sensitive APIs.

The most important property for a capsule used in a DPI is its ability to be cut or punctured in a reproducible manner to enable the powder to be emptied from it as completely as possible. The challenge in this process is to ensure a minimum amount of shell is broken off during cutting or puncturing. These particles could be inhaled – although they are too large to be deposited in the lungs.

Studies comparing gelatin and hypromellose capsules have shown the superior performance of hypromellose over gelatin in the production of these fragments particularly after storage at lower relative humidities.[5,6]

The quality of the cut can be assessed from the straightness of the edge produced (see Figure 2), which is also an indicator of the likelihood of fragments being generated. The quality of the punctures can by assessed by several factors: the shape of the hole determined by the shape of the pin head, and the nature of the flap formed, whether it is attached/detached and its angle to the shell wall – it must not have recovered and partly reclose the opening (see Figures 3 & 4).

CAPSULE POWDER FILLING

When inhalation products were first formulated in hard gelatin capsules they presented a

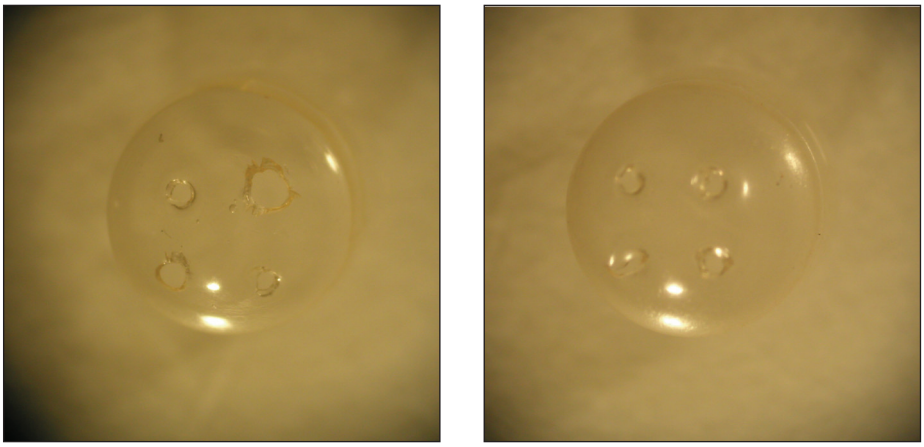

Figure 3: Capsule caps punctured in a Pharmachemie Cyclohaler® inhaler: A) Qualicaps gelatin capsule; B) Qualicaps Quali-V-I capsule. Capsules equilibrated at 35% relative humidity before testing.

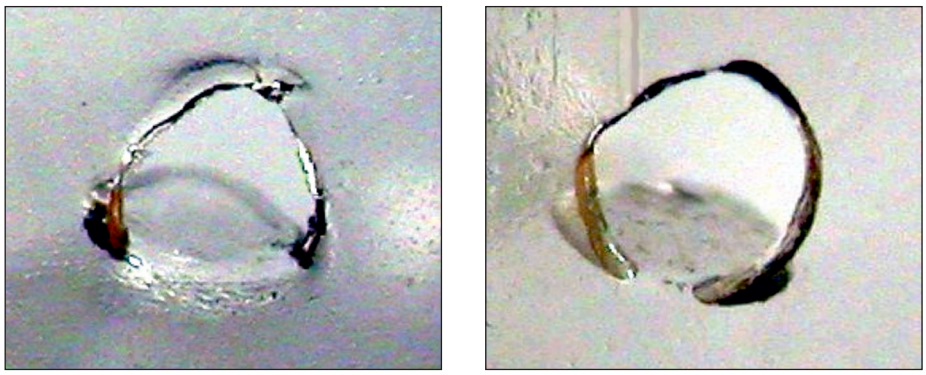

Figure 4: Capsules punctured in an Aventis Spinhaler®: A) Gelatin capsule; B) Quali-V-I, hypromellose, capsule. Capsules equilibrated at 35% relative humidity before testing.

completely different challenge to the control of filling. The powder-fill-weight of standard capsule products is typically four or five times the weight of the shell and because of this the filling operation can be monitored by measuring the gross weight of the filled capsules. This is because the total variance is equal to the square root of the sum of the squares of the individual variances, and thus the practical effect of the shell weight variance on the process in minimal.

However, in the case of the capsules for inhalation the reverse is true, because the fill weights are always less than the shell weights. The pioneer product, the Intal Spincap, had a fill weight of 40 mg in a size 2 capsule weighing 64 mg. The filling problem was solved initially by the adaptation of a manual filling machine, but the demand soon became too great for this process to keep up. Fisons then sponsored academic research studies into the relationship between powder properties and powder plug formation in a dosator-type filling and this led to the development of an automatic filling machine, by MG2 (Bologna, Italy) , that had a mini-dosator able to measure this small amount of powder at filling machine high-speeds.

Since then the fill-weights of formulation have become less and some formulation have fill weights of less than 10 mg. This problem has been tackled in two ways.[7] Firstly machines have been developed by both MG2 and Harro Höfliger (Allmersbach im Tal, Germany) that are able to weigh the capsule shell empty and then again after it has been filled. MG2, for example, developed the G100 machine which is capable of operating at speeds up to 90,000/hr at fill weights ≥ 3 mg/capsule. Secondly machines have been developed that can accurately measure even smaller amounts of powders. For example, Harro Höfliger has developed a vacuum-drum system that is able to operate at dose weights <1 mg, and which can be fitted on their Modu-C machine, which can also weigh capsules pre- and post-filling.

"THE SUITABILITY OF QUALI-V-I CAPSULES FOR DPI PRODUCTS HAS BEEN DEMONSTRATED BY ITS SUCCESSFUL USE BY VARIOUS MAJOR PHARMACEUTICAL COMPANIES"

LATEST PRODUCT DEVELOPMENTS

The initial use for this product type was for prophylactic treatment of asthma. There is still a demand for new products in the field of chronic obstructive pulmonary disease COPD. This disease affects 210 million people worldwide and it is projected that it will be the third leading cause of death by 2030.[8] The use of DPI systems has been expanded into the delivery of actives for systemic administration and this is demonstrated by the increasing numbers of papers published.[9]

The suitability of Quali-V-I capsules for DPI products has been demonstrated by its successful use by various major pharmaceutical companies and includes products in phase III clinical development as well as the registration phase.

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