

## Time Capsules The hard two-piece capsule: A history of continuous change and improvement

### The hard two-piece capsule: A history of continuous change and improvement

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The hard two-piece capsule has always carried an allure of being modern and up-to-date despite the fact that capsules have been in widespread use in the U.S. since the 1880s. They have stood the test of time because they have been continuously improved to meet the challenges posed by user demands for higher filling speeds, stricter quality goals and new types of formulations. Capsules have traditionally been made from gelatin that has perfect properties for manufacture as it changes from a liquid to a solid, thus forming a film, at a temperature just above ambient. It does have some drawbacks and now capsules are available made from other materials.



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People tend to think that two-piece capsules are the same as they always have been but when examined closely it can be seen that they have been adapted to face modern day challenges.

### Capsule shell manufacture

The big expansion in the industrial filling of hard capsules occurred in the 1950/1960s when filling machines were manually operated at speeds of 20,000 to 25,000 capsules/hour. Since then, there has been a steady rise in machine speeds, with the fastest operating at >150,000 capsules/hour. To achieve this, capsule manufacturers have converted their plants to cGMP standards, have improved the controls and sensors fitted to their machines and in the latest models, such as those made by Technophar, have installed computer controls and replaced cams with servo-motors. If the quality levels of the capsules were still at their 1960s levels, the high-speed machines would be shutting down every few minutes due to blockages, which does not happen. Another aid to better processing has been the improvement in the quality of the gelatin: the manufacturers have gained a better understanding of their processes. This has resulted in greater uniformity within and between lots, which has enabled capsule manufacturers to control their machines better. This in turn has led to better quality capsules with the attendant gain in filling machine output.

During this period the design of the capsule shells has been improved to help their filling performance. All capsule shells have molded into their surfaces features to ensure better handling. There are sets of indents on the cap, called pre-locks, to hold the empty capsules together during transit from the manufacturer until they are separated on the filling machine. After filling, the capsule parts are rejoined at high speed and the caps and bodies are modified to assist in this process. Air vents are built in to prevent a build-up of internal pressure inside the capsule. When the capsules are closed to their correct joined lengths, locking features hold the capsules securely together sufficient to withstand stresses during automatic packaging, distribution and final handling.

### The type of capsule fills

There are three popular solid oral dosage forms: soft capsules, two-piece capsules and tablets. Of these, the most versatile is the two-piece capsule because it can be filled with formulations ranging from dry powders and pellets, through tablets, non-aqueous liquids and suspensions. The capsules themselves are robust, all filling machines handle them in the same way and the only difference is the dosing mechanism used, which can be easily changed.

In the 1950s capsules were used only for dry powder fills because the APIs were readily water soluble, given in reasonably-sized doses, and released their contents in the stomach. Since then the nature of APIs has changed; now many are very poorly soluble, are given in low doses and are required to be delivered to specific sites within the G.I. tract for absorption. To accommodate this, formulation forms have changed. The 1960/1970s saw the filling of coated pellets or granules designed to prolong release of the active, tablets to separate incompatible substances or to modify release, and semi-solid matrices as liquids. None of these required any radical changes to the capsule shell. The 1980s saw the introduction of a high-speed band sealing machine, the Qualicaps' Hicapseal, designed to make a capsule liquid-tight after filling with mobile liquids.

### New capsule shell materials

The change in formulations has required different types of excipients to be used and some induce stresses in gelatin capsules because they are hygroscopic. One of the drawbacks of gelatin is that its water content acts as a plasticizer and when removed, capsules become brittle. This has been known since the 19th century but attempts to find suitable alternatives failed until the 1980s when G.S Technologies in the U.S. and Qualicaps in Japan started experimentation with hypromellose: a polymer widely used in pharmaceuticals with a well-established safety record. In order to form a film on a mold pin, solutions of this need to be converted into 'setting' systems. G.S. Technologies used the hot pin process, developed by Eli Lilly in 1950, which relies on a rapid viscosity increase with heat to form a film, whereas to get the same effect Qualicaps added carrageenan as a network former and potassium chloride as a network promoter. Only the latter system produced a capsule with the correct kinds of properties for pharmaceutical use, such as good acid dissolution. Other manufacturers now make hypromellose capsules but each have their own setting systems, and as a result, have slightly

different properties. Hypromellose capsules have advantages over gelatin in two main areas: water does not act as a plasticizer and thus they can be dried down to give a very low moisture environment inside the capsule if required and hypromellose does not undergo cross-linking reactions like gelatin and is thus unaffected by I.C.H. accelerated storage conditions (6 months at 40°C & 75% RH).

Others materials have been used. In Japan a significant number of capsules are made using Pullulan, which has similar moisture content properties to gelatin. It has been used there more than other countries because hypromellose was not permitted for use in foods and nutraceuticals. Capsule manufacturers are still looking for alternative polymers with the correct properties: ones that have been investigated are Pondac (polyvinyl alcohol copolymer), Chitosan and Carrageenan, but none have resulted in capsules in wide-spread use.

#### **New types of capsule formulations**

It takes a long time from the conception of a new formulation technique to its use in approved products because of the inherent conservatism of the pharmaceutical industry and the length of time it takes to get a new product to the market place. Liquid-fills for capsules are now getting more attention in R&D groups because of the increasing numbers of very poorly soluble compounds. These formulations are lipid-based and utilize the normal process of fat digestion and absorption to get these compounds through the intestinal wall into the blood stream. The excipients used are mixtures of solvents, surfactants, glycerides etc. Some of these interact strongly with the capsule shell. Work is underway by the capsule manufacturers to see how they can improve the mechanical strength of capsules to cope with these stresses.

Capsules filled with pellets and tablets have been used for many years: the former produces a multiparticulate system to avoid the problem of dose-dumping, as single pellet failure is not a problem. Tablets have advantages because of their lower surface to weight ratio that makes it much easier to apply a uniform coat and uses significantly less material. In the 1990s the idea of a mini-tablet (diameters 1.0–2.0 mm) was proposed as an intermediate between the previous two; a multiparticulate with a minimum of surface area. The problem for filling them into capsules was none of the machines could count them quickly and accurately enough. Qualicaps in collaboration with one of their customers designed the LIQFILsuper40 that was able to count groups of 16 mini-tablets and feed them into capsules in the time available.

Many new APIs are peptides or protein fragments and oral delivery presents a significant challenge because of the digestive system. Much work has been undertaken looking at delivering these to the colon where there are no proteolytic enzymes. One solution filled material into low-moisture content hypromellose capsules and coated them with a glassy amylase-based polymer that is broken down only by colonic enzymes. Another potential route is pulmonary delivery using powder-filled capsules in dry-powder inhalers. Capsules need first to be cut or punctured to release the powder into the patient's inspirational air-stream, which must be done without parts of the shell breaking off. Hypromellose capsules for inhalation have the correct properties for this application because of their lack of brittleness if they lose moisture and they shed significantly less particles than gelatin when cut or punctured.

#### **Summary**

Hard two-piece capsules have a history of continuous evolution to meet the changing demands of the users. The innovations come from the manufacturers of empty capsules, filling machines and other ancillary equipment. They continue to be adapted with improved quality.

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