

liquid-filled capsules

FORMULATING WITH LIQUIDS:
TWO-PIECE OR SOFTGEL CAPSULES?

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When developing a new drug product, you eventually must decide on the dosage form. In the realm of solid dosage, a tablet is often the default choice. But if the API is to be delivered as a liquid, you'll have to decide between a two-piece and a softgel capsule. This article summarizes the factors that influence that decision.

Liquid fills can deliver active pharmaceutical ingredients (APIs) that are otherwise difficult or impossible to deliver via other solid dosage forms. That has led many research and development scientists to reappraise their library of compounds to identify promising substances. If any were rejected solely because their poor stability and bioavailability posed formulation challenges, then liquid delivery could offer a solution because it would improve bioavailability and absorption. It's even better if the API exists in liquid form because then it's already solubilized and readily dis-

persible. In that state, even a poorly soluble API could be absorbed.

The liquid form also provides a stable environment for labile actives and protects against oxidation. Liquids also promote fill weight uniformity, efficacy, stability, and safety, especially when the API is highly potent or toxic. Liquid fills can also reduce development time because they are typically a mixture of only one or two excipients. As a result, less time is spent on development and scale-up because fewer experimental replicates are required.

On the business side, liquid fills can lengthen product lifecycles and patent protection because they enable you to reformulate old products and re-introduce them in a new form. That creates exclusivity and protects your market share.

Advantages of two-piece capsules

A major advantage of using two-piece capsules for liquid fills: They can be used at all stages of product development, from early bench testing to full-scale production. That simplifies the work and accelerates it, allowing you to get the product to market faster. And because most pharmaceutical companies manufacture their two-piece capsule products in-house, production efficiency is higher compared to softgels, which are typically made off-site.

Two-piece capsules also offer many trade-dress options, including custom colors and imprints to establish and solidify brand identity. Furthermore, because the cap and body of liquid-filled capsules are typically band-sealed (photo) or fused, they ensure product integrity and tamper evidence. Band-sealing also helps prevent odors, reduces oxygen diffusion, and strengthens the capsule shell. That extra strength is especially important when the capsules are packaged in a blister.



A gelatin band prevents liquid from leaking from filled two-piece capsules. It also strengthens the capsule and provides tamper evidence.

Two-piece capsules can be made from a number of substances, but gelatin and hydroxypropyl methylcellulose—also known as HPMC or hypromellose—are the primary materials. Hypromellose capsules are used when filling a liquid into gelatin capsules would lead to stability limitations or cross-linking. Hypromellose capsules are better suited to moisture-sensitive APIs and hygroscopic fills because they don't become brittle. They also accommodate a broader range of excipients suitable for liquid fills, thereby increasing the odds of identifying compatible excipients

that can improve the bioavailability of poorly soluble drugs. Some hypromellose capsules have a moisture content of only 4 to 6 percent and can be exposed to low relative humidity without becoming brittle [1].

Advantages of softgels

Softgels are formed, filled, and hermetically sealed in a single operation, and there is an elegance to the final dosage form, which helps differentiate them. Softgels are also well accepted by consumers and come in a variety of shapes, sizes, and colors, so they offer excellent branding opportunities (photo).



The large variety of softgel shapes, sizes, and colors offer excellent branding opportunities.

There are also formulation advantages. Softgels are ideal for oils and fat-soluble fills, and because they fully encapsulate the fill, sensitive ingredients are protected from contamination, oxidation, and photo-degradation. Softgels also withstand temperature fluctuations, making them convenient to store and transport. Furthermore, patients who have difficulty swallowing tablets find softgels easier to ingest. Softgels also mask some unpleasant flavors of fills and deter tampering.



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Challenges of two-piece capsules

Every dosage form has disadvantages, and for gelatin two-piece capsules they include the possibility of fills that are incompatible with gelatin. Fills that steal moisture from the capsule shell, for example, could lead to brittle or broken capsules. That's why determining excipient compatibility is paramount: You must identify which excipients work well with both the fill and capsule material to get the desired result.

Furthermore, liquid fills reduce the volume available within the two-piece capsule shell because the capsule body cannot be overfilled (as it can with powders) without spilling fill onto the machine, where's it wasted. The practical fill limit for liquids is 90 percent of the capsule's normal body volume. Another drawback: Liquid-filled two-piece capsules must be sealed, an extra step compared to softgels. However, if the fill turns solid or semi-solid after it's encapsulated—because it cools, is thixotropic, or reacts in some other way—leakage may not be an issue. Low-viscosity fills, however, are prone to leakage and the capsules that contain them must be sealed. The ideal viscosity range of fills is 100 to 1,000 centipoise. Anything thicker is difficult to encapsulate.

Depending on the machinery and the formulation, it could take 30 to 200 hours to produce 10 million softgels.



Challenges of softgels

While softgels appeal to patients and consumers, there are challenges in developing and manufacturing them, especially if the fill material reacts poorly to high temperatures and humidity. It's also difficult to fill anything but the simplest oils into softgels made from a vegetable-gelatin blend, and all-vegetable softgel shells are not as strong as those made from gelatin.

Manufacturing softgels also requires a large space and a variety of special equipment, which entails a big capital investment. That prompts most companies to outsource softgel manufacturing. The process also requires special expertise and experience, and that too weighs in favor of outsourcing [2]. Manufacturing softgels is also slower than filling two-piece capsules. Depending on the machinery and the formulation, it could take 30 to 200 hours to produce 10 million softgels. Manufacturing lead time could add another 3 to 10 days to the process.

Two-piece capsule equipment

Filling two-piece capsules with liquids requires specialized equipment or modules that equip a powder filler to handle liquids, such as a heat-jacketed hopper that helps the fill material flow better [3].

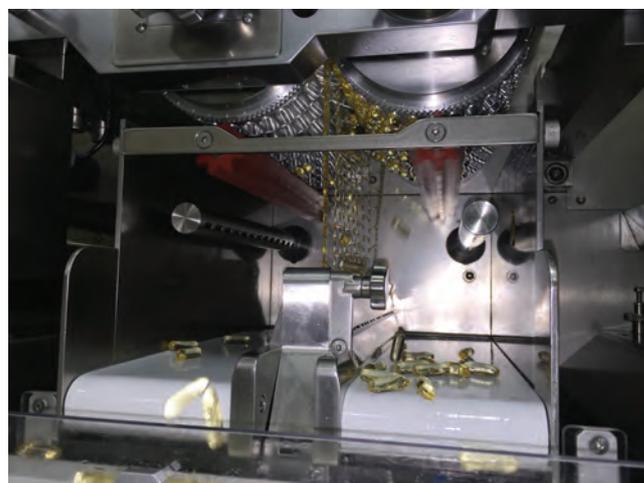
Cleanliness is another consideration, because it relates to filling accuracy, waste reduction, yields, and production time. In short, the cleaner the operation, the more efficient it is. Cleanliness, however, may entail indexing at low speed to reduce drips between doses, minimize splashes, and prevent pressure buildup in the capsules when they're rejoined. Suction can also help with cleanliness, as can a system that

detects missing caps or bodies in the segments and prevents the machine from dosing to them.

Depending on the capsule filling machine's output, a typical two-shift operation can produce about 600,000 capsules per day, including setup and cleaning time. That presumes the machinery assembles and disassembles quickly and has few areas where alignment is critical.

Softgel equipment

The softgel process differs markedly from two-piece capsule filling. Not only does the machinery fill, it also forms and seals the capsule. That makes the operation more complex and necessitates a variety of special equipment, including a gelatin melter, reactor to prepare the fill material, encapsulator, tumble dryer (photo), drying trays, and drying tunnel. The operation may also require a printer or marking system and a system that inspects the size, appearance, and weight of the softgels.



Most CMOs manufacture softgels 24 hours a day, 7 days a week over a 350-day year.

As noted above, the need to invest in manufacturing space and machinery leads most companies to outsource softgel production to a contract manufacturing organization (CMO). As with any other project, it's important that you vet the CMOs you're considering. But with softgels, it's even more important to verify the reliability of the CMO's equipment because most sites operate 24 hours a day, 7 days a week over a 350-day year. That leaves just 2 weeks for maintenance. Plus, softgel encapsulators have tight tolerances, and misalignments of just a few microns can lead to serious quality issues.

However, if your product volumes warrant an in-house softgel line, look for a supplier that offers turnkey systems, including equipment design, training, and technical assistance at startup and during the first weeks of manufacturing.

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References

1. Quali-V capsules from Qualicaps, Whitsett, NC.
2. Including Technophar Equipment and Service, Windsor, ON, Canada, a business unit of Qualicaps Group.
3. F Series capsule fillers from Qualicaps.

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