ALTASCIENCES

APPLICATIONS OF LIQUID-FILLED CAPSULES FOR CHALLENGING APIs IN PHARMACEUTICAL MANUFACTURING

APIs=active pharmaceutical ingredients

Liquid-filled capsules (LFCs) are a convenient, efficient, scalable, drug manufacturing option that offer advantages in several key areas.

In this paper, we will review the process of liquid-filled capsule manufacturing, as well as provide an overview of the specific situations where LFCs offer unparalleled benefits.

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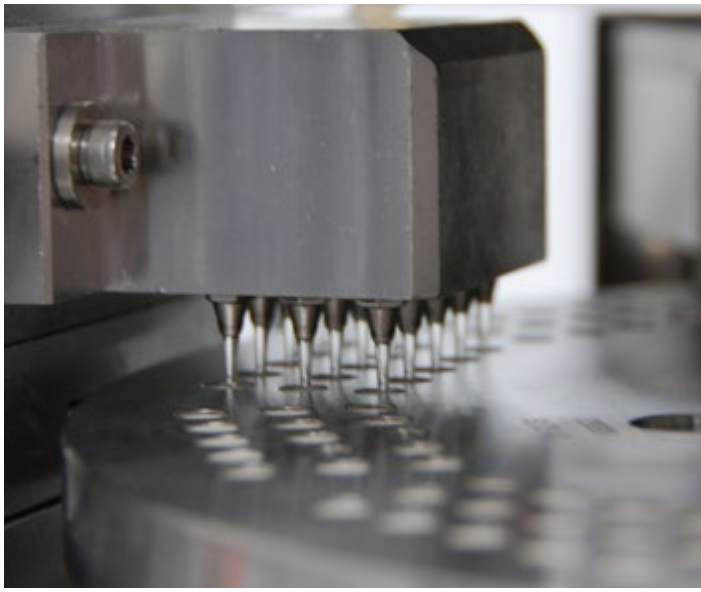
PROCESS OVERVIEW

The encapsulation of drugs as liquid-filled capsules is a relatively simple and efficient process. Gelatin, largely sourced from collagen, is the base material for the shell matrix of liquid-filled capsules. Vegetarian options include a polymer, such as hydroxypropyl methylcellulose (HPMC), potato starch, and carrageenan from seaweed.

The API is suppended or dissolved inside a heated, jacketed kettle via mixing with excipients as needed. The excipients are chosen based on the properties of the API, and typically include triglycerides, mixed glycerides, pharmaceutically acceptable co-solvents, such as polyethylene glycol, and propylene glycol, water-soluble and water-insoluble surfactants, solubility enhancers, and other additives such as α-tocopherol. These excipients can help improve bioavailability, ensure equal distribution of the active ingredient throughout the mixture, and keeps the drug substance contained.



The formulation is delivered to filling machinery through heated hoses, if necessary, to maintain optimal temperature, and is used to fill two-piece, hard-shell capsules. The capsules come in a variety of sizes, depending on the mixture and API concentration being developed. Once filled, the capsules are sealed to prevent leaking, usually with a colored band. When cooled to room temperature, the mixture solidifies to a wax-like consistency, except in the case of vitamin E oil or other fully liquid products.

The simplicity of the process offers many advantages during the different phases of drug development.

Early-Phase Testing

- Speed of development – fewer excipients, simpler process, rapid delivery to clinical site
- Flexibility of manufacture – small batches can be filled by hand
- Ease of dosage adjustment – modify the amount of API in the mixture, or use a different size capsule for the new dosage

Late-Phase Testing

- Ease of scale-up – small to large batches can be filled via the same efficient process
- Rapid availability for clinical trial site
- Ease of dosage adjustment
- Range of dosage options easily produced for different trial arms.

Commercialization

- Ease of scale-up without significant change in equipment or process
- Range of dosage options can be manufactured for commercial use
- Variety of band colors offer customized marketing opportunities

IDEAL DRUG CANDIDATES

Poorly Water-Soluble

The oral absorption of a drug is directly related to its water solubility and gastrointestinal permeability. In recent decades, updated screening methods and bioavailability enhancements have led to increasing numbers of poorly water-soluble small molecules being considered for development — liquid fill technology is ideal for new molecular entities (NMEs) classified as having low solubility and high permeability.

For instance, candesartan is a highly potent drug that is poorly absorbed when administered as tablets. Deepthy and Murthy[1] used liquid-filled, hard-shell capsules to improve the bioavailability of the prodrug candesartan cilexetil, using different surfactants and excipients. The study determined that the encapsulation of candesartan cilexetil with sodium lauryl sulfate as a surfactant, and other excipients in the formulation, significantly influences *in vitro* drug release.

A study published in the journal *Pharmazie* confirmed the efficiency of liquid-filled, hard-shell capsules and the appropriate carrier material "... to improve peroral bioavailability of the very poorly water-soluble hepatoprotectant silymarin through formation of a semisolid dispersion (SD) system..."[2]

A related but somewhat different option to improve solubility of an API is to reduce the particle size via nano milling, develop a suspension for the nano milled particles, and deliver in liquid-filled capsules.[3]

Low Dose/High Potency

Compounds in the low dose/high potency category include Schedule I drugs, hormones, and cytotoxic APIs. These products present two main challenges for the manufacture of solid dosage forms such as tablets:

1. Content uniformity. When working with low dose APIs in solid format, ensuring that each tablet has the same quantity of active ingredient is challenging. By dissolving the active ingredient and creating a solution, improvements in unit dose homogeneity are realized. In a Japanese study, 100% of the capsules investigated met the requirement for content uniformity.[4]
2. Containment of potent drug material during processing. Highly potent APIs (HPAPIs) are increasingly numerous in development, with more classes of molecules and new chemical entities being formulated for a broad range of conditions. Liquid-filled capsules provide a safer alternative to powders, in that the HPAPI powder is dissolved in the confines of a closed system, and operators are not exposed to airborne particles during the manufacturing process.[5]

   To demonstrate the containment of API during capsule filling, a semi-solid formulation of phenacetin (3-mg dose) was used as a model compound.[6] Swab tests were conducted on the surfaces of different parts of the filling machinery after a filling operation. The results demonstrated that no API was found on any of the machine bushings of the capsule-filling equipment, a result that would not be possible when filling with powder. The lower detectable limit of the analytical method was 0.25 µg. This result demonstrated that the incorporation of potent APIs into liquid fill materials can drastically reduce the exposure of CDMO machine operators to fine particles of HPAPIs.

Low Melting Point

During the drug manufacturing process, heat is created, and a solid-form API with a low melting point is likely to stick to the equipment, which creates processing and stability issues, as well as unnecessary waste or loss of API. In this scenario, a liquid formulation that takes advantage of the low melting point, filled into capsules, effectively eliminates such issues.

Commercially available products which fall into this category include fish oils, vitamins A and E, and phospholipids.

Critical Stability Profile

Drug stability can be negatively impacted by environmental conditions during processing, particularly when there is high humidity that may be absorbed by the drug product. The antibiotic vancomycin is a good example, with many different formulation options.[7] Vancomycin hydrochloride is hygroscopic and freely water-soluble, and will absorb large amounts of moisture if not packaged appropriately. When vancomycin first arrived on the market, each unit dose was dispensed in a glass vial, and reconstituted immediately prior to use. In the 1980s, vancomycin was incorporated into a polyethylene glycol (PEG) matrix filled into hard gelatin capsules, which protected the drug product from moisture and produced a convenient, stable dosage form. The hard-shell capsule formulation demonstrated systemic equivalency to the solution of the API.[8]

Liquid-filled, hard-shell capsules offer significant benefits for APIs that present formulation or manufacturing challenges, and they are also an **attractive option** for sustained release products, line extensions, and brand differentiation. Their use is beneficial throughout the drug development continuum, from preclinical to commercialization.

ALTASCIENCES' CASE STUDY – CUSTOM PARTS FOR EFFECTIVE SOLUTIONS

Challenge

A leading developer of novel cancer therapeutics was experiencing persistent manufacturing process issues. Their contract manufacturing partners were unable to deliver a consistent process for liquid-filled capsules, which resulted in the loss of very expensive batches of product.

Their technicians and engineers could not accurately diagnose the problem, and thus were at a loss to develop a solution. They outsourced diagnosis and resolution to half a dozen larger CMOs, each without success, and finally, they turned to Altasciences.

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(CASE STUDY CONTINUED)

Solution

Altasciences' engineers applied their particular expertise in liquid-filled capsules of APIs in suspensions and extensive experience working with virtual, small, and mid-sized pharma companies, and were able to diagnose two different problems.

The first problem was the hydrophobic nature of the API and the interaction with the capsule banding material. Working closely with the client and the manufacturer of the equipment, Altasciences was able to develop an out-of-the-box solution for applying the banding material to the capsule.

The second problem was the excessively high viscosity of the suspension, rendering the suspension too thick to fill the capsules using conventional equipment. Altasciences was able to engineer custom parts, creating a specialized filling nozzle to efficiently deliver the suspension into the capsule.

Results

Altasciences' state-of-the-art capsule-filling facility was capable of engineering customized equipment to help solve this complex manufacturing problem, reducing potential product waste, and saving time and money on drug batches.

Key drivers of Altasciences' success in general are the genuine care that their experts have for their clients and their clients' molecular products, along with the expertise to quickly and cost effectively deliver innovative results that deliver on all the benefits and advantages of LFCs.

Altasciences takes pride in being a collaborative partner to all sponsors, and is ready to help you develop a challenging API you may have shelved. If you have an API that has therapeutic promise, but efficient manufacture and convenient dosing has eluded you, **contact us**.

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