

Liquid-Filled Capsules for Highly Potent Drug Compounds

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INTRODUCTION

The challenge of delivering highly potent active pharmaceutical ingredients (HPAPIs) is substantial and one that formulators face with increasing frequency. More than 25% of all drug products in development are highly toxic or contain highly potent compounds that require some sort of specialized handling. For oncology, this figure is likely closer to 70%.

Developing new drug products based on HPAPIs requires a sophisticated approach because they are generally highly toxic, requiring controlled handling during manufacture to minimize risk to operators. In addition, these drug products—which may also be targeted for delivery at the specific site of therapy—typically require low concentrations because of their high potency. This makes accurate dosing essential, and challenging, since each dose may contain a single microgram, or less, of the HPAPI. To add further complications, given the more-complex molecules common in pharma pipelines today, these HPAPIs may also require enabling technologies to increase solubility and bioavailability or address other drug delivery issues.

One promising approach to address this list of issues is the use of liquid-filled hard capsules (LFHC), a precedented technology that maximizes safe handling and produces accurately dosed, homogeneous formulations for low-dose products. This drug delivery technology is applicable to a wide range of compounds and target product profiles and ensures pinpoint accuracy and control in a well-understood processing environment. Here, we describe micro-dosing and advantages in using liquid-filled hard capsules, offered by this innovative technology for HPAPI products.

THE PROMISE OF MICRO-DOSING

Traditional micro-dosing is a powder handling approach that is automated and uses specialized, high-precision weighing equipment to dose, usually, unformulated API powder individually in hard capsule shells. With liquid-filled hard capsules delivering an equivalent microdose can offer handling advantages including bioavailability enabling advantages for many HPAPI products. Because the liquid four-step process mentioned below is simple, it allows rapid product development of an oral dosage form typically preferred by

patients. Traditional micro-dosing can be performed using simple isolator systems, which is often sufficient for operator protection with HPAPI applications, which



Figure 1
Example liquid-fill capsules

typically require handling only small quantities of material. However, on their own, many HPAPIs may have material properties that preclude the use of conventional micro-dosing. They may be sticky, semisolid, or liquid, too light, or too “fluffy.” The powder may have poor flow properties or the size and shape of the HPAPI particle may be inconsistent. In some cases, HPAPI compounds may be so potent that a safe containment level cannot be easily achieved or the dosage itself may be below the weighable range of micro-dosing.

All these problems can be solved by incorporating the HPAPI powder into a liquid, either as a suspended solid or a solution, and then incorporating the liquid into a solid oral dosage form (e.g., a hard capsule) for easy administration to patients.¹

LIQUID-FILLED HARD CAPSULES

Precedence: A Well-Established Technology

Liquid-filled hard capsules have a long history of innovation and market precedence since they were first patented in 1834. In addition, market precedence exists for the technology required for developing, scaling, and manufacturing liquid-filled capsule products incorporating challenging, potent, or toxic APIs.

¹ Alternatively, this approach can be used with a softgel capsule format.

Lonza manufactures more than 25 commercial liquid-filled hard capsule products. Currently, about 40% of the liquid-filled hard capsule products in pharmaceutical pipelines contain HPAPIs.

Advantages

Liquid-filled hard capsules offer important advantages to formulators and process engineers today.

Flexibility. Liquid-filled hard capsules can accommodate a wide range of active ingredients with challenging material properties, dose requirements, and formulation specifications. Excipients, such as thixotropic agents to promote gelling and prevent dehomogenization of suspensions, can be added in a generic, single-step mixing process. Lipid formulations—commonly used for compounds that require enabling technologies to enhance solubility and, hence, bioavailability—are also readily accommodated. Formulations are well-suited for combination products and can be designed for targeted (e.g., colonic) delivery at a specific site.

Safety and Efficiency. By incorporating the dry HPAPI particles into liquid excipients, the risk of exposure during powder handling in subsequent formulation and processing steps is eliminated. Operators do not risk airborne powder exposure through most of manufacturing. Since it is simple to pump liquids between processes, efficiency is maximized.

Easy Scalability. It is simpler to scale up production to commercial manufacturing scale than most other processes because most of the liquid filling process is independent of scale. This simplicity makes it ideal as a rapid product development and screening tool for promising compounds with low solubility, specialized handling requirements, and other formulation challenges. Cycles for manufacture and scale-up of clinical trial material (CTM) are shortened.

No Reformulation Needed. Liquid-filled capsules do not require reformulation when production is scaled up. The process used at development scale is nearly identical to that used at full scale. Parallel filling heads and automated capsule processing equipment provide the increased capacity and speed needed to produce commercial volumes.

THE PROCESS

The liquid-filling process is straightforward, involving only four steps: dispense, mix, fill, and seal. Liquid-filled hard capsules contain either (1) room-temperature liquids or (2) thermo-softening materials (manufactured as molten liquids at

temperatures of up to 65°C). Typically, sticky semisolid and liquid HPAPIs are miscible in liquid excipients, forming a homogeneous mixture, no matter how low the dose is. Less-miscible HPAPIs, such as particles that have inconsistent sizes and shapes, can be homogeneously suspended in liquid excipients. High-shear mixing is routine for suspensions in liquid and allows sufficient homogenization to overcome most particle dispersion issues and can even break down agglomerates.

Lonza has developed extensive expertise in the formulation and manufacture of liquid-filled hard capsules, including proprietary equipment and processing techniques. Some specialized processing capabilities are outlined in Figure 2.

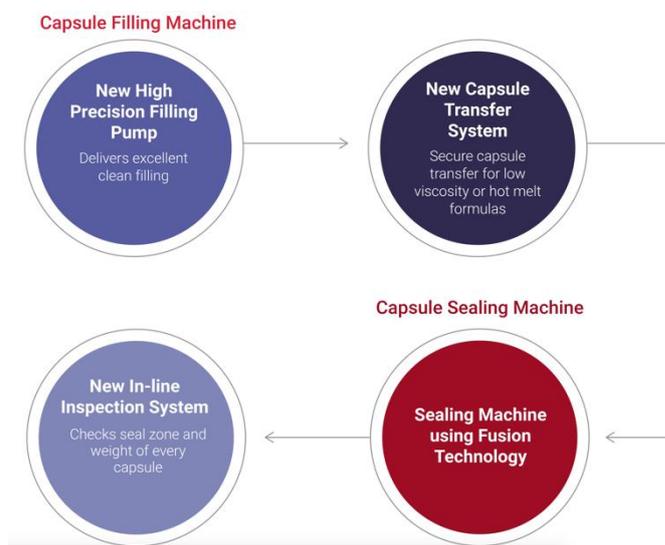


Figure 2
Lonza capsule processing expertise

Our equipment, expertise, and resulting capabilities improve the efficiency, reliability, and productivity of the development and manufacturing processes and result in shortened timelines.

SUMMARY

Lonza has decades of experience in the development of liquid-filled hard capsules across numerous drug substance and processing challenges, including extensive expertise in the handling and manufacture of highly potent compounds and micro-dosing. We also provide integrated product development, analytical method development, and manufacturing services. To learn more, please visit our [website](#) and our [knowledge center](#).