Capsule filling for research and development or small-scale production

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This article discusses important factors to consider when selecting a capsule filler for research and development (R&D) or small-scale production.

The two-piece hard-shell gelatin capsule is a tried and true technology for oral delivery of solid dosage compounds, but capsule filling processes still require R&D testing to ensure accurate filling. Many active pharmaceutical ingredients (APIs) are difficult to obtain, so capsule filling testing methods must be frugal to get as much test data as possible from limited amounts of API.

Therefore, it is imperative to find small, research-scale equipment that can be scaled up for production.
as necessary. When searching for such equipment, it is good to look for machines that are as versatile as possible. Typically, this means having a basic unit onto which researchers can add modules as needed to test the different capsule filling processes in the market. In general, these processes and process variations include the following:

**Powder filling**

a. Gravity feeding powder into the capsule with no tamping.

b. Using tamping pins to create a dense powder slug for more weight.

c. Dosator style—using vacuum to lift and deposit powder into the capsule.

d. Dosator style—using vacuum and then tamping inside a vacuum tube to create a dense powder slug.

**Liquid filling**

a. Using a jacketed vessel with a mixer to keep the fill in a liquid state with solids in suspension. Oils can also be filled if compatible with the capsules.

b. Using a volumetric piston pump to provide a high level of fill volume accuracy.

c. Using special “liquid” capsules that are properly designed to prevent leaking of the liquid fill. After filling, the capsules are sealed using a bander or capsule sealer to further prevent leakage.

**Tablet or minitablet filling**

a. Having an exact count of the number of tablets or minitablets placed into each capsule.

b. Choosing the capsule size (such as EL, DB, or standard capsule sizes) that allows the required number of tablets or minitablets to fit in each capsule.

c. Ensuring that the transfer mechanism and laser counter performance is precise and reproducible so that only one tablet falls into the transfer plate hole and transfers into the capsule at a time.

**Pellet filling**

a. Providing an accurate volume of pellets into each capsule.

b. Having flexibility to provide a range of pellet volumes for different capsule sizes, which can be accomplished by using dosing valves of various volumes.

**Capsule-in-capsule**

a. Placing a smaller capsule into a larger capsule, sometimes with powder or pellets.

b. Performing a first run to fill the smaller capsules under one set of conditions then, with the filled smaller capsules loaded into the product hopper, feeding them into the larger empty capsules using a method similar to tablet filling with a plate with holes cut out in the shape of the small capsules as a transfer mechanism.
Selecting an R&D capsule filler

For R&D, using a bench-top capsule filler is ideal because it takes up less space and is easier to maintain than a larger, floor-standing unit. Also, it is important to select a machine that accepts the full range of capsule sizes as well as modifications or variations on capsule bushings that hold different capsule types with different tolerances. The most common capsule types are gelatin and hydroxypropyl methylcellulose (HPMC). Capsule sizes range from size 000 on the large end to size 4 or 5 on the small end, with the most common sizes being 0, 1, and 2. Several capsule sizes are also available in less common elongated (EL) versions, and double-blind (DB) capsules are also available for over-encapsulating comparator products during clinical trials.

Dosing disks. Capsule filler dosing disks may vary in thickness depending on the capsule weight required. This means that the disk thickness can be used to provide a specific weight range based on factors such as powder density and tamping-pin setting. The tamping-pin setting determines the amount of compaction applied to the slugs. Tamping pins are usually set by starting at the highest position to allow the greatest volume of uncompacted powder into the capsule then incrementally reducing the setting to increase the compaction until attaining the required capsule weight. A thicker dosing disk provides a larger powder slug and weight, while a thinner dosing disk provides a smaller slug and weight.

A technique that can be useful when encapsulating lightweight powders is to use a dosing disk that is one size smaller than the capsule size. For example, you might set up the machine with a size 4 dosing disk when using size 3 capsules. The size 4 slug will give you less weight in the size 3 capsule, which can help to avoid weight-variation issues that can be associated with light powders.

Basic features. Basic features to look for include a variable-speed drive, data transfer capability, doors that open on all sides for observation and access for maintenance, and ease of modular installation using control connectors and power plugs. Built-in internal and external (but inside the cabinet to reduce noise) vacuum pumps for process operation are necessary for a clean operation. Depending on the user’s location, an air compressor inside the portable cabinet may also be needed. If you plan to process a large number of capsules upon completing the research, a
unit that allows you to set parameters for automatic operation will be useful.

**Containment.** Some formulations, such as those containing highly potent compounds, may require wash-in-place (WIP) cleaning and/or an isolator for controlling the formulation’s exposure to humidity or oxygen. WIP capsule fillers are typically installed inside an isolator, so it is very important to plan ahead. Start with a stainless-steel WIP capsule filler, then consider which processes or modules may be needed in the future.

If possible, the capsule filler supplier should also supply the isolator or at least be consulted about the isolator design. Adding modules for different processes may require features to be incorporated into the isolator design, such as exterior controls to operate the unit with the needed modules. If the isolator is not designed to accept these future modules, you may find it very difficult to add them later. While the capsule filler may have the capability to add modules, it may be challenging to communicate functions from the module to the capsule filler for variables such as indexing the capsules to feed a fixed number of tablets into each capsule. The capsule filler rotation must wait for the tablets to be filled at each station before rotating. This can become even more complicated if the requirement is to fill, for example, three different minitablets into each capsule at different quantities.

**Double-sided operation.** Another variation on the standard design is a double-sided unit to allow two powder feeders or dosators in combination with other modules. This design can be useful for filling capsules with multiple formulations as well as to increase capacity.

**Maintenance and utilities.** Proper maintenance is necessary to keep the unit performing properly and accurately. When selecting an equipment supplier, be sure to consider ongoing service and support as well as the availability of change kits and parts.

Required utilities include compressed air and electricity. Also, if you will be encapsulating dusty formulations, an external dust collection system similar to the type used in tablet presses is recommended. Such a system will require regular filter changes to avoid problems. Room air conditions are also important to avoid sticking. Low humidity is recommended.

Finally, a portable storage cart will keep the unit at a comfortable working height and allow you to easily move it between rooms. The cart can also provide convenient storage for change kits, so they are not misplaced.

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