capsule filling

Answers to 10 common questions about capsule filling

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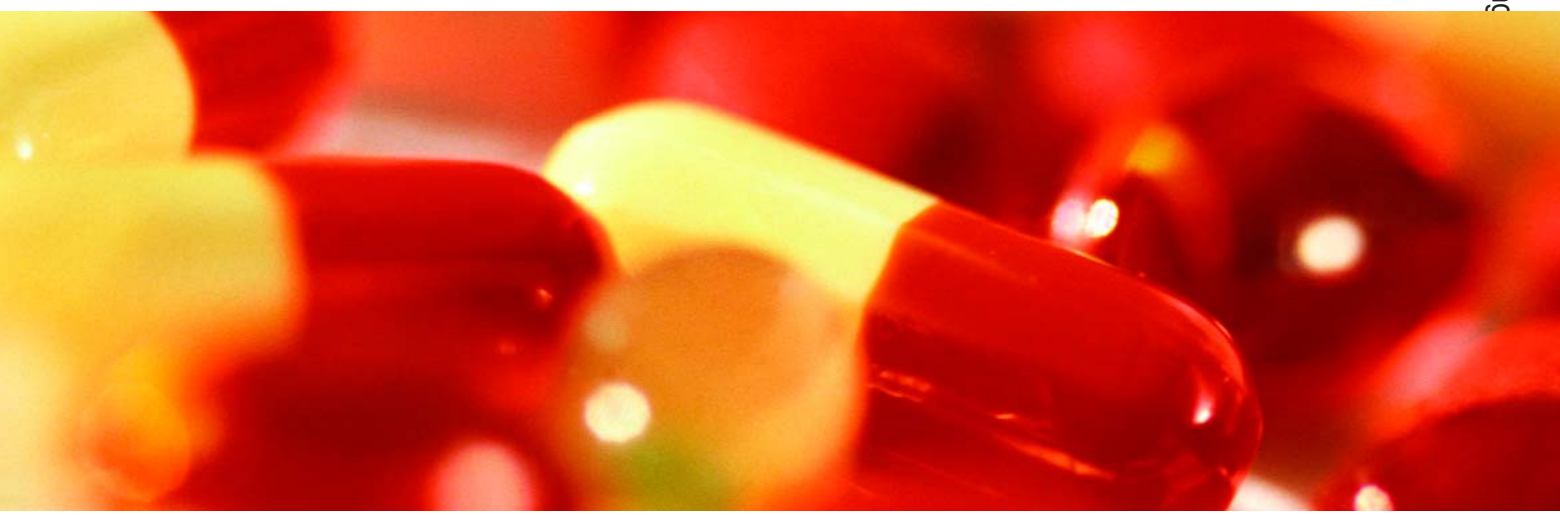


Today's capsule filling machines produce as many as 200,000 capsules per hour thanks to better equipment, better controls, and a better understanding of the process. But if you're just getting started in capsule filling, you probably have some basic questions about the operation. This article provides answers to some common questions about capsule filling.

Table 1

Capsule volumes and filling capacities

Size	000	00el	00	0el	0	1el	1	2el	2	3	4	5
Capsule volume (ml)	1.37	1.02	0.91	0.78	0.68	0.54	0.50	0.41	0.37	0.30	0.21	0.13
Powder tapped density	**Capsule capacity (mg)**											
0.6 g/ml	822	612	546	468	408	324	300	246	222	180	126	78
0.8 g/ml	1096	816	728	624	544	432	400	308	296	240	168	104
1 g/ml	1370	1020	910	780	680	540	500	410	370	300	210	130
1.2 g/ml	1644	1224	1092	936	816	648	600	492	444	360	252	156

1 How do I determine the appropriate capsule size for my formulation?

You need to determine the density of the formulation to answer this question. For powder formulations, use the tapped density value. For pellets or granules, use the bulk density. Once you have this information and you know the target fill weight, ask a capsule supplier for a capacity chart, such as the one shown in Table 1. Using this chart as an example, encapsulating 500 milligrams of a powder with a tapped density of 0.8 gram per milliliter would require a size 0 capsule.

Figure 1

Example of a weight control chart

Product: _____ Strength: mg Date: _____

Batch number: _____ Operator/Checker _____/_____ Page No. 1

Filling Limits(Avg.): UCL 260 mg LCL 248 mg Range: 20

Sample	Time/Weights (mg)								
	11:17AM	11:18AM	11:30AM	11:45AM	12:00PM	12:15PM	12:30PM	12:45PM	1:00PM
1	254	262	259	251	254	257	252	255	258
2	261	263	257	246	258	255	252	255	252
3	254	257	252	260	256	256	250	249	250
4	258	259	248	253	251	255	251	254	251
5	256	254	255	251	246	255	260	257	255
6	256	261	258	255	254	254	253	259	251
7	257	254	253	250	250	253	254	252	240
8	256	259	249	251	248	251	248	250	261
9	258	258	256	258	255	253	255	248	259
10	253	259	258	252	248	252	253	252	260
Avg.	**256**	**259**	**255**	**253**	**252**	**254**	**253**	**253**	**254**
Range	**8**	**9**	**11**	**14**	**12**	**6**	**12**	**11**	**21**

2 How do I establish proper filling limits to effectively monitor and control a capsule filling run?

You can accomplish this with statistical process control (SPC) techniques. SPC establishes the process capability for a specific formulation being encapsulated on a designated filling machine. Most statistical textbooks and publications on "lean sigma" provide the procedures and formulas for establishing process control limits. I've also found a website that is particularly helpful [1], and a variety of SPC software is available.

I've had excellent results monitoring capsule filling runs by charting the average weights and range of weights of the samples. Figure 1 provides an example of a control chart (UCL stands for upper control limit. LCL stands for lower control limit). Making a chart like this requires using SPC procedures to determine the upper and lower control weight limits and the upper and lower control limits for the average weight and weight range. Then follow these steps:

- Take a sample of 10 capsules at regular intervals (every 15 to 30 minutes), calculate the average and range of their weights, and plot the results on the control chart. These plots provide a simple graphical technique for determining if the average or range val ues are outside the control limits. See Figure 2.
- If the data points are within the acceptable limits, don't adjust the weight settings unless there is a trend where the previous six average weight checks were consistently above or below the centerline.
- If either the average or range of weights falls outside the control limits, stop the filling run and investigate to determine the cause(s).
- Isolate all the production collected from the previous satisfactory weight check and evaluate it to determine the disposition for this segment of production. In most cases, this segment of production is either discarded or weight-sorted.
- Resume processing only when you have ascertained the causes of the change and taken the required corrective action to bring the average and range back within control limits. We would usually perform two weight checks a minute apart to verify this.

In summary, the upper and lower control limits for both the average weight and range of weights are used to identify conditions where the process weight variation has changed due to an assignable cause. Such changes indicate that the capsule filling machine is no longer in a state of statistical control.

3 How do I ensure capsule filling quality?

The traditional approach is to perform a quality check on a small sample (usually 10 capsules) every 30 or 60 minutes when you take a weight-check sample. While this is certainly a good procedure and one that my capsule filling department followed for many years, we still visually inspected the batches to remove defects that were not always found in the routine quality checks.

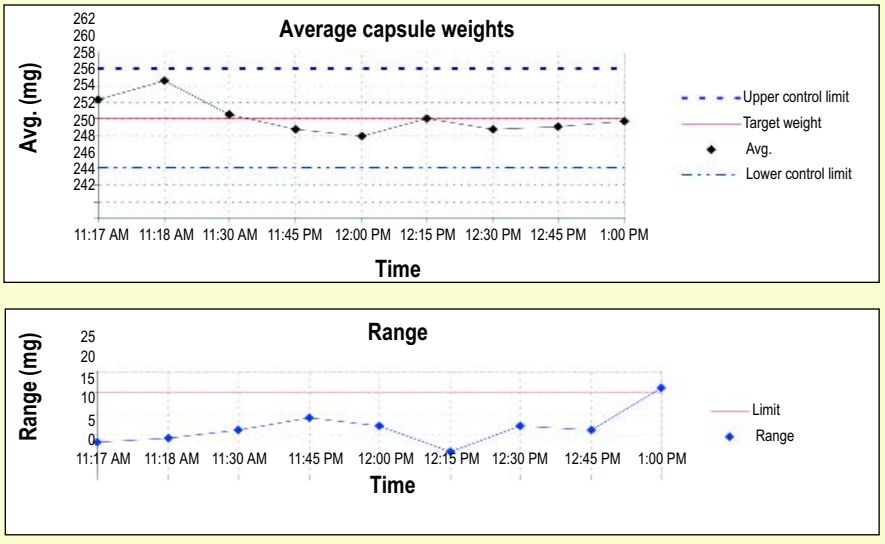
Every time we analyzed a quality problem, we discovered a high correlation between the setup of the capsule filling machine and the incidence rate of defects. Based on this, we began to check a large sample for acceptable quality level (AQL) after every machine setup and after every major repair. After adjusting the machine to hit the target fill weight, we would perform a sustained run for 5 to 10 minutes, stop, and then carefully inspect every capsule for defects. Using such a large sample highlighted specific defects that, in most cases, we could attribute to machine setup.

For example, a high incidence rate of "telescoped" or split capsules indicates either a misalignment of the upper and lower capsule segments (or bushings) or an incorrect setting of the cap hold-down pin (or plate) in the joining station. Dents in the capsule body indicate either an incorrect setting of the body joining pins or an incorrect pin size or pin configuration. Most manufacturers of capsule filling machines supply a troubleshooting guide to assist with this kind of analysis.

Based on the information obtained from these procedures, we developed a detailed checklist for machine

FIGURE 2

Weight control chart plot



setup, which required operators to measure components and settings precisely at each critical step. The operator or mechanic then had to sign off that everything on the checklist was indeed checked. These procedures allowed us to build quality into the process and to reduce by 85 percent the time we spent visually inspecting for defects. That represented a significant labor savings.

4 What are some of the key factors to make a formulation run effectively on high-speed capsule filling machines?

The majority of high-speed filling machines dose capsules using either a dosator and piston system or a tamping and dosing disc method. Each has specific formulation requirements.

Dosator and piston machines require a formulation that is well lubricated to ensure clean ejection by the piston. It also must compact well so that the plug does not break up when the dosator is withdrawn from the powder bed.

Tamping and dosing disc machines need formulations with adequate lubrication for efficient plug ejection to prevent filming and to reduce friction of the sliding components. While the formulation must have compactability to make coherent plugs that eject cleanly, this is less critical for tamping and dosing disc machines than it is for dosator and piston systems. Tamping and dosing machines also require formulations with good flow characteristics to ensure a uniform powder bed level in the large-diameter dosing bowl.

5 What type of formulations may not be suitable for two-piece gelatin capsules?

The best method for determining suitability is to conduct compatibility studies of the API and the excipients. There are two major API characteristics that can be problematic: moisture sensitivity and hygroscopicity.

Moisture sensitivity. Two-piece gelatin capsule shells have a moisture content between 13 and 16 percent, and the moisture can interact with the encapsulated product and cause stability problems.

Hygroscopicity. Once encapsulated, hygroscopic products will remove moisture from the gelatin capsule shell, which leads to brittleness once moisture content drops below 10 percent.

There are two capsule alternatives to address the problems associated with these types of formulations: Hydroxypropyl methylcellulose (HPMC) capsules and gelatin-polyethylene glycol (PEG) capsules.

HPMC capsules have a low moisture content (4 to 6 percent), an attractive feature when dealing with moisture-sensitive and hygroscopic formulations. HPMC capsules have an excellent stability profile and resist physical changes at low humidities.

There are also gelatin capsules that have been specially developed with PEG 400 to reduce brittleness when exposed to low-moisture fills. These capsules are more compatible with hygroscopic formulations or moisture-sensitive ingredients than standard gelatin capsules.

6 What are some of the difficulties of filling capsules with pellets?

The capsule filling and dosing mechanisms for pellets and granules are based on volumetric filling, by using either a dosing chamber or a vacuum dosator or by directly filling into the capsule body. Inconsistency can result from

- Large differences in the pellet/granule particle size
- Agglomeration of the pellets/granules
- Poor flow characteristics
- Insufficient level of pellets in the supply hopper that fills the dosing chamber
- Electrostatic charge that retards the transfer from the dosing chamber to the capsule body

In many cases, the pellets or granules have a functional coating that controls release. It's important to verify that the dosing system and the material handling system (product feeder) are not abrading the coating, which could affect the release profile.

Products that comprise a blend of different pellets raise the issue of content uniformity, particularly when the blend includes high- and low-dose pellet groups. The pellets may segregate (de-blend) during feeding or encapsulation. Since many of the modern filling machines can be equipped with more than one pellet feeding system, you can resolve this problem by feeding the pellet products separately.

One challenging formulation from my experience comprised four pellet groups: 1) Product A immediate release, 75 milligrams; 2) Product A controlled release, 75 milligrams; 3) Product B immediate release, 12.5 milligrams; and 4) Product B controlled release, 12.5 milligrams. This formulation was filled using an MG Futura machine equipped with two pellet dosing systems, each of which had two dosing chambers. By dosing each pellet group separately, we resolved the problems of blend uniformity and release profiles.

7 Where and how should I store my capsules?

Empty capsules. Empty two-piece gelatin capsules are shipped with a moisture content between 13 to 16 percent. It is important that this moisture content is maintained. Avoid exposing the capsules to high temperatures or to cycles of high and low temperatures. There is also a tremendous volume of air inside the capsule that can extract or release moisture from the capsule. Maintain the area where you store the capsules at 15° to 25°C and 35 to 55 percent relative humidity (RH). Do not store empty

capsules in freezers. The empty capsules are also very susceptible to damage because the capsule walls are unsupported.

Filled capsules. The storage requirements for filled capsules are based on the product stability profile. The warehouse storage areas should be temperature-mapped and monitored to ensure the room temperature is under control and that product-specific refrigeration/RH requirements are maintained. Ideally, the storage area would be equipped with alarms and there would be product-specific product handling procedures that explain how to deal with out-of-limit temperature/humidity incidents. If the product is stored in bulk containers for a significant period of time prior to packaging, you should institute procedures to monitor bulk product stability.

General storage recommendations. Protect the capsules from direct sunlight by storing them away from windows and skylights. They should also be stored away from radiators, heat registers, hot water pipes, and steam pipes. Keep the capsules out from under potential sources of water condensation, such as water pipes, and keep pallet loads off the floor.

TABLE 2

Capsule banders

Supplier	Model	Capsules/hour	Other features
IMA North America Bristol, PA	Hermetica (two models)	50,000 100,000	•Automatic single-band sealer • Built-in viscometer •Sealing and drying plates have double row of capsules to reduce change parts
www.ima.it			
Qualicaps Whitsett, NC	Lab scale	3,500	Automatic double-band sealer
	S-40	40,000	Automatic double-band sealer
	S-100	100,000	Automatic double-band sealer
www.qualicaps.com			
Schaefer Technologies Indianapolis, IN	STI Lab top bander	Depends on number of banding slats	Semi-automatic double-band sealer
	STI CB-15	15,000	Automatic double-band sealer
	Bonapace BD-3000	3,000	Automatic single-band sealer
www.schaefer-technologies.com			

8 What are the tamper-evident requirements for capsules?

The requirements for OTC capsule products are specified in 21 CFR Part 211. Section 211.132, paragraph (b) (2) states that "In addition to the tamper-evident packaging feature described in paragraph (b) (1) of this section, any two-piece, hard gelatin capsule covered by this section must be sealed using an acceptable tamper-evident technology."

Paragraph (c) (i) states that container labels must include a statement that "identifies all tamper-evident feature(s) and any capsule sealing technologies used to comply with paragraph (b) of this section."

9 Capsule banders or sealers that apply a gelatin band around the seam area of the capsule (cap-body interface) are considered an acceptable tamper-evident technology. Table 2 lists the available capsule banders.

One company offers a capsule sealing system alternative to banding [2]. The FDA is currently evaluating whether this system provides acceptable tamper-evidence. See the article on page 12 for more information.

TABLE 3

Excipients and packaging materials containing low levels of aldehydes

Excipient	Formaldehyde content (ppm)	Packaging material	Formaldehyde content (ppm)
Starch	2.4	Rayon	2.0
Lactose	0.1	Plastic caps	2.4
Croscarmellose	0.3	Inserts	0.8
HPMC	1.1		
Tween	0.3		
Sodium lauryl sulfate	0.3		

10 What are some things that can go wrong that people don't anticipate?

I spent more than 30 years of my career involved with capsule filling, so I could probably fill a novel with my response to this question. Instead, I'll describe just two challenging issues I encountered.

The first involved pinholes and cracks that resulted in gradual leakage of the product from the capsule. Recovering the batch by weight-sorting was not totally effective, because some of the acceptable capsules would continue to leak and would eventually become low-fills in the package, which could trigger a product recall. Instead, we first subjected the capsules to excessive vibration in a vibratory sieve. That accelerated the leakage, creating low-fills, and then we could successfully weight-sort the batch.

In most cases, pinholes and cracks occur when the dome of the capsule body fractures due to excessive vacuum during separation. The problem can also stem from incorrect setup of the joining pin. Preventing these situations is easy: Follow the setup procedures described in the response to question 3. Installing a check valve on the vacuum separator line to limit the maximum suction is also helpful.

The second incident involved the cross-linking of filled capsules. The problem came to our attention during a site transfer of some products, when an accelerated stability evaluation indicated a significant decrease in dissolution profiles. An investigation revealed that this was the result of the gelatin cross-linking under stress conditions. In addition, it was discovered that some of the formulation's excipi-

ents contained trace amounts of aldehyde, which caused chemical interactions with the gelatin.

From searching the literature we learned that low levels of aldehydes had been detected both in excipients and in packaging materials and that they could cause gelatin cross-linking. See Table 3. Consequently, we added aldehyde testing to our acceptance specifications for all excipent and packaging materials used with capsule products.

TABLE 4

Capsule separators/recovery machinery

Manufacturer/US supplier	Maximum output
Sejong Pharmatech (CMS Technologies) Cranbury, NJ E-mail: chiminsunwoo@hotmail.com	40,000 capsules/hr
Vanguard Pharmaceutical Machinery Spring, TX www.pharmaceutical-equipment.com	36,000 capsules/hr

It should be noted that recent studies of the cross-linking phenomena indicate that the bio-availability of the drug is not significantly altered [3, 4]. The first of these referenced studies suggests conducting two-stage in vitro dissolution tests on dosage forms that contain hard gelatin. In the first test, use a dissolution medium without enzymes and in the second, use a dissolution media that contains enzymes (gastric and intestinal media).

What is the best way to recover product from capsules?

Any method of recovering fill materials from capsules must

- Minimize gelatin fines;
- Avoid grinding or particle size reduction of the fill material;
- Minimize attrition of the pellet/granule coating system;
- Allow for validation and stability evaluation of the recovered product; and
- Be included in the filing or update if the product is an NDA.

The traditional methods of milling and sieving do not adequately address the above issues. You may want to evaluate the recently introduced capsule separator/recovery units listed in Table 4. These machines pull the capsules apart mechanically without damaging the contents.

T&C

References

1. See www.murtongroup.com. At the bottom of the page, click on "Free-SPC Companion" to download a helpful 10-page document.

2. Liquid encapsulation microspray sealing (LEMS), Capsugel, Greenwood, SC.

3. Digenis, G.A., Gold, T.B., and Shah, V.P. Cross-linking of gelatin capsules and its relevance to their in vitro-in vivo performance. J Pharm Sci 83 (7) 915-921 (1994).

4. Meyer, M.C., Straughn, A.B., Mhatre, R.M., Hussain, A., Shah, V.P., Bottom, C.C., Cole, E.T., Lesko, L.L., Mallinowski, H., and Williams, R.L. The effect of gelatin cross-linking on the bioequivalence of hard and soft gelatin acetaminophen capsules. Pharm Res 17 (8) 962-966 (2000).

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