

ANSWERS TO COMMON QUESTIONS ABOUT CAPSULE

Today's capsule filling machines produce as many as 200,000 capsules per hour. Thank to better equipments, 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 the capsule filling.

TABLE 1												
Capsule volumes and filling capacities												
Size Capsule	000	00e1	00	0e1	0	1e1	1	2e1	2	3	4	5
volume (ml)	1.37	1.02	0.91	0.78	0.68	0.54	0.5	0.41	0.37	0.3	0.21	0.13
Powder tapped density	Capsule capacity (mg)											
.06 g/ml	822	612	546	468	408	324	300	246	222	180	126	78
.08 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	482	444	360	252	156

1 HOW DO I DETERMINE THE APPROPRIATE CAPSULE SIZE FOR ANY FORMULATION?

You need to determine the density of the formulation to answer this question for powder formulation, 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 the capsule supplier for a capacity chart, such as the one shown in Table.1. Using this chart as an

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	11:17	11:18	11:30	11:45	12:00	12:15	12:30	12:45	1:00
	AM	AM	AM	AM	PM	PM	PM	PM	PM
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

example, encapsulating 500 milligrams of a powder with a tapped density of 0.8 gram per millilitre would require a size "0" capsule.

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 textbook and publications on 'lean sigma' provide the procedures and formulas for establishing process control limits. We've also found a website that is particularly helpful {1}, and a variety of SPC software is available.

We had excellent results monitoring capsules 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. This plot provides a simple graphical technique for determining if the average or range values are outside the control limits. See Figure 2.

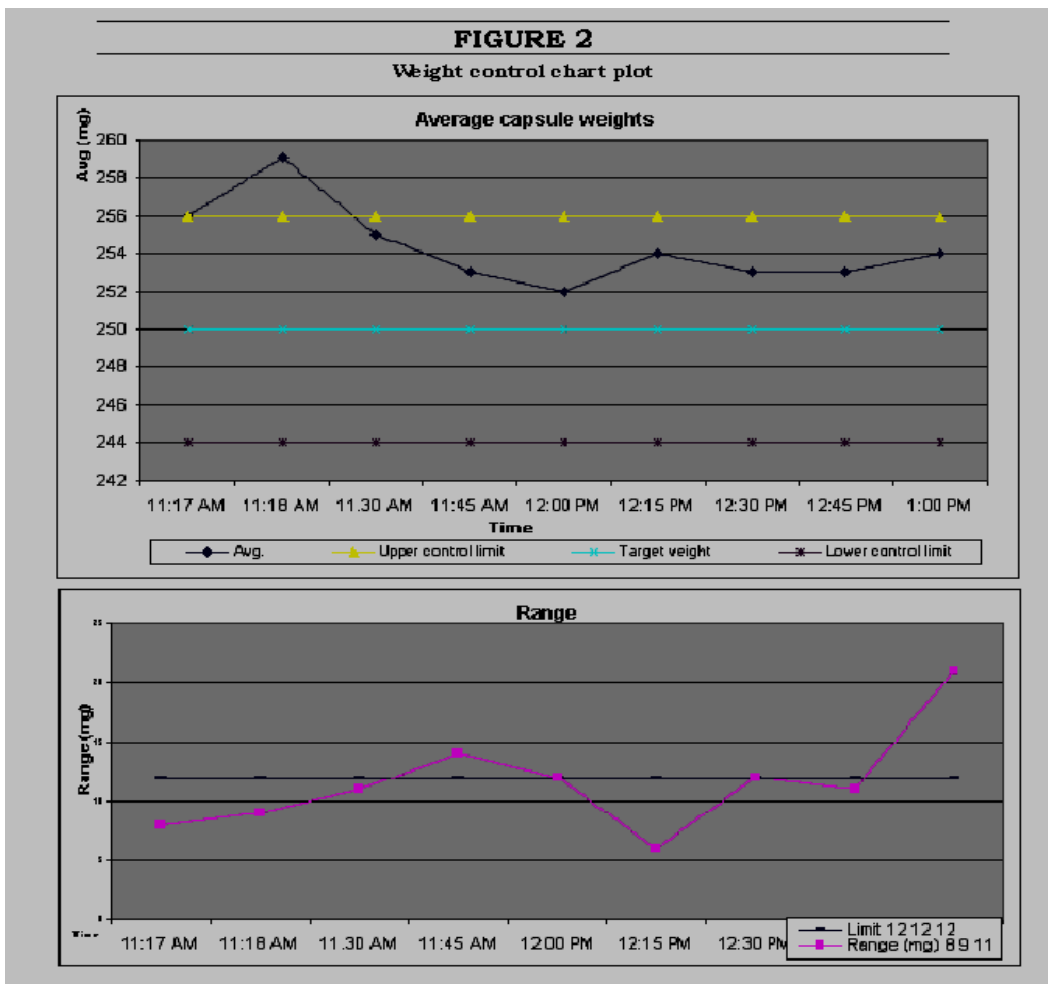
- If the data points are within the acceptable limits, don't adjust the weight settings unless there is a trend where the previous six average weight checks were consistently above or below the centerline.

- 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

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

Every time we analysed 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 begin 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 ran 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 spilt capsules, indicates either a misalignment of the upper or 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 setup, which required operators to measure components and setting precisely at each critical step. The operator or mechanic then had to sign off that everything on checklist was indeed checked. These procedures allowed us to build quality into the process and to reduce by 85% the time we spent visually inspecting for defects. That represented a significant labour savings.

4 WHAT ARE SOME OF THE KEY FACTORS TO MAKE A FORMULATION RUN EFFECTIVELY ON A HIGH-SPEED CAPSULE FILLING MACHINE?

The majority of high-speed filling machines does capsule filling using either a dosator and piston system or a tamping and dosating 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 prevent filming and to reduce friction of the sliding components. While the formulation must have computability to make coherent plugs that eject cleanly, this is less for dosator and piston systems. Tamping and dosing machines also requires 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 capsules shells have a moisture contents between 13 and 16%, and the moisture can interact with the encapsulated product and cause stability problem.

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

There are two capsule alternatives to address the problems associated with these types of formulations. Hydroxypropyl methylcellulose (HPMC) capsule and Gelatin-polyethylene Glycol (PEG) Capsules. HPMC capsules have low moisture content (4 to 6%), 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. Those 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 mechanism for pellets and granules are based on volumetric filling, by using either dosing chamber or a vacuum dosator or by directly filling into the capsule body. Inconsistency can result from:

- Large differences in the pellets/granules 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 is 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 image of contents uniformity, particularly when the blend includes high and low dose pellet groups. The pellets may segregate (de-blend) during the 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 controlled release, 12.5 milligrams;
- 4) Product B controlled release, 12.5 milligrams.

This formulation was filled using an MG Future machines equipped with two pellet dosing systems, each of which had two dosing chambers. By dosing each pellet group separately, we resolved the problem of blend uniformity and release profiles.

7 WHERE AND HOW SHOULD I STORE MY CAPSULES?

Empty capsules: Empty capsules are shipped with a moisture contents between 13 to 16%. It is important that this moisture contents 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 capsule at 15 to 25 ° C and 35 to 55% relative humidity (RH). Do not store empty capsules in freezers. The empty capsules are also very susceptible to damage because of 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 control requirements are maintained. Ideally, the storage areas would be equipped with alarms and there would be a product-specific product handling procedure that explains 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 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 load off the floor.

8 WHAT ARE THE TAMPER-EVIDENT REQUIREMENTS FOR THE CAPSULES?

Supplier	Model	Capsules/hour	other features
IMA North America Bristol, PA	Hemetica (two models)	50,000 100,000	*Automatic single-band sealer * Built-in vis cometer. * Sealing and drying plates have double row of capsules to reduce change parts.
www.ima.it Qualicaps Whitself, 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		Depends on number of banding slats	Semi-automatic double-band sealer
Schaefer Technologies Indianpolc,IN	STI Lab top bander	15,000	Automatic double-band sealer
	STI CB-15	3,000	Automatic single-band sealer
	Bonapace BD-3000		Automatic single-band sealer
www.schaefer-technologies.com			

"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 the acceptable temper-evident technology."

Paragraph © (1) states that container labels must include a statement that "I identified all tamper-evident feature(s) and any capsule technologies used to comply with paragraph (b) of this section".

Capsule banders of sealers that apply a gelatin band around the searn 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 temper-evidence.

Excipient	Formaldehyde Content (ppm)	Packaging material	Formaldehyde Content (ppm)
Starch	2.40	Rayon	2.00
Laclose	0.10	Plastic caps inserts	2.40
Croscarmellose	0.30		0.80
HPMC	1.10		
Tween	0.30		
Sodium lauryl sulfate	0.30		

9 WHAT ARE SOME THINGS THAT CAN GO WRONG THAT PEOPLE DON'T ANTICIPATE?

We spent more than 30 years of 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 is involved pinholes and cracks which results in gradual leakage of the product from the capsule. Recovering the batch by weight-sorting was not totally effective to leak and would eventually become low fills in package, which could trigger a product recall. Instead, we first subjected the capsule 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 occurs when the dome of the capsule body fractures due to excessive vacuum during separation. The problem can also stem from incorrect scup 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 formulations excipients contained tract amount 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 excipients and packaging materials used with capsule products.


It should be noted that recent studies of 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 the dissolution media that contains enzymes (gastric and intestinal media).

10 WHAT IS THE BEST WAY TO RECOVER PRODUCT FROM CAPSULES?

Any method of recovering fill material from capsule must:

- Minimize gelatin finer;
- 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 filling or update if the product is an NDA.

The traditional methods of milling and sieving do not adequately address the above issues. You might 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.

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

11 INGREDIENTS OF CAPSULE?

The major ingredient of capsule is gelatin. Gelatin is widely used in many food products such as puddings, desserts, marshmallows, chewable candies, glazes, whipped toppings, and dips. One popular consumer product is Jell-O® brand gelatin. In food applications, gelatin's ability to gel, thicken, stabilize, and aerate make it a highly desirable, nutritive, fat-free component. Gelatin also finds its way into many households in the form of cosmetics and toiletries, which utilize gelatin for its hypoallergenic and hydrating properties.

Gelatin itself is a mixture of water-soluble proteins derived primarily from collagen, which is the main naturally-occurring protein constituent of connective tissue. Gelatin is obtained from collagen

by exposing animal skins and bones to a controlled extraction process. Gelatin comes in various types. Capsules are made from pharmaceutical-grade gelatin that has met the stringent requirements of the United States Pharmacopoeia and other international organizations that set standards for products that are used in medicines.

In addition to gelatin, capsules can also be created using non-animal sources suitable for addressing a variety of cultural and dietary requirements, including vegetarians, as well as patients with restricted diets. Two such non-animal capsule materials are PULLULAN and HYPROMELLOSE.

PULLULAN is a water-soluble polysaccharide produced through a fermentation process, has achieved wide regulatory acceptance with its proven safety record. It has been in commercial production for more than 25 years, having numerous uses in the food and pharmaceutical industries where as HYPROMELLOSE or HPMC is made from cellulosic raw materials and is also widely accepted globally.

In the production of capsules, a thin film of gelatin, pullulan or hypromellose is prepared by using stainless steel pins. As the gel forming film dries on the pin, it hardens to form the capsule which is later removed from the pin. Two different size pins are used one for the body and other whose diameter is of large size for the cap of a two-piece capsule. After that the capsule is transferred to a machine, which fills a powder, liquid, or paste in the capsule.

12 IS THE USE OF GELATIN CAPSULE SAFE?

Various studies on gelatin can be obtained by an intensive search of the GOOGLE or other search engines, the most significant assurance of the safety of gelatin relates to its long-term use and it is not only used in capsule, but also it is a part of many other food products used in general.

13 HOW DOES IT WORK AFTER SWALLOWING THE CAPSULE?

As gelatin shell dissolves in the stomach, releasing its contents within the first few minutes of swallowing.

14 WHICH NEEDS TO BE OPTED, CAPSULE OR TABLET?

Both tablets and capsules are acceptable as dosage. The original ratio for developing the capsule as a dosage form is based on its ability to avoid the taste and/or odor of specific medicinal compounds. It is also popular due to: easy to swallow, good & attractive appearance and of a neutral taste, as well as the ability to be filled and processed easily.

Apart from Capsules, Tablets are formed by compression of a powdered form of the active ingredients i.e. primarily sugars, starches and other fillers are often added to tablets to enable efficient and stable tablet formation. Some tablets have a chemical coating, which is added to make them easy to swallow or avoid the dis-taste.

15 SOME TABLETS ARE FOUND LABELED AS "GELCAPS" AND "SOFTGELS" DOES IT HAVE ANY SIGNIFICANCE?

Gelcaps are basically a tablet which is coated with a thin layer of gelatin. Softgels are composed of thick layer of gelatin; plasticizers are also added to maintain flexibility and stability. The inner section of the softgel normally contains a liquid form of the active ingredient.

T & C

REFERENCE

1. See www.murtangroup.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., Battam, C.C., Cole, E.T., Lesko L.K., 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).
5. Donald K. Lightfoot is an independent consultant, 2826 W. Placita Paciente, Tucson, AZ 85742. Tel 520 229 3506. E-mail- Donald.lightfoot@comcast.net. He recently retired from GlaxoSmithKline after 46 years of service. As a director of manufacturing and R&D, he gained extensive production experience in capsule filling and other processes, including granulation, tablet compression, tablet coating, pellet coating, and suppository manufacturing. His expertise spans pharmaceutical manufacturing of both clinical and commercial supplies.