Section 8

Hard Shell Capsules
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Hard Shell Capsules

Types of Capsules

Capsules are “container” dosage forms in which the formulation is contained in shells usually comprised of gelatin. Gelatin capsules are classified as soft or hard, depending on the nature of the shell and its contents. The original gelatin capsule is the soft gelatin capsule. In this case, the shell is plasticized with glycerin, sorbitol or other polyhydric alcohols that impart a degree of flexibility to the shell material. Typically, these capsules are considered “one-piece” capsules. They are formed, filled and sealed in a single, continuous process, usually in a rotary die machine. Generally, soft gelatin capsules are filled with a pumpable liquid phase (solution, suspension, etc.): in most cases, these formulations are developed and filled for the industry by specialty soft gelatin capsule contractors.

The two-piece hard gelatin capsule consists of a cap-piece that slips over the open end of a body-piece. The shells are fabricated and supplied empty to the pharmaceutical industry by shell suppliers. The contents are formulated and filled into the hard gelatin capsules by the pharmaceutical manufacturer without resort to a specialty contractor. Sealing is most often accomplished by a separate process that applies a band of gelatin around the midsection of the filled capsule where the cap overlaps the body. Generally, the fill materials will be dry solids, e.g., powders, granules, beads, or tablets. Pumpable liquid phases also may be filled into hard gelatin capsules; however, effective sealing is required to assure no leakage. In other cases, a warm liquid phase may be filled into the capsule that sets to a semi-solid matrix upon cooling.

Although hard shell capsules are traditionally made from gelatin, capsules fabricated from hydroxypropyl methylcellulose or a starch hydrolysate have appeared on the market in recent years. Such alternatives to gelatin will be of interest to those who, for religious, cultural or other reasons wish to avoid capsules made from animal derived components. However, hard gelatin capsules remain the heavily predominant type of hard shell capsule.

This discussion will focus on the formulation and filling of hard shell capsules.

Why Capsules?

Among solid dosage forms, the capsule is second only to the compressed tablet in frequency of utilization for drug delivery. Given the unique advantages of this dosage form, the popularity of the capsule should not be surprising. For instance, because the medication is contained within the capsule shell, the capsule provides a tasteless, odorless delivery system without the need for a secondary coating step. And many patients perceive that swallowing capsules is easier than swallowing tablets. Easy swallowing may derive from the tendency for the shell to hydrate rapidly and become slippery in the mouth, the tendency for the capsule to float when taken with a fluid and, because of its oblong shape, a tendency to assume an orientation that favors passage down the throat. Indeed, surveys have consistently supported a generally favorable attitude of consumers toward capsules.

From the formulator’s point of view, hard shell capsules provide unique capabilities and options for dosage form design and formulation. Because the contents are contained within the shell, there is no need to form a compact that must stand up to handling in the same sense as a compressed tablet. This means that with an appropriate choice of excipients, it may be possible to direct-fill into capsules many larger dose actives that could not be tableted without a granulation step. In addition, modern capsule filling machines make possible the multiple filling of beads, granules, tablets, powders and pumpable liquids into hard shells, and this provides the formulator with numerous options to design unique delivery systems or simply to separate incompatible substances within the same capsule. Because tablets may be filled
into capsules ("super-encapsulation" or "over-encapsulation"), capsules are frequently used to double-blind clinical studies. Finally, most Phase I development studies are carried out with capsule formulations because of the relative simplicity of formulation and manufacture, even though the final formulation may be slated to be a compressed tablet. In certain instances, it may be possible to design a formulation that will run on a capsule filling machine or a tablet press with equal facility.

The ability of automatic filling machines to fill pumpable liquids into hard shell capsules also provides flexibility for the formulator. Liquid filled capsules may offer special advantages for formulating poorly soluble drugs, since they could be solubilized or dispersed (in micronized form) in the liquid vehicle. At the same time, the utilization of liquid filling may enhance the chances of attaining desired content uniformity of very low dose drugs owing to the accuracy of liquid pumping mechanisms and the avoidance of dry-solids mixing problems, through dissolution or dispersion of the drug in micronized form in the liquid vehicle.

Finally, hard shell capsules provide ideal vehicles for dispensing modified-release beads or granules, since these may be filled into the capsules without the need for a compression step that could rupture or otherwise damage controlled-release coatings and thus, undermine the designed-in drug release profile.

What Are the Down-Sides?

The size capsule selected will be governed by the powder bulk. Low bulk density, bulky substances may require granulation prior to capsule filling. In general, capsule sizes should be as small as practical. This not only facilitates swallowing but also reduces packaging and shipping costs. Although larger capsules are sometimes employed, most consumers can manage capsule sizes up to #0.

Capsule filling machines are not as fast as tablet presses; however, fully automatic machines are available which are capable of filling as many as 100,000 or more capsules per hour.

Gelatin capsules may not be appropriate for certain, strongly hygroscopic substances. The physical stability of gelatin capsules is dependent upon maintaining an equilibrium moisture content in the shell of about 13-16%. If the moisture content drops much below this range, the shells tend to become brittle. At moisture contents much above this range, the shells tend to become soft and sticky at the extreme. Since most of the moisture associated with hard gelatin capsules is free water, it can move into or out of the shell fairly easily, and the direction will depend on the relative hygroscopicity of the contents and the nature of the surrounding atmosphere.

Gelatin capsules are also subject to cross-linking on exposure to traces of aldehydes, or upon storage for sufficiently long periods of time at extremes of temperature or humidity. This cross-linking leads to loss of aqueous solubility of the shell. Moderately stressed capsules may fail to meet USP dissolution standards in media without enzymes, but bioavailability may not necessarily be compromised in such cases owing to the presence of proteolytic enzymes in gastrointestinal fluids that can metabolize the cross-linked gelatin. An FDA/Industry Working Group has recommended a two-tiered dissolution test: if the capsules fail the dissolution test [vehicle not containing enzymes], “conduct the second tier in the same medium and under the same conditions as the first tier, with the exception that enzyme will be added to the medium.” If the gelatin capsule passes the second tier test, its performance is considered to be acceptable.

The hydroxypropyl methylcellulose-based capsules now commercially available may avoid both the cross-linking and moisture sensitivity concerns; however, there currently is limited literature on the properties and performance of these capsules compared to gelatin.
### Filling Hard Shell Capsules

Regardless of their mechanical design, all hard shell capsule filling machines have the same operational steps in common: rectification, capsule separation, filling, closure of the capsule, and ejection of the filled and closed capsule from the machine. Rectification is a mechanical process that causes the empty capsules to be lined up all in the same direction, i.e., body-end downward, as they are introduced into the filling mechanism. For capsule separation, the rectified capsules are introduced into a split bushing, or its equivalent. The bushing consists of an upper part and a lower part. A vacuum is applied from the bottom piece to cause the body to be drawn into the lower section of the bushing. The cap remains in the upper bushing piece because its diameter is too large to permit it to follow the body piece. The two bushing pieces are then separated to expose the body piece for filling. In the filling step, one of several possible mechanisms is utilized to fill the body. In capsule closure, the cap and body bushings are brought back together and the cap and body pieces are rejoined via push pins. In most cases, ejection of the filled and closed capsules from the bushing is caused by push pins; in some cases, compressed air may be utilized for this purpose.

### Semi-Automatic Machines

Semi-automatic machines, which require an operator to be in attendance at all times, were once the workhorses of the capsule filling industry. Today, they are more likely to be employed when smaller batch sizes are required, such as production of early phase clinical supplies. Quoted production capacities for powder filling range from 6000-8000 capsules/hour up to as high as 15,000 capsules/hour, depending on the capsule size. The rectified capsules are delivered into holes in a split ring (equivalent to the split bushings above). As the ring rotates on a turntable, vacuum pulls the capsule bodies into the lower ring, leaving the caps behind in the upper ring. After capsule separation, the operator separates the rings and places the body ring on another turntable that rotates beneath the foot of the powder hopper. An auger in the hopper rotates to encourage a more or less constant downward flow of the formulation while the filling ring rotates. The amount of formulation delivered to the capsule bodies depends primarily on the dwell time of the bodies under the foot of the hopper, i.e., the speed of rotation of the filling ring. Fill weight uniformity depends primarily on uniformity of flow from the hopper, and formulations should be designed accordingly. Maintaining a more or less uniform bed height in the hopper is also important to the maintenance of a uniform powder feed rate. However, any overrun of already filled capsules under the hopper can cause an increase in the fill weight of those capsules. Some fill weight variation also can result because of differences in the angular velocity of capsule bodies in the filling ring at different radial distances from the center of rotation. Examples of these “ring machines” are Capsugel Cap 8 and Qualifill 8S machines.

Reier, et al. (6) and Ito, et al. (7) have contributed excellent discussions of the factors affecting encapsulation of powders on such machines.

### Fully Automatic Machines

Most modern automatic filling machines employ pistons or tamping pins that lightly compress the powder into plugs (sometimes referred to as “slugs”), and eject the plugs into the empty capsule bodies. The compression forces are low, often in the range of 50–150N, up to about 100-fold less than that employed in typical tablet compression. Often, the plugs will be very soft compacts and not able to be recovered intact from filled capsules. There are two main types of these fillers: dosator machines and dosing-disc machines. In a recent survey of the pharmaceutical industry, it was reported that dosator machines were used slightly more frequently among the firms responding; however, about 18% of the firms indicated that they use both types of filling machines (8).
Dosing-Disc Machines: This filling principle has been described in numerous places\textsuperscript{(9,10)}. The basic operation is illustrated in Figure 1. The dosing-disc forms the base of the dosing or filling chamber. The dosing-disc is provided with holes that are closed off by a solid brass “stop” plate that slides along the bottom of the disc to form the dosing cavities. In most machines, the cavities are indexed under tamping pins at each of five tamping stations (Fig. 1). The formulation is maintained at a somewhat constant level over the dosing-disc. A capacitance probe senses the powder level and activates an auger feed mechanism when the powder depth falls below a preset level. As the disc rotates (indexes), the formulation is distributed over the disc by centrifugation with the assistance of baffles mounted to the disc. Powder falls into the dosing cavities as they move from one tamping station to the next. Additional powder is pushed into the dosing cavities by the descending tamping pins at each tamping station. Each plug is thus tamped five times. Excess powder over the disc is scraped off as the dosing-disc indexes the plugs to the ejection station where they are positioned over empty capsule bodies and ejected by transfer pins. For a given formulation, size of tooling and powder depth over the disc, the fill weight achieved is determined primarily by the thickness of the dosing disc and the piston penetration setting (or tamping force).

Kurihara and Ichikawa\textsuperscript{(11)} found a minimum in the relationship between the angle of repose of the powder and the coefficient of variation of fill weight in a dosing-disc machine. This observation suggests that a certain flow criterion may be required for maximum fill weight uniformity. At higher angles of repose, powders may not have sufficient mobility to distribute well over the dosing disc. At lower angles of repose, the powder may be too fluid to maintain a uniform bed. A different situation can be expected for machines fitted with agitators to facilitate distribution of the powder over the dosing disc.

Formulations for these machines should be adequately lubricated to prevent filming on pins, to reduce friction between any sliding components that the formulation comes into contact with, and to facilitate plug ejection. Some degree of formulation compactibility is desirable for clean, efficient plug transfer at ejection.

\textbf{Figure 1: Diagrammatic representation of the dosing disc filling principle.} Five tamping stations (1–5) and plug ejection are illustrated.
**Dosator Machines:** Figure 2 illustrates the dosator principle, which has been previously described\(^{12,13}\). The dosator consists of a moveable piston inserted in a cylindrical tube. The position of the piston is preset to a height that defines a volume that would contain the desired dose of the formulation (Fig. 2, A). During the filling process, the open end of the dosator is first pushed down into a powder bed the depth of which has been pre-set and is maintained at that level by agitators and scrapers. Powder thus enters the open end of the dosing tube where it is slightly compressed against the piston (Fig. 2, B). Before the dosator is lifted from the powder bed, the piston may be used to deliver a tamping blow that further compresses the forming plug (Fig. 2, C). The dosator bearing the plug is then lifted from the powder bed (Fig. 2, D) and positioned over an empty capsule body where the piston is thrust downward to eject the plug (Fig. 2, E). In certain machines, the empty capsule body is moved into position under the raised dosator to receive the ejected plug. For a given size of tooling, the fill weight attained for a given formulation is determined primarily by the initial height of the piston in the dosing tube, and secondarily by the height of the powder bed.

**Figure 2: Diagrammatic representation of the dosator filling principle.**

**Key:**

- **A** – Initial piston height setting;
- **B** – Modest plug compression as dosator dips into powder bed;
- **C** – Active piston compression of the plug;
- **D** – Plug transport to ejection station;
- **E** – Ejection of plug into capsule body.
**SUPAC Equipment Guidance**

The manufacturing equipment addendum to the SUPAC-IR/MR guidances place the dosator and dosing-disc types of capsule filling machines in different subclasses of the same class of machines. If machines fall within the same class and subclass, they are considered to have the same design and operating principle. A post-approval change of manufacturing equipment between subclasses within the same class of equipment likely would not require a pre-approval supplement, provided certain other conditions are met. But, changes in equipment that are in the same class, but different subclasses, as would be case for a change between a dosator machine and a dosing-disc machine, should be carefully considered and evaluated on a case-by-case basis. The guidance places the burden on the applicant to provide the data and rationale at the time of change to determine whether or not a preapproval supplement is justified. The reader should refer to “Guidance for Industry, SUPAC-IR/MR – Manufacturing Equipment Addendum,” FDA, CDER, January 1999 for a full discussion.

**Instrumented Filling Machines and Filling Machine Simulators**

Both dosator and dosing-disc machines have been instrumented to permit measurement of the tamping or compression forces developed in plug formation and plug ejections forces. These developments have enabled systematic study of the relationship of formulation and process variables to manufacturability and drug dissolution from capsules. More recently, that research has been extended by the use of simulators that can mimic certain filling machines or certain aspects of machine filling under controlled laboratory conditions with small quantities of material.

**Design of Direct-Fill Formulations**

Although hard shell capsules may be filled with modified release beads, liquids or semi-solid matrices, this discussion will focus on the use and selection of excipients for direct-fill formulation.

**Selection of Excipients**

As a general rule, all excipients used in a formulation should be screened for compatibility with the drug substance.

**Fillers:** Depending on the dose of the drug, fillers may be required to increase bulk. Starch and lactose are the most common capsule fillers; certain inorganic salts such as magnesium and calcium carbonate and calcium phosphate are also sometimes used in this role. Using fillers whose flowability and compactibility have been enhanced through physical modification (i.e., filler-binders for direct compression tableting) is particularly advantageous in the development of direct-fill formulations for automatic capsule filling machines. These include, for example, pregelatinized starch (Starch 1500®), spray processed lactose (Fast-Flo® Lactose) and unmilled dicalcium phosphate dihydrate (Ditab®; Emcompress®), and microcrystalline cellulose (Avicel®). Formulations for dosator machines in particular may benefit from the greater compactibility of such fillers, particularly when drug dosage is large, since it is essential to prevent powder loss from the end of the cylinder during the transfer from the powder bed to ejection into the capsule body. The compactibility of such fillers should contribute to the formation of a stable arch at the dosator open orifice and the formation of mechanically strong plugs. The failure to have a cohesive plug may also cause a “blow off” of powder as the plug is ejected into the shell. The high compactibility of microcrystalline cellulose that is well recognized in direct compression tableting may be of particular benefit in direct-fill capsule formulations. Numerous studies reporting the use of microcrystalline cellulose in direct-fill capsule formulations filled on dosator or dosing disc
machines or simulators have been reported\(^8, 15, 13, 15-18, 20\). Patel and Podczeck\(^{24}\) studied several microcrystalline celluloses in a dosator machine (Zanasi AZ5) and concluded that medium and coarse particle size grades can be considered good excipients for capsules. In a more recent study, silicified microcrystalline cellulose and microcrystalline cellulose were found to be good plug formers when tested in a compaction simulator at tamping forces and piston speeds similar to those found in some filling machines\(^{25}\). The materials were tested neat using a prelubricated die. Several grades of silicified microcrystalline cellulose and a control grade of microcrystalline cellulose (typical particle size of 90 µm) produced plugs having higher maximum breaking force than anhydrous lactose and Starch 1500 under similar compression conditions.

Although the choice of the filler can impact on running characteristics, formulators must also consider any potential impact on drug dissolution. The solubility characteristics of both the drug and the filler should be considered. Following are some considerations that may be helpful to formulators:

1. Generally, soluble fillers should be selected for poorly soluble drugs.

In one commonly cited example\(^{26}\) the dissolution of poorly soluble ethinamate from capsules improved greatly upon increasing the concentration of lactose in the formulation to 50%. In another example\(^{27}\), lactose at a concentration of 50% was found to enhance the dissolution of phenobarbital from capsules, but had no effect on the dissolution of the water soluble sodium phenobarbital.

The intrinsic dissolution rates of some fillers have been reported\(^{28}\). Anhydrous lactose (predominantly the more soluble b-lactose) was found to exhibit almost twice the intrinsic dissolution rate of a-lactose monohydrate.

2. Caution may need to be observed when large amounts of soluble fillers are used in combination with soluble drugs, as the dissolution of the filler may interfere with the dissolution of the drug.

For example, it was reported\(^{29}\) that the inclusion of 80% lactose in a capsule formulation severely slowed the dissolution of water-soluble chloramphenicol, and there was little or no effect on dissolution when adding up to 50% lactose.

3. Formulators may need to consider the potential impact of the pH-dependence of the filler on the population to be served by the product.

The intrinsic dissolution rates of dicalcium phosphate dihydrate, anhydrous dicalcium phosphate, and calcium sulfate dihydrate have been reported\(^{28}\). The dramatically reduced intrinsic dissolution rates exhibited by these fillers under less acidic conditions suggested that they should be used with caution in formulations intended for populations that may exhibit achlorhydria, such as the elderly. The presence of high levels in the formulation may substantially delay disintegration and dissolution.

Glidants: Glidants in the form of finely divided dry powders may be added to formulations in small quantities to improve their flow properties. Usually, there is a concentration for best flow. For the colloidal silicas (e.g., Cab-O-Sil\(^{\circledR}\), Aerosil\(^{\circledR}\)) this concentration is often less than 1%. This optimum concentration varies with the glidant and may be a function of the amount needed to just coat the bulk powder particles\(^{30, 31}\). Higher concentrations often will result in either no further improvement in flow or a worsening of flow. In addition to the colloidal silicas, cornstarch, talc, and magnesium stearate may exhibit glidant activity in a formulation. York\(^{32}\) compared glidants and reported their order of effectiveness for two powder systems as follows: fine silica > magnesium stearate > purified talc.
Lubricants: Like tablet formulations, capsule formulation usually requires lubrication. The same lubricants and concentrations in formulations that are used in tablet formulations are used in capsule formulations, and they provide essentially the same functionality. Lubricants can facilitate plug ejection and reduce filming on piston or tamping pin faces. They can reduce adhesion of powder to metal surfaces and friction between sliding surfaces in contact with the formulation. Hydrophobic substances such as magnesium stearate, calcium stearate and stearic acid are generally the most effective lubricants. Of these, magnesium stearate is used the most widely. The proper use of these excipients involves several considerations:

1. Excessive concentrations of hydrophobic lubricants such as magnesium stearate are likely to retard drug release by making formulations more hydrophobic.

2. Laminar lubricants (magnesium stearate, calcium stearate) are “shear sensitive.” During mixing the particles delaminate, i.e., shear, to form a film on the surfaces of the bulk powder. If blended for a sufficient length of time, even a low concentration of a laminar lubricant can slow drug dissolution. In practice, it is best to add the appropriate level of lubricant last and blend for a minimum amount of time, typically 2-5 minutes.

3. Mixing and delamination doesn’t necessarily end after a blender is stopped: the powder feed mechanism and/or the filling principle of the filling machine can cause additional mixing and shearing. It may be necessary to reduce the level of the laminar lubricant or consider other lubricant options to compensate for such effects.

Overmixing of magnesium stearate in the hopper of an MG2 dosator machine in which the powder in the hopper is continuously mixed with a rotating blade was reported by Desai, et al. Dissolution of three drugs was markedly reduced after running the machine for 30 minutes when the magnesium stearate level was 1%. Reducing the level of magnesium stearate to 0.25% was found to provide adequate lubrication and dissolution was satisfactory over a 30 minute run. Satisfactory dissolution was also reported when the magnesium stearate was replaced with the more hydrophilic Stear-O-Wet® (magnesium stearate coprocessed with sodium lauryl sulfate) and sodium stearyl fumarate.

Ullah, et al. reported a similar problem when scaling up a cefadroxil monohydrate formulation containing 1% magnesium stearate that was initially developed on a Zanasi LZ-64 dosator machine. When scaled up to a GKF 1500 dosing disc production machine, dissolution was significantly slower compared to the development batch. It was suggested that shearing of magnesium stearate during the tamping step may increase the coating of the drug particles with the hydrophobic lubricant. Based on laboratory experiments with a small scale mixer/grinder aimed at simulating the shearing action of the filling machine, they selected a level of 0.3% magnesium stearate for scale up to 570 kg and 1100 kg (full production) size batches. Dissolution from both scale up batches was found satisfactory.

4. In certain cases, an optimum level of magnesium stearate has been reported for best dissolution.

Stewart et al. studied the effect of magnesium stearate concentration on the dissolution of a model low dose drug, riboflavin from capsules. They found that the effect of the lubricant level was dependent on the type of filler. Soluble fillers exhibited prolonged dissolution times with increasing lubricant levels, but less predictable trends were found with insoluble fillers. In certain instances, insoluble fillers were only slightly affected by the magnesium stearate; whereas, with microcrystalline cellulose, there appeared to be an intermediate concentra-
tion at which the dissolution rate was fastest.

Mehta and Augsburger(37) reported an intermediate level of magnesium stearate at which the dissolution rate of hydrochlorothiazide from capsules was best. Microcrystalline cellulose was the filler making up more than 90% of the formulation. Based on measurements of plug breaking strength it was suggested that as the magnesium stearate level was increased, any initial increase in hydrophobicity of the formulation may be more than offset by reduced plug cohesiveness which probably promotes plug dispersion and dissolution. At higher magnesium stearate levels, the hydrophobic effect may be overwhelming, since dissolution was observed to slow down. This possible dual effect of magnesium stearate has also been suggested by others(38) who found that the dissolution rate of rifampicin from capsules increased with lubricant blending time.

5. The metallic stearates are alkaline and should not be used if the drug substance is subject to alkaline hydrolysis or other untoward reaction.

Disintegrants: Disintegrants can facilitate liquid uptake and the dispersion of capsule plugs in dissolution fluids. The newer classes of disintegrants, which have been called “super disintegrants,” have strong liquid uptake and swelling potential, should be considered for inclusion in direct-fill formulations for tamping or dosator machines(39,41). These include croscarmellose sodium (Ac-Di-Sol®), sodium starch glycolate (Primojel®, Explotab®) and crospovidone (Polyplasdone® XL). For capsules, the required level of addition is often double that required for tablets, and may be 4–8% or more, depending on the formulation.

Surfactants: Surfactants can enhance drug dissolution by increasing the wetting of the powder mass, and at concentrations exceeding the critical micelle concentration, they can increase drug solubility(42). Common surfactants employed in capsule formulations include sodium lauryl sulfate and sodium docusate(36,43). Generally, levels of 0.1-0.5% are sufficient. For best results, surfactants should be finely divided, especially if they have a low solubility and dissolution rate.

Hydrophilization

The wetability of poorly soluble drugs can be enhanced by applying a hydrophilic polymer to the drug surfaces(44). In this process, a solution of the hydrophilic polymer, e.g., methyl cellulose, is distributed onto the drug in a high-shear mixer. The resultant mixture is dried and screened.

Granulation

Often employed to increase the bulk of powders for encapsulation, granulation also improves flowability and can reduce the tendency of fine particles to agglomerate or adhere to metal surfaces. Wet granulation provides for the addition of a liquid phase in which a low dose drug may be dissolved to promote its uniform dispersion throughout the mass. Once locked into granules, any subsequent segregation of the low dose active is prevented. Since binders typically are hydrophilic polymers, the wet granulation process effectively accomplishes the hydrophilization process described above. When actives are sensitive to exposure to heat and/or aqueous binder solution, formulations may be dry granulated by slugging or roller compaction, although the dry process does not provide for the addition of the drug in solution. The liquid addition of a low dose drug to fillers may also be accomplished by dissolving the drug in a non-aqueous solvent, spraying the solution onto the filler, and evaporating the solvent.
**Direct-Fill Formulation Strategy and Capsule Size**

The required dose and tapped bulk density of the drug substance provide an initial estimate of the minimum size of capsule that will contain the medication. The actual size capsule formulated will depend on any excipient requirements and/or marketing or patient acceptability considerations. Although larger sizes are sometimes used, generally the largest size capsule that can be easily managed by patients is a #0. The difference between the tapped volume of the desired drug dose and the volume of capsule selected provides an initial estimate of the volume available for excipients.

A comparison of the loose (poured) bulk density to the tapped density also gives an indication of the flowability of the drug substance through calculation of Carr’s compressibility index, CI, as follows:

\[
CI = \left( \frac{\rho_t - \rho_b}{\rho_t} \right) \times 100
\]

Where \(\rho_t\) is the tapped density and \(\rho_b\) is the loose bulk density. Powders with CI values less than 15% are considered to have excellent flow; those with values greater than 40% have very poor flowability. As discussed, excipients may be chosen to enhance both flowability and plug formation. Powders having CI values in the range of about 20-25 or lower should be acceptable in many cases. Limitations owing to the bulk of the drug may require the formulator to consider granulation.

During development, formulations may be evaluated in a simulator or other laboratory plug forming device, such as a dosator mounted to a physical testing machine (e.g., Instron) or a plug tester such as that supplied by Bosch. Plugs should be compressed with forces in the operating range of the filling machine, often 50–100N. The required capsule size can be related to the length of plugs so formed. Further, the plug forming ability of the formulation can be judged from their breaking force, and the ejectability of the plugs from the device can be related to lubrication requirements.

**Statistical Methods in Formulation Development**

Increasingly, statistical techniques are being used in the development of pharmaceutical formulations or at least to clarify the critical formulation and process variables and their interactions. Recent examples of the application of such techniques to hard gelatin capsule formulations include the response surface analysis of Piscitelli et al. and the multivariate analysis of Hogan et al.

**Expert Systems for Formulation Support**

Expert Systems are computer programs that attempt to capture the expertise of experts in a given field. Based on rules or decision trees, these programs can facilitate the development of a formulation by suggesting excipient and levels and procedures after certain facts about the drug are input (e.g., dose, solubility, flowability and others). Several expert systems for capsule formulation support have been described in the literature.
General References


Literature Cited


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