CAPSULES

Hard Gelatin Capsules

In addition of having the advantages of portability and ease of use, capsules become a popular dosage form because they provide an easily swallowed and tasteless shell for drugs; the last advantage is particularly beneficial for drugs having an unpleasant taste or odor. They are easily produced in large quantities (large scale). They generally provide rapid availability of the contained drug, since minimal excipient and little pressure are required to compact the material.

Not all drugs can be formulated as capsule. Capsules are not usually used for the administration of highly soluble materials such as potassium chloride since the sudden release of such compounds in the stomach could result in irritating concentration. Capsules should not be used for highly deliquescent materials because they attract water from the capsule shell which may cause capsule brittleness.

Capsule Shell Synthesis

Capsules are synthesized by dipping cold stainless steel molds into a hot gelatin solution. They are made principally of gelatin and may contain small amounts of dyes, opaquing agents, plasticizers and preservatives. Materials such as methyl cellulose and polyvinyl alcohols have been used to modify the solubility of gelatin or to produce an enteric capsule.

Gelatin is obtained from extraction of animal collagen. Its physical and chemical properties depend on the parent collagen, method of extraction and pH value. Common sources of collagen are bones and skins of animals (calf and pork) as shown in figure 1.

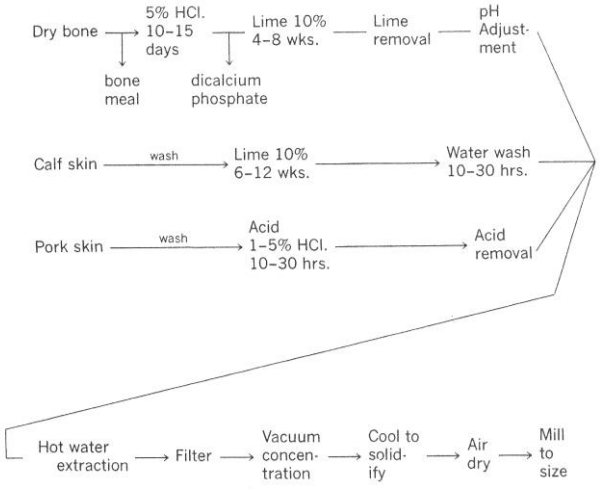


Figure 1: gelatin synthesis (not for save)

Type A gelatin is derived from an acid-treated precursor whereas type B gelatin is from an alkali-treated precursor. Although capsules may be made from either type of gelatin, the usual practice is to use a mixture of both types.

Mixtures of bone and skin gelatins are usually used for hard gelatin capsule production. Bones produce tough, firm shells but tend to be cloudy. Skin gelatin contributes plasticity and clarity to the blend thereby reducing cloudiness in the finished capsule.

It is worth to mention that there is especial test used to measure the strength of gelatin material. This test is called the *bloom test* (gel strength). The bloom test of gelatin is a measure of the cohesive strength of the cross-linking that occurs between gelatin molecules and is proportional to the molecular weight of the gelatin. Bloom is determined by measuring the weight in grams required to move a plastic plunger 4 mm into a 6.6% gelatin gel that has been held at 10 ^{0}C for 17 hours. The bloom value usually ranges from 150-250 g. In general, the higher the bloom value, the more stable the resulting capsule shell. The cost of gelatin is directly proportional to its bloom value.

Thickness of the capsule shell is controlled by the viscosity of the gelatin solution and the speed and time of dipping.

In-process control of the capsule manufacturing includes periodic monitoring of film thickness, color and moisture content. Inspection processes to remove imperfect capsules (which was done visually) have recently been automated following the development of electronic sorting machine. This equipment transports capsules to a series of optical scanners, and those having detectable imperfections are automatically rejected.

Empty capsules subject to size variation as a result of moisture content variation; which can be caused by exposure to extreme variations in humidity or elevated temperature.

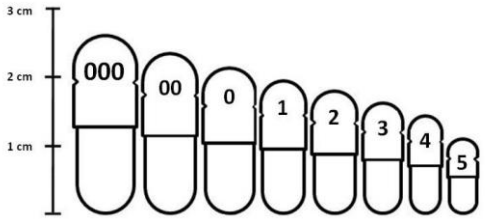
Capsule Filling Machines

There are nine types of capsule filling machine each of which utilize different mechanism.

Empty Capsules Size

Empty capsules are classified according to their sizes. The most commonly employed size range from 0 (the largest) to 5 (the smallest). Size 00 capsules may occasionally be used if the amount to be filled is large. The following table gives an approximation of the aspirin powder (as an example) that may be contained in the various sizes. The powder weights

listed are approximate and vary with the amount of pressure employed in hand filling, or with the type of equipment utilized in machine filling.



Capsule size	Aspirin weight (mg)
0	550
1	330
2	250
3	200
4	150
5	100

There are new equipments that determine the weight of individual capsules, providing an automatic rejection of over filled and under filled capsules. For ex., the Rotoweight is a high speed capsule weighing machine. It is a unique weight detection system, which measures the reflected energy of x-ray beam directed at each capsule. This reflected energy is proportional to the weight of the filled capsule, permitting automatic rejection of any individual capsule above or below preset weights. The machine operates at 73,000 capsules per hour and its accuracy is more than adequate to assure compliance with the USP weight requirements.

Finishing

Finished capsules from filling equipment require some type of dust removal and/or polishing before the remaining operations of inspection, bottling and labeling are done. The following equipments are commonly used for this purpose:

1. Pan polishing: A piece of cloth is placed in the pan, and this cloth is used to trap the removed dust as well as to impart a gloss to the capsules.

2. Hand polishing: the capsules are rubbed with a cloth manually. This procedure imparts somewhat improved gloss to the capsule.

Soft Gelatin Capsules

Advantages:

1. They permit liquid medications to become easily portable.
2. Uniformity of dosage because they contain liquid which is more uniform than powder.
3. The disintegration and dissolution rates are faster than that of other solid dosage forms.
4. The bioavailability of drugs is often improved since these capsules contain the drug in liquid form. In general, the bioavailability of a drug from various oral formulations usually decreases in the following order: solution, suspension, soft gelatin capsules, hard gelatin capsule, compressed tablet, coated tablet.
5. They produce less irritation to the stomach since they contain liquid that distributes throughout the stomach and do not form localized area of high drug concentration.

Capsule Shell Synthesis

As in hard gelatin capsule, the shell of the capsule is composed of gelatin, water and plasticizer. In addition, it may contain compounds such as preservatives, colors and opaquing agent. The difference from hard gelatin capsule is the high amount of water which may constitute up to 50%.

Capsule Content Nature

The content of soft gelatin capsules may be solution or suspension. Only those liquids that are both water-miscible and volatile cannot be included as major constituents of the capsule content since they can migrate into the hydrophilic gelatin shell and volatilize from the surface. Water and ethyl alcohol fall into this category. However, up to 5%, water and alcohol can be used as minor constituents (e.g., as cosolvents to aid in the preparation of solution).

Similarly, gelatin plasticizers such as glycerin and propylene glycol cannot be major constituents of the capsule content, owing to their softening effect on the gelatin shell and they can be used only in a concentration of 5% or less.

All liquids (solutions and suspensions) should be homogeneous and air-free, and preferably should flow by gravity at room temperature. Preparations for encapsulation should have a pH between 2.5-7.5 since preparations that are more acidic can cause hydrolysis of

the gelatin shell while those that are more alkaline can tan the gelatin and thus affect the solubility of the shell.

Solids are incorporated into the soft gelatin capsules as either a solution or suspension. The preparation of a suitable solution of a solid medicament should be the first goal of the pharmacist. Usually, a solution is more easily encapsulated and exhibits better uniformity and *physical* stability than does a suspension. Solids that are not sufficiently soluble in liquids are encapsulated as suspension. Accordingly, most organic and inorganic solids may be encapsulated by this manner. Such materials should have particle size of 80 mesh or finer in order to suit the ability of the capsule machine and for maximum homogeneity of the suspension. Many solids cannot be encapsulated, owing to their solubility in water and thus their ability to affect the gelatin shell, unless they are mirror constituent of the formula. Examples of such compounds are strong acids (e.g. citric acid) and strong alkali (e.g. sodium salts).

Microencapsulation

It is a means of applying relatively thin coating to small particles of solids or droplets of liquids. It provides a mean of converting liquids to solids, providing environmental protection and controlling the release profile of the coated material.

Microencapsulation is very useful method. Because of the smallness of the particles, the active ingredient can be widely distributed throughout the GIT, thus improving drug absorption. Other applications of microencapsulation include taste-masking and formulation of tablets or capsules containing incompatible ingredients.

Unfortunately, no single microencapsulation process is useful for all materials. Difficulties, such as incomplete or discontinuous coating, inadequate stability of sensitive drugs, nonreproducible release characteristics of the coated material, and economic limitations are often encountered in the microencapsulation process.

Core Material

The core material (the drug particles) can be liquid or solid in nature. The composition of the core material can be varied, as the liquid core can include dispersed and/or dissolved material. The solid core material can be an active ingredient alone or as mixture with diluents

and other excipients. To aid in illustrating the diversity of the materials and their applications, some of these products are listed below (*not for save*).

Examples of Core Material	Characteristic Property	Purpose of Encapsulation	Final Dosage Form
Acetaminophen	Slightly water soluble solid	Taste masking	Tablet
Aspirin	Slightly water soluble solid	Taste masking, sustained release, reduced gastric irritation.	Dry powder
Islet of Langerhans	Viable cells	Replacement therapy for diabetic patients	Injection
Isosorbide dinitrate	Water soluble solid	Sustained release	Capsule
Menthol, methyl Salicylate, camphor mixture	Volatile solution	Reduction of volatility; sustained release	Lotion
Vitamin A palmitate	Nonvolatile liquid	Stabilization to prevent oxidation	Dry powder

Coating Materials

As with tablet coating, the coating material should be capable of forming a film that is cohesive with the core material; be chemically compatible and noncreative with the core material, and provide the desired coating properties, such as strength, flexibility, impermeability and stability.

Methods of Microencapsulation

It can be achieved by a variety of methods, the most important are:

1. Air suspension:

This method consists of suspending the solid material in the air and the spraying the air suspended particles (as described previously in tablet coating).

In the coating chamber, particles receive an increment of the coating material each time they pass through the coating zone. The cyclic process is repeated, perhaps several hundred times during the process, depending on the coating thickness desired.

This process has the ability of applying coating to powders ranging from 0.5-450 kg. However, this process generally is considered to be suitable only for the encapsulation of solid core materials.

2. Pan Coating:

In this method, the coating is applied as an atomized spray to the desired ***solid*** core material in the coating pan. To remove the coating solvent, a warm air is used in a process similar to that of tablet coating.

3. Coacervation-Phase Separation:

It can be used for both liquid and solid drugs. It consists of three steps carried out under continuous agitation:

Step 1: Formation of three immiscible phases.

Step 2: Deposition of the coating.

Step 3: Rigidization of the coating.

(Please refer to Fig. 13-38, page 421 in the text book).

Step 1: is the formation of three immiscible phases which are the solvent phase, the liquid coating material phase and the core material phase. To form the three phases, the coating polymer solution is mixed with ***immiscible*** solvent to form two immiscible liquids, then the core material is added to form the third phase.

Step 2: it consists of depositing the liquid coating material on the core material. Deposition of the liquid polymer coating around the core material occurs if the coating polymer is adsorbed at the interface between the core material and the immiscible solvent phase, and this adsorption phenomenon is a prerequisite to effective coating.

Step 3: it involves rigidizing the coating, usually by thermal techniques, to form the microcapsules.

The following example illustrates this technique. Ethyl cellulose (a water insoluble polymer) is applied to aminophenol powder (core material) by utilizing the temperature characteristics of the polymer in the cyclohexane (solvent). The Ethyl cellulose is insoluble in cyclohexane at room temperature, but it is soluble at elevated temperature. The ethyl

cellulose and cyclohexane mixture is heated to form a homogeneous (one phase) solution. The aminophenol is dispersed (as insoluble powder) in the solution with stirring. Allowing the mixture to cool with continuous stirring results in coacervation-phase separation of the ethyl cellulose from cyclohexane and microencapsulation of the core material. Allowing the mixture to cool further to room temperature causes gelation and solidification of the coating. The microencapsulated product can then be collected from the cyclohexane by filtration.

4. Spray Drying and Spray congealing:

These methods can be used for both liquid and solid drugs. Because of the similarity of these two processes, they are discussed together. Spray-drying and spray-congealing processes are similar in that both involve dispersing the core material in a liquid coating material and spraying the core-coating mixture into certain environmental condition, whereby rapid solidification of the coating is achieved. The principal difference between the two methods is the means by which the solidification is achieved. Coating solidification in the case of spray drying is achieved by rapid evaporation of a solvent in which the coating material is dissolved. Coating solidification in spray congealing methods is accomplished by thermally congealing (cooling) of a molten coating material.

In practice, microencapsulation by spray drying is done by dispersing a core material in a coating solution, in which the core material is insoluble and then atomizing the mixture into an air stream. The air (hot air) supplies the heat of vaporization required to remove the solvent from the coating material, thus forming the microencapsulated product. The equipment used for this purpose is the usual spray dryer.

Microencapsulation by spray congealing can be accomplished with spray drying device also. General process variables and conditions are quite similar to those of spray drying, except that the core material is dispersed in a coating material **melt** rather than the usual coating solution. Coating solidification (and microencapsulation) is accomplished by spraying the hot mixture into a **cool** air. Waxes, fatty acids and certain polymers which are solids at room temperature but melt-able at high temperatures, are applicable to spray congealing technique.