

Preparation of filled hard gelatin capsules (Cap 2, lect.9)

- **The large-scale or small-scale preparation of filled hard gelatin capsules is divided into the following general steps.**
 - 1. Developing and preparing the formulation and selecting the capsule size**
 - 2. Filling the capsule shells**
 - 3. Capsule sealing (optional)**
 - 4. Cleaning and polishing the filled capsules**

Developing the capsule formulation

- **In developing a capsule formulation, the goal is to prepare a capsule with;**
 - 1. Accurate dosage,**
 - 2. Good bioavailability,**
 - 3. Ease of filling and production,**
 - 4. Stability, and**
 - 5. Elegance.**

Developing the capsule formulation

- ❑ In dry formulations, the active and inactive components must be **blended thoroughly** to ensure a **uniform powder mix** for the fill.
- ❑ Care in blending is especially important for **low-dose drugs** since, **lack of homogeneity** in blending may result in **significant therapeutic consequences**.
- ❑ Preformulation studies are performed to determine whether all of the formulation's bulk powders may be effectively blended together as such or require **reduction of particle size** or any other processing to achieve homogeneity.

Developing the capsule formulation

- A **diluent or filler** may be added to the formulation to produce the proper capsule fill volume. **Lactose, microcrystalline cellulose, and starch** are commonly used for this purpose. In addition to providing **bulk**, these materials often provide **cohesion to the powders**, which is beneficial in the **transfer of the powder blend into capsule shells**.
- **Disintegrants** are frequently included in a capsule formulation to **assist the breakup and distribution of the capsule's contents** in the stomach. Among the disintegrants used are **pregelatinized starch, croscarmellose, and sodium starch glycolate**.

- In preparing capsules on an **industrial scale using high-speed automated equipment**, the powder mix or granules must be **free-flowing to allow steady passage** of the capsule fill **from the hopper through the encapsulating equipment and into the capsule shells**. The **addition of a lubricant or glidant such as fumed silicon dioxide, magnesium stearate, calcium stearate, stearic acid, or talc (about 0.25% to 1%)** to the powder mix enhances **flow properties**.
- When **magnesium stearate** is used as the **lubricant**, the **waterproofing characteristics** of this water-insoluble material can **retard penetration by the gastrointestinal fluids and delay drug dissolution and absorption**. A **surface-active agent, such as sodium lauryl sulfate, is used to facilitate wetting** by the gastrointestinal fluids to overcome the problem.

- To achieve **uniform drug distribution**, it is advantageous if the **density and particle size of the drug and nondrug components are similar**.
- This is particularly **important when a drug of low dosage is blended with other drugs or nondrug fill** .
- When necessary, particle size may be reduced by milling to produce particles ranging from about **50 to 1,000 μm** .
- Milled powders may be blended effectively for uniform distribution throughout a powder mix when the drug's dosage is **10 mg or greater**.
- For drugs of **lower dose or when smaller particles are required, micronization is employed**. Depending on the materials and equipment used, micronization produces particles ranging from about **1 to 20 μm** .

Encapsulation of different ingredients

1. Inserting **tablets or small capsules into capsules** is sometimes useful in the commercial production of capsules and in a pharmacist's extemporaneous preparation of capsules. This may be done to **separate chemically incompatible agents** or **to add premeasured amounts of potent drug substances**. Rather than weighing a potent drug, a pharmacist may choose **to insert a prefabricated tablet of the desired strength in each capsule**. Other less potent agents and diluents may then be weighed and added.
2. On an industrial scale, **coated pellets designed for modified-release drug delivery** are also commonly placed in capsule shells.



Examples of fill in hard gelatin capsules.

- 1, powder or granulate; 2, pellet mixture; 3, paste; 4, capsule; and 5, tablet

Liquid fill

- Gelatin capsules are **unsuitable for aqueous liquids** because water softens gelatin and distorts the capsules, resulting in leakage of the contents.
- However, **some liquids**, such as **fixed or volatile oils**, that do not interfere with the stability of the gelatin shells may be placed in **locking gelatin capsules** (or the capsules may be sealed with a **solution** of gelatin thinly coating the interface of the cap and body) to ensure retention of the liquid.
- Rather than placing a liquid as such in a capsule, **the liquid may be mixed with an inert powder to make a wet mass or paste**, which may then be placed in capsules in the usual manner.
- **Eutectic mixtures of drugs**, or **mixtures of agents that have a propensity to liquefy when admixed**, may be mixed with a diluent or **absorbent such as magnesium carbonate, kaolin, or light magnesium oxide** to separate the interacting agents and to absorb any liquefied material that may form.
- In **large-scale** capsule production, **liquids are placed in soft gelatin capsules that are sealed during filling and manufacturing.**

Extemporaneous compounding of prescriptions

1. Calculate for the preparation of **one or two more capsules than required** to fill the prescription, **to compensate a slight loss** of powder
2. **Selection of the capsule size**, If the dose of the drug is **inadequate** to fill the volume of the capsule body, a **diluent** is added.
3. **A properly filled** capsule should have its **body filled** with the drug mixture, **not the cap**.
4. The cap is intended to fit snugly over the body to retain the contents.

- In most instances, the amount of drug in a capsule is a single dose. When the **usual dose of the drug is too large for a single capsule, two or more capsules may be required**, in this case, tells the patient to take two or more capsules instead of one.
- An easy method **to select the proper capsule is to weigh the ingredients for the required number of capsules to be prepared. Place the powders in a graduated cylinder and obtain the volume occupied by the powders. Divide the volume by the number of capsules to be prepared and this provides the volume that will be occupied by the powder for each capsule. Compare this volume (in mls) with the appropriate line of Table 7.1 and select the size that will accommodate the powder.**

Filling hard capsule shells

- When **filling a small number of capsules** in the pharmacy, the pharmacist may use the **punch method**.
- The pharmacist takes the precise number of empty capsules to be filled from the stock container. By counting the capsules as the initial step rather than taking a capsule from stock as each one is filled,
 1. the pharmacist guards against filling the wrong number of capsules and
 2. avoids contaminating the stock container with drug powder.

The powder to be encapsulated is placed on a sheet of clean paper or on a glass or porcelain plate. Using the spatula, the powder mix is formed into a cake having a depth of approximately one-fourth to one-third the length of the capsule body.

Then an empty capsule body is held between the thumb and forefinger and punched vertically into the powder cake repeatedly until filled. **Some pharmacists wear surgical gloves or latex finger cots to avoid handling the capsules with bare fingers.**

Because the amount of powder packed into a capsule depends on the degree of compression, **the pharmacist should punch each capsule in the same manner and weigh the product after capping.**

Filling of capsules

- When non-potent materials are placed in capsules, **the first filled capsule should be weighed** (using an empty capsule of the same size on the opposite balance pan to counter the weight of the shell) to determine the capsule size to use and the degree of compaction to be used. After this determination, **the other capsules** should be prepared and **weighed periodically** to check **the uniformity of the process**.
- When potent drugs are being used, **each capsule should be weighed after filling to ensure accuracy**. Such weighings protect against uneven filling of capsules and premature exhaustion or underuse of the powder. **After the body of a capsule has been filled and the cap placed on the body, the body may** be squeezed or tapped gently to distribute some powder to the cap end to give the capsule a full appearance.
- **Granular material that does not lend itself to the punch method of filling capsules may be poured into each capsule from the powder paper** on which it is weighed.

Filling of capsules

- Pharmacists who prepare capsules on a regular or extensive basis may use a **hand-operated filling machine**. The various types of machines have capacities ranging from 24 to 300 capsules.



The Feton capsule-filling machine

A. With empty capsules in the loader tray, the tray placed on top of the filler unit.

B. The loader inserts the capsules into the filling unit and is removed, and the top plate is lifted to separate the caps from the bodies.

C. The powder is placed on the unit and the capsule bodies are filled.

D. The top plate is returned to the unit and the caps are placed on filled capsule bodies.

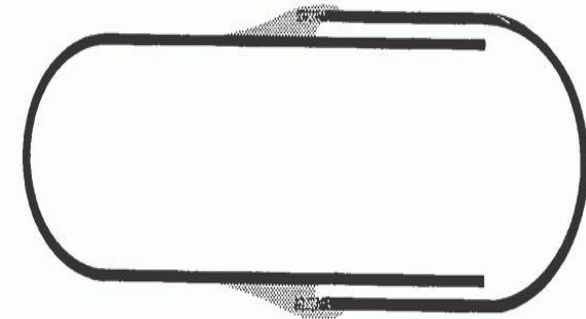
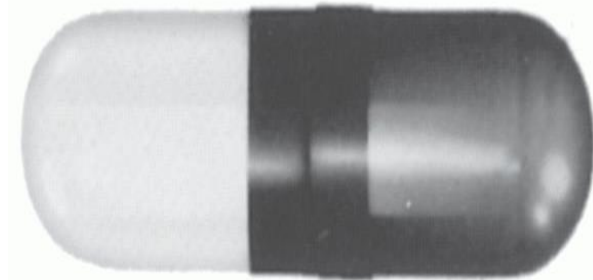
(Courtesy of Chemical and Pharmaceutical Industry Company.)

Filling of capsules

- **Machines developed for industrial use automatically**
 - 1- separate the caps from empty capsules,
 - 2- fill the bodies,
 - 3- scrape off the excess powder,
 - 4- replace the caps,
 - 5- seal the capsules as desired, and
 - 6- clean the outside of the filled capsulesat up to 165,000 capsules per hour.

Capsule sealing

- Some manufacturers **make tamper-evident capsules by sealing the joint between the two capsule parts**. One manufacturer makes **distinctive-looking capsules by sealing them with a colored band of gelatin** (Kapseals, Parke-Davis).
- If removed, the band cannot be restored without expert resealing with gelatin.
- Capsules may also be **sealed through a heat-welding process that fuses the capsule cap to the body through the double wall thickness at their juncture**. The process results in a distinctive ring around the capsule where heat welded.
- Still another process **uses a liquid wetting agent that lowers the melting point in the contact areas of the capsule's cap and body and then thermally bonds the two parts using low temperatures (40°C-45°C)**. Industrial capsule sealing machines are capable of producing 60,000 to 150,000 gelatin-banded, heat-welded, or thermally coupled capsules per hour



Capsule identification

- Capsules and tablets also may be **imprinted** with the **names** or **monograms** of the manufacturer, the **assigned national drug code number**, and other **markings** making the product identifiable and distinguishable from other products.



Cleaning and polishing capsules

- Small amounts of powder may adhere to the outside of capsules after filling. The powder may be **bitter** or otherwise **unpalatable** and should be removed before packaging or dispensing.
- **On a small scale**, capsules may be cleaned individually or in small numbers **by rubbing** them with a clean gauze or cloth.
- **On a large scale**, many capsule-filling machines are **affixed with a cleaning vacuum** that removes any extraneous material from the capsules as they exit the equipment, using the **Accela-Cota apparatus**



THANK YOU