



Hard Gelatin Capsules

Pharmaceutics III
Lecture 6

Learning Objectives



By the end of this lecture, the student will be able to:

1. Compare and contrast advantages and disadvantages of hard gelatin capsules.
2. List different materials that are employed to produce capsules.
3. Discuss the merits of using gelatin to prepare capsules.
4. Describe the different steps and requirements to produce hard gelatin capsules.
5. Give examples of some materials that be used to fill capsules.
6. Provide some remedies to some of the technical problems that may occur during hard gelatin capsule production.

Capsules

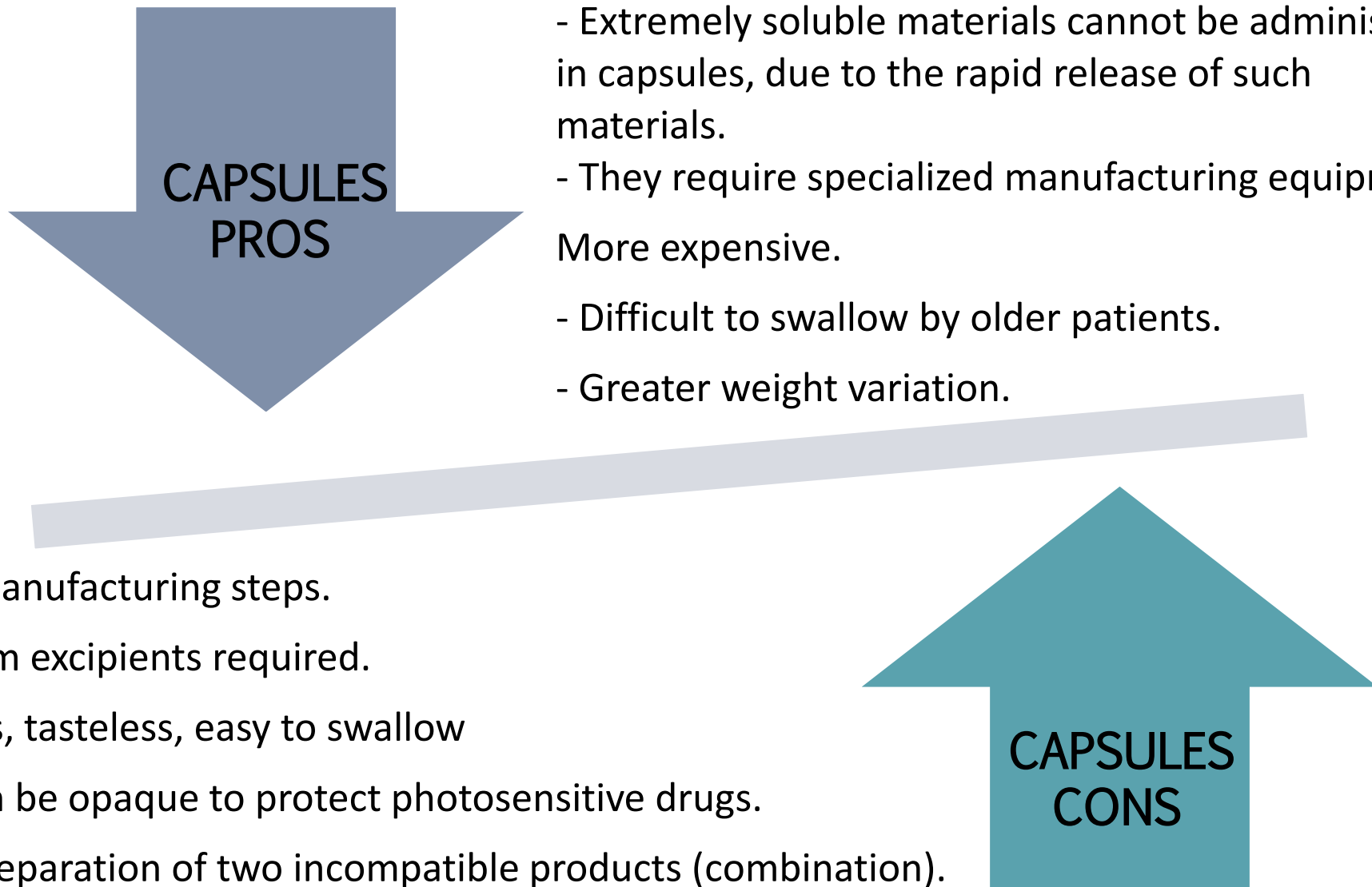
- Capsule is a word derived from the Latin word “capsula”, which means a small box or package.
- A **capsule (def)** is solid dosage forms made from gelatin or other suitable material which is filled with medicines, mainly for oral use.
- **Two types of capsules:**

1. Hard (two-pieces)



2. Soft (one-piece)





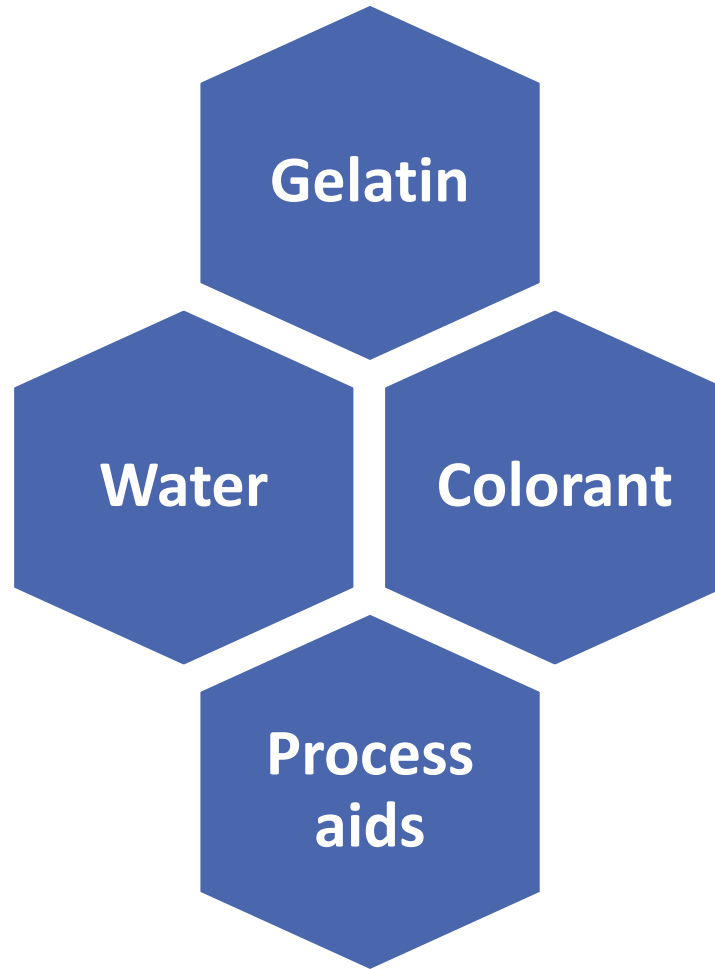
CAPSULES PROS

- Extremely soluble materials cannot be administered in capsules, due to the rapid release of such materials.
 - They require specialized manufacturing equipment.
- More expensive.
- Difficult to swallow by older patients.
 - Greater weight variation.

- Fewer manufacturing steps.
- Minimum excipients required.
- Odorless, tasteless, easy to swallow
- They can be opaque to protect photosensitive drugs.
- Simple separation of two incompatible products (combination).
- The solubility of gelatin at gastric pH provides rapid release of drug in the stomach.

CAPSULES CONS

Materials Used To Produce Capsule Shells



- ❑ Similar raw materials have been used in the manufacture of both types of capsule.
- ❑ Soft capsules also contains plasticizers such as glycerin and sorbitol.

1. Gelatin

- ☐ Gelatin is the major component used to prepare capsules.
- ☐ Gelatin is a product obtained by partial hydrolysis of collagen derived from animal skin, white connective tissue, and bones.
- ☐ After hydrolysis, the gelatin is extracted, concentrated and chilled to form a gel.
- ☐ The gel is dried and blended to produce gelatin with various specification.
- ☐ Replacements for gelatin from plant sources: carrageenan (from seaweed), agar (or agar-agar, also from seaweed), pectin, guar gum and starch and wheat.



1. Gelatin

Gelatin properties that make it suitable to produce capsules:

- ☐ Non-toxic.
- ☐ Readily soluble in biological fluids at body temperature.
- ☐ Good film-forming material produces a strong flexible film.
- ☐ Solution mobility at high concentration and high temperature, while other biological polymers, such as agar, are not.
- ☐ A gelatin solution in water or in water-plasticizer mixture can undergo a reversible change from a sol to a gel at slightly high temperature (to achieve this with other materials, a large quantity is needed).

3. Process Aids

- ❑ Sodium lauryl sulfate functions as wetting agent, to ensure even mold lubrication when dipped into the gelatin solution.
- ❑ The moisture level in finished capsules is about 13-16% w/v, at this level water activity does not support bacterial growth because the moisture is too strongly bonded to the gelatin molecule (that's why the use of preservatives is restricted).

Diluents

→ Improved plug formation and compression

- Mannitol
- Lactose
- Corn starch
- Microcrystalline cellulose
- Starch 1500

Lubricants

→ Improved flow properties and reduced powder adhesion to metal parts

- Magnesium stearate
- Stearic acid
- Glyceryl monostearate

Glidants

→ Improved powder flow properties

- Aerosil
- Talcum

Disintegrants

→ To ensure disintegration of powder mixture

- Croscarmellose
- Crospovidone
- Sodium glycol starch
- Corn starch
- Starch 1500
- Alginic acid

Wetting agents

→ Improved water penetration into powder mixture

- Sodium lauryl sulphate
- Tween 80

Table 4: Excipients used in formulations of immediate-release hard gelatin capsules.

2. Colorants

- ☐ Colorants can be: water soluble dyes or insoluble pigments.
- ☐ The two types can be mixed together as solutions or suspensions.
- ☐ Colors are added for light protection and easy identification.

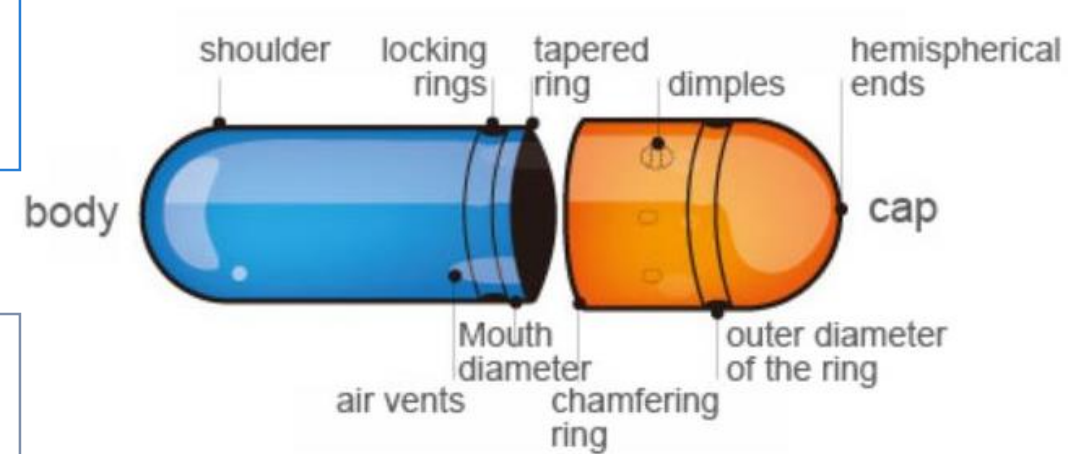


Hard Gelatin Capsules

❑ Hard gelatin capsules consist of two main parts:

The body contains the drug and the diluent.

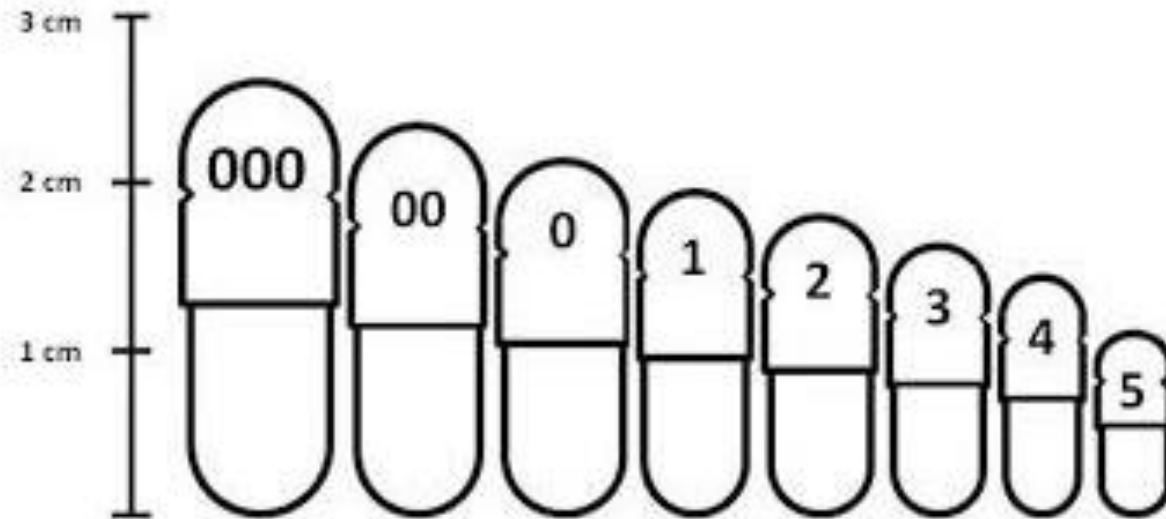
The cap is approximately half as long as the body.



Hard Gelatin Capsules

- ☐ Hard capsules are available in a variety of standard sizes and are designated by numbers from 000 to 5.
- ☐ The size of the 000 capsule is the largest and that of the number 5 capsule is the smallest.
- ☐ Large range of weights of powders that can be filled into different sized capsules depends on their bulk densities and compressibility.
- ☐ Powder, granules, or pellets can be placed in the body and the capsule closed by bringing the body and the cap together.

Hard Gelatin Capsules



Sizes of hard gelatin capsules and their approximate capacities

Size	000	00	0	1	2	3	4	5
Content (mg)	950	650	450	300	250	200	150	100

Manufacturing of Hard Gelatin Capsules

Hard Gelatin Capsule Shells:

- ❑ The shells are produced by mechanical dipping of pins of the required size and shape into a temperature controlled reservoir of melted gelatin mixture.
- ❑ When dried, each capsule part is trimmed mechanically to the proper length, joined together, and removed from the machine.



Manufacturing of Hard Gelatin Capsules

Filling Hard Gelatin Capsule Shells:

Bench-scale filling:

- ❑ Used to fill small quantities of capsules(50-10,000) in hospital pharmacies or industry.
- ❑ E.g. Feton filling set
- ❑ Sets of plastic plates which have holes to place capsules in different sizes.
- ❑ The loading and filling are done manually.



[Feton capsule filling machine-How does it work?](#)

Manufacturing of Hard Gelatin Capsules

Filling Hard Gelatin Capsule Shells:

Industrial-scale filling:

- ❑ Used to fill large quantities of capsules(5000-150,000 per hour).
- ❑ Mostly, they operate automatically or semi-automatic.
- ❑ Milling, sieving, blending and filling are done in one unit.



[Automatic capsule filling machine-How does it work?](#)



Manufacturing of Hard Gelatin Capsules

General steps to prepare filled hard gelatin capsules:

The large-scale or small-scale preparation of filled hard gelatin capsules, both have similar steps:

1. Developing and preparing the formulation and selecting capsule size.
2. Filling the capsule shells.
3. Capsule sealing (sealing the joint between the two capsule parts by applying heat at 40-45 °C).
4. Cleaning and polishing the filled capsules (Filled capsules may have small amounts of powder adhering to the outside of the capsule).

Manufacturing of Hard Gelatin Capsules

Cleaning and polishing the prepared capsules :

- ❑ For small-scale operations: clean cloths or cleaning wipes may be used to de-dust the capsules.
- ❑ Large-scale operations:
 - *Pan polishing*: Accela-Cota pan coating machines lined with a polyurethane is used.
 - *Cloth dusting*: Capsules are rubbed with a cloth that immersed with an inert oil.
 - *Brushing*: Capsules are placed under rotating soft brushes that remove the dust from the capsule surface, followed by the use of a vacuum system for dust removal.

Materials To Fill Hard Gelatin Capsules

- ❑ Hard gelatin capsules can be filled with a wide range of materials of different physicochemical properties.

Limitation in properties of materials for filling into capsules:

- ❑ Must not react with gelatin. E.g.: Formaldehyde causes crosslinking reaction with gelatin making the capsule insoluble.
- ❑ Must not contain a high level of moisture. E.g.: substances containing free water absorbed by the gelatin, which causes softening or distortion.
- ❑ The volume of the unit dose must not exceed the sizes of capsule available.

Materials To Fill Hard Gelatin Capsules

Types of materials for filling into hard gelatin capsules:

Dry
Solids

- Powders (mainly).
- Granules.
- Tablets.

Semi-
solids

- Thermo-softening mixtures.
- Thixotropic mixtures.

Liquids

- Non-aqueous liquids.



Technical Problems During Capsule Filling

Problem	Causes	Remedies
Improper flow of the powder mixture during the filling operation.	Bad powder flowability.	Adding a suitable amount of glidants or lubricants into the powder mixture.
Segregation and inhomogeneity .	The vibration of automatic machines during operation can cause segregation of particles and inhomogeneity.	Segregation minimized by keeping particle sizes and densities of the powders as uniform as possible.

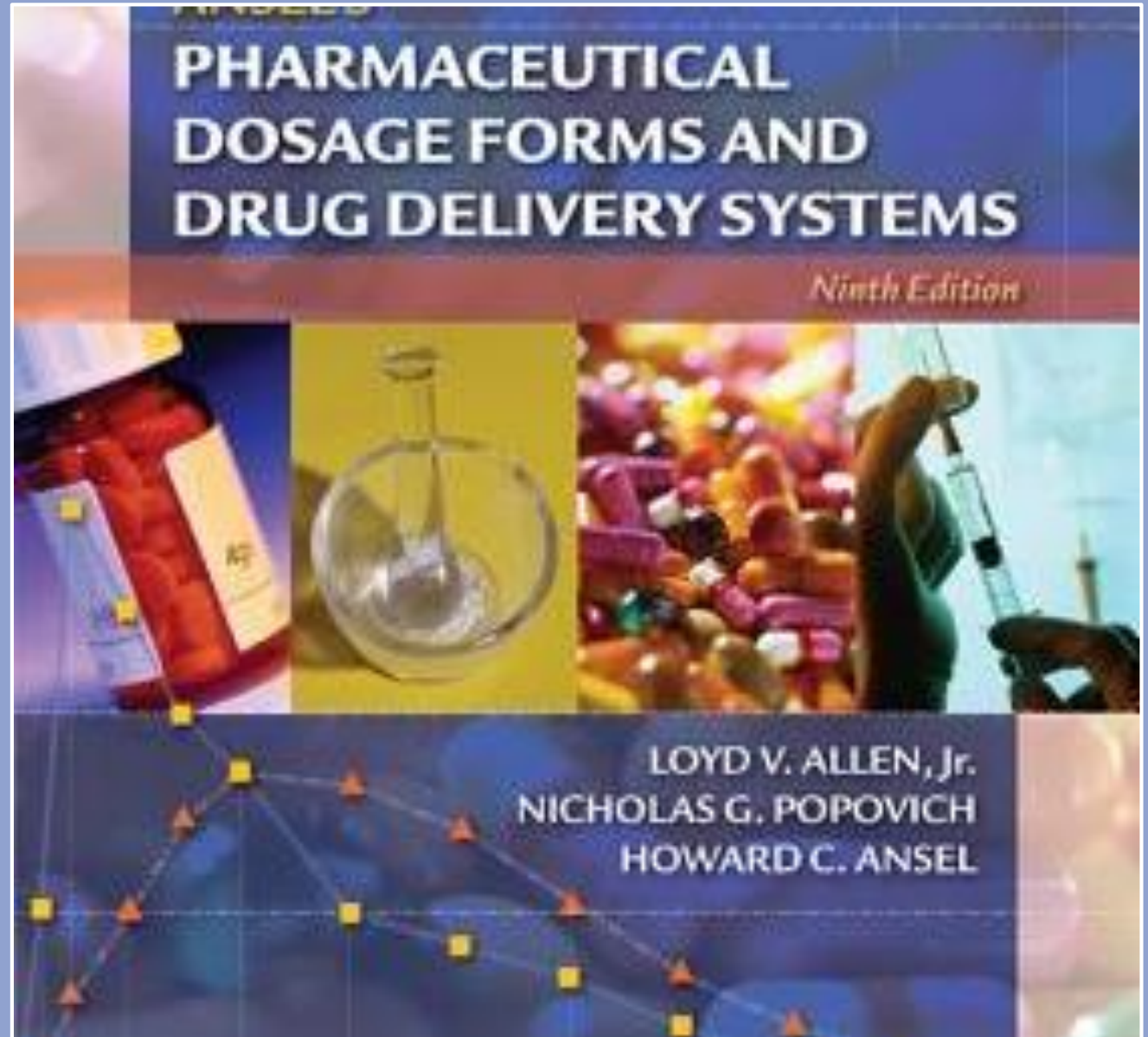
Technical Problems During Capsule Filling

Problem	Causes	Remedies
Weight variations, sticky caps, or two parts can't join together.	Incompatibility between formulation ingredients, components, and the capsule shell may create problems.	A proper understanding of the physicochemical properties of each ingredient may avoid such incompatibility issues.

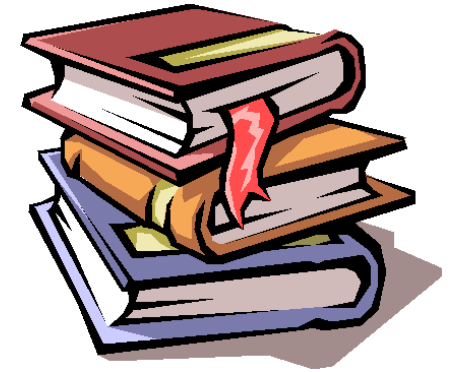
FLIP

L E A R N I N G

- Read and understand pages (215-220) chapter 7 of Ansel's pharmaceutical dosage forms and drug delivery system 9th ed.
- Prepare for the discussion next week!



References



1. Allen L. Ansel's pharmaceutical dosage forms and drug delivery systems. 11th ed. Philadelphia: Wolters-Kluwer; 2017.
2. Aulton M, Taylor K. Aulton's pharmaceuticals. 4th ed. Edinburgh: Elsevier; 2018.
3. Dash A, Singh S, Tolman J. Pharmaceuticals: Basic Principles and Application to Pharmacy Practice. 1st ed. Amsterdam: Elsevier-Academic Press; 2014.
4. Winfield A.J., Richards R.M.E. Pharmaceutical Practice. 3rd ed. Oxford: Churchill Livingstone; 2004.
5. <https://www.pharmapproach.com/solid-pharmaceutical-dosage-forms-capsules/>
6. Various materials and images obtained from the web.