COLLEGE OF PHARMACY
UMM AL-QURA UNIVERSITY

Suppositories

Pharmaceutics III
Lecture 11

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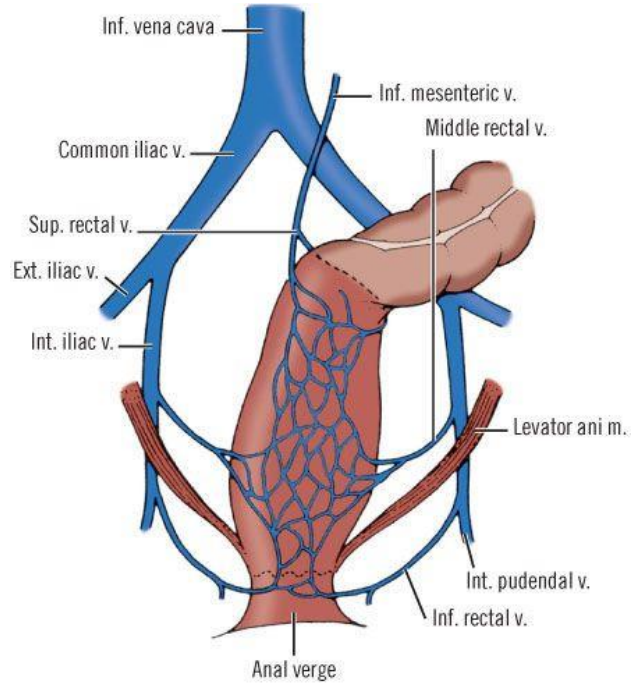
Learning Objectives

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

1. Describe suppositories on the basis of route of administration, use, shape and size.
2. Discuss the process of drug absorption from the rectum.
3. List some of the required properties of a suppository base.
4. Classify the different types of suppository bases with examples.
5. Explain briefly the different methods to prepare suppositories.
6. Provide some remedies to some of the technical problems that may occur during suppository production.

The Rectal Route

- The rectum is the final segment of the large intestine, and it is a part of the colon (15-200 mm).
- The rectal wall is composed of epithelium, and contains cylindrical cells and goblet cells which secrete mucus.
- The rectum has three drainage veins: lower and middle haemorrhoidal veins drain directly into the general circulation, while the upper one drains into the portal veins which flows into the liver.



Suppositories

- Suppositories are solid dosage forms containing medicinal agents intended for insertion into body cavities, including the rectum, vaginal cavity, or urethral tract but not through the oral cavity.

- When inserted into the rectum, they melt, often, or dissolve and exert local and systemic effects.

Suppositories

- Suppositories are usually about 3.2 cm long, cylindrical, and have one or both ends tapered.
- Infant and children suppositories are usually half the size and weight of the adult suppositories and assume a more pencil-like shape.
- Vaginal suppositories are called Pessaries, are usually globular, oviform, or cone-shaped.

Suppositories

PROS

- Irregular absorption and bioavailability.
- May cause irritation to rectal mucosa.
- Not acceptable by many patients.

CONS

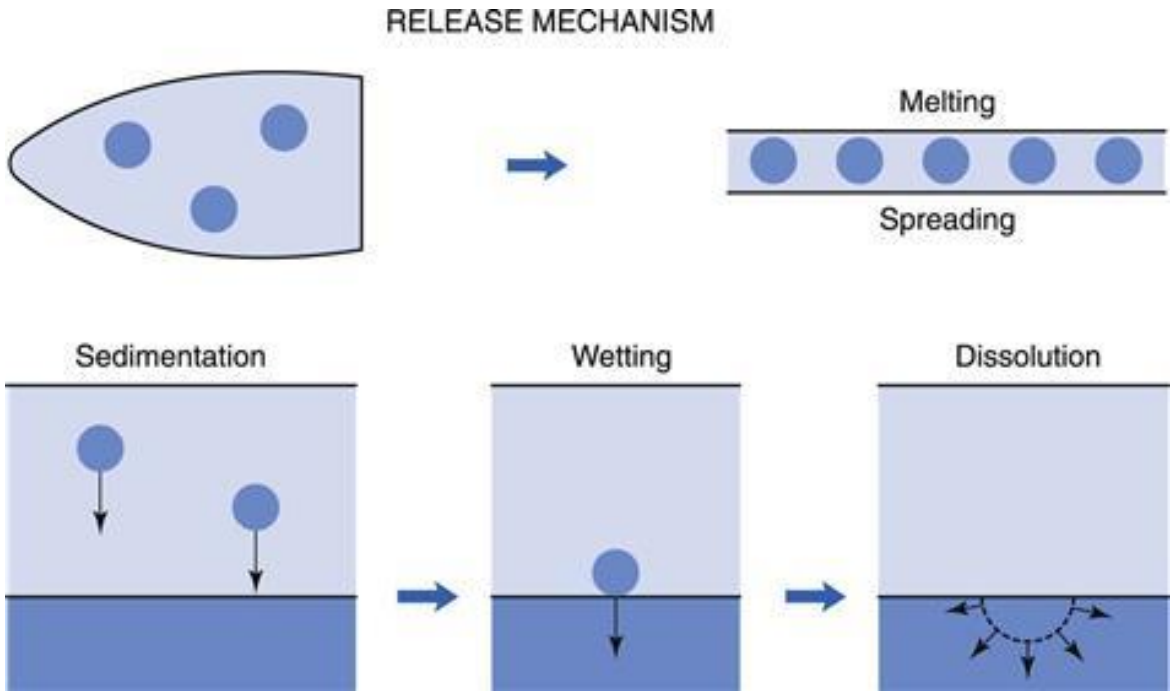
- Suitable for children and very elderly patients.
- Suitable for irritant drugs, vomiting and unconscious patients.
- Avoids first pass metabolism.

Absorption of Drug from The Rectum

- A suppository will either dissolve in the rectal fluid or melt on the mucous layer.
- Because of the limited fluids (3mL) available in the rectum, the drug is not diluted completely after rectal administration.
- However, due to osmotic effects (of the dissolving vehicle) water is attracted which usually cause pain to the patient.
- Drugs dissolved in the suppository will diffuse out toward the rectum membranes.
- Drug absorption is usually transcellular by passive diffusion or paracellular through the aqueous pores.

Absorption of Drug from The Rectum

Process of drug release from a suspension suppositories



Absorption of Drug from The Rectum

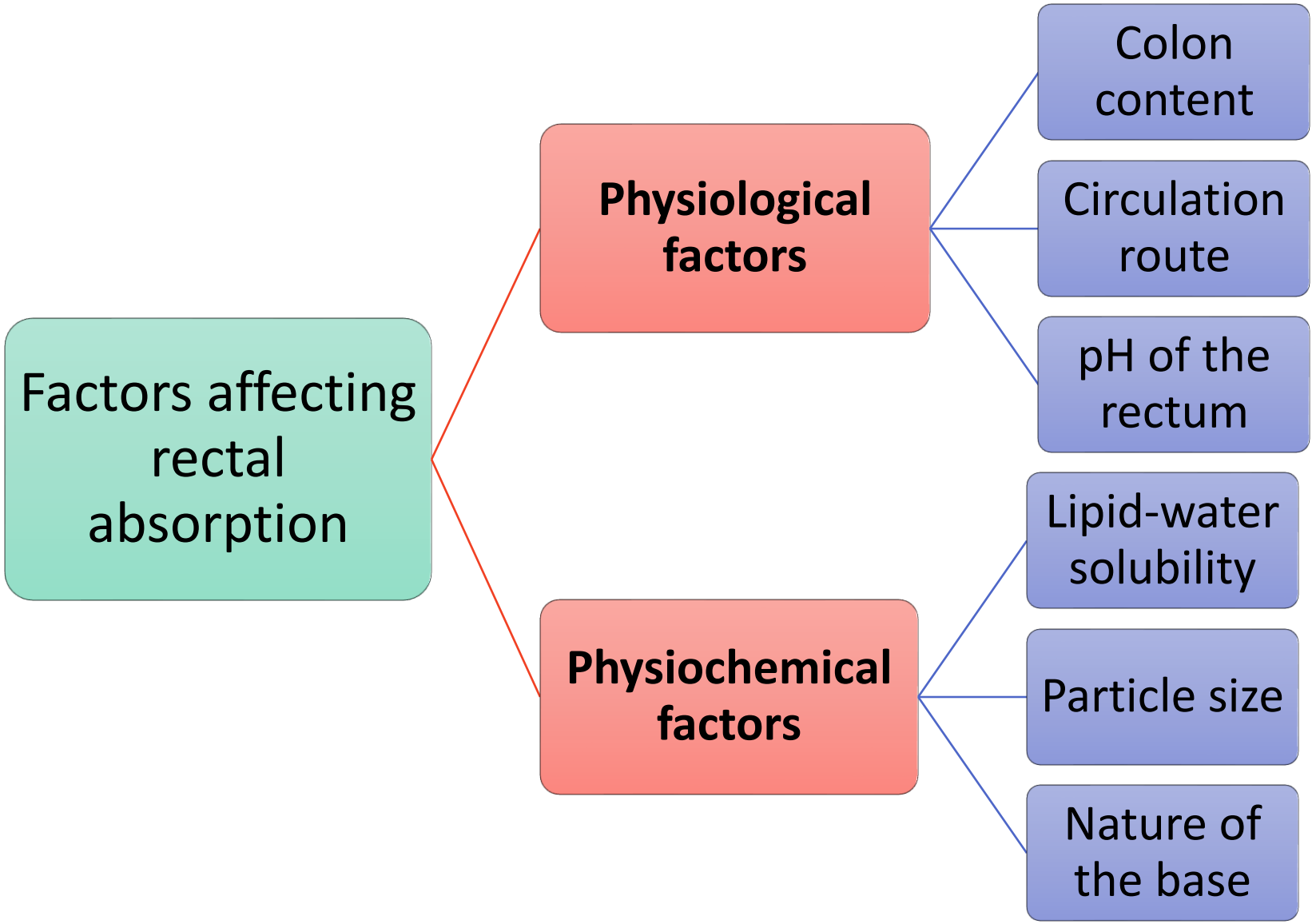
- After rectal administration, the absorbed drug can escape the first-pass hepatic metabolism if the drug is administered to the lower part of the rectum because the venous return from this part of the rectum does not go through the portal circulation.

- The rate of drug absorption is usually dependent on the rate of drug release from the suppository.

- **Rapid drug release from rectal formulation is preferred due to:**

1. The small area of the absorptive surface of the rectum.
2. The relatively short rectal transit time.
3. The limited spreading of the rectally administered drugs to the colon.

Factors of Drug Absorption From Rectal Suppositories



Factors of Drug Absorption From Rectal Suppositories

Physiological Factors:

Colonic Content:

- Greater absorption is expected when the rectum is void than from one that is distended with fecal matter (the contact between the absorbing surface of rectum and the suppository will be great).
- Diseases and conditions such as diarrhea, colon construction and tumors may also affect the rate and degree of drug absorption from the rectum.

Factors of Drug Absorption From Rectal Suppositories

Physiochemical Factors:

Circulation Route:

- The lower hemorrhoidal veins surrounding the colon receive the absorbed drug and initiate its circulation throughout the body, bypassing the liver.

pH and Lack of Buffering Capacity of the Rectal Fluids:

- Rectal fluids are neutral in pH, and have no effective buffer capacity. This makes the drug stable and changed by the environment.

Factors of Drug Absorption From Rectal Suppositories

Physiochemical Factors:

Lipid-Water Solubility:

- Hydrophilic drugs are released faster from lipophilic bases and slower from hydrophilic bases, whereas lipophilic drugs are released faster from hydrophilic bases and slower from lipophilic bases.
- The reason has to do with the solubility of hydrophilic drugs in hydrophilic bases, and the solubility of lipophilic drugs in lipophilic bases will slow the rate of drug release from the dosage forms.

Factors of Drug Absorption From Rectal Suppositories

Physiochemical Factors:

Nature of the base:

- If the base interacts with the drug to inhibit its release, drug absorption will be impaired or even prevented.
- If the base irritates the mucous membranes of the rectum, it may initiate a colonic response and cause a bowel movement which eventually eliminates the drug.

1. Suppositories Base

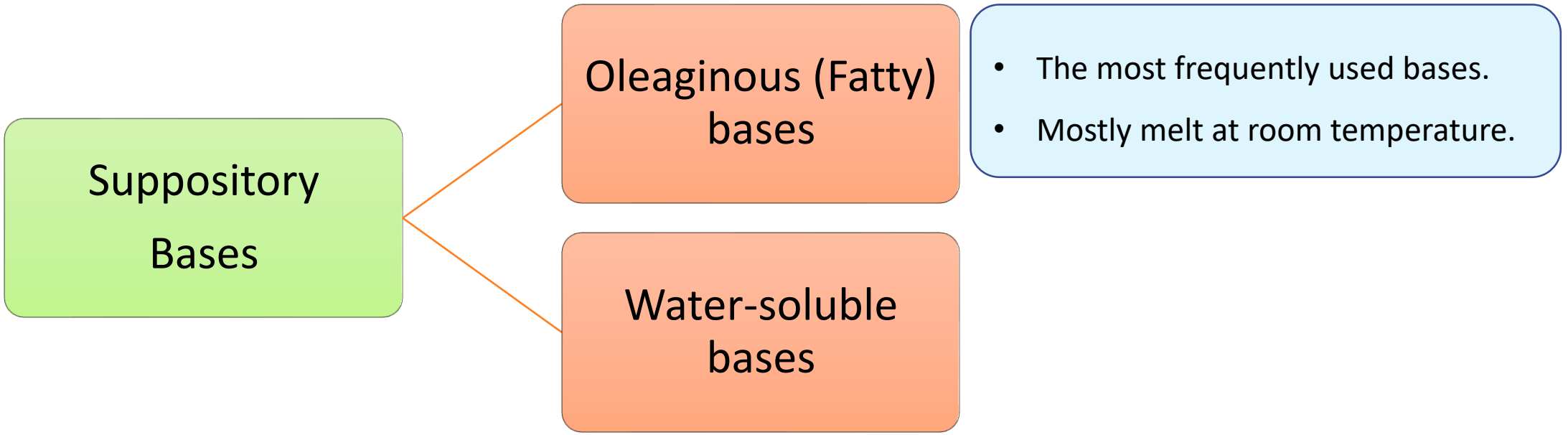
- The major inactive component of a suppository dosage form is the suppository base (vehicle).
- The base play an important role in the drug release.

Properties of an ideal suppository base:

- Melts at rectal temperature 37.5 °C.
- Nontoxic and non-irritating to sensitive and inflamed tissues.
- Physically stable and compatible with a variety of drugs.
- Convenient for the patient to handle (does not break or melt).
- Des not leak from the rectum.
- Stable on storage and does not change color, odor, and drug release pattern.

1. Suppositories Base

- Suppository bases can be classified in three categories according to physical properties:



1. Suppositories Base

Oleaginous (Fatty) Bases

1. Cocoa Butter (Theobroma oil):

- It is a fat obtained from the roasted seed of Theobroma cacao.
- At room temperature, it is yellowish-white solid with a hint of chocolate-like odor.
- Chemically, It is a triglyceride (glycerin+ one or more fatty acids).
- Melts at body temperature, but maintain the solidity at room temperature.
- Because of its triglyceride content, CB exhibits polymorphism (the existence of more than one crystal forms).

1. Suppositories Base

1. Cocoa Butter (Theobroma oil):

- **Polymorphism** occurs when CB is carelessly melted at a temperature greatly exceeding the minimum required temperature and then quickly cooled, the result is a metastable crystalline form (alpha form) which has a lower melting point than the original CB.
- CB must be slowly and evenly melted over a bath of warm water, to avoid formation of the unstable crystalline form.

Polymorphic form	Phase	Melting point
Form I	sub-α	16-18°C
Form II	α	22-24°C
Form III	$\beta 2'$	24-26°C
Form IV	$\beta 1'$	26-28°C
Form V	$\beta 2$	32-34°C (stable form)
Form VI	$\beta 1$	34-36°C (fat bloom)

1. Suppositories Base

1. Cocoa Butter (Theobroma oil):

- **CB is no longer used because of many disadvantages:**

1. polymorphism.
2. Insufficient contraction at cooling.
3. Low softening point.
4. Chemical instability.
5. Poor water-absorptive power.

1. Suppositories Base

2. Cocoa Butter Substitutes:

- Bases that have melting point range is 32-36 °C.
- Examples: hydrogenated fatty acids of vegetable oil such as palm oil and cottonseed oil.
- These bases reduces the potential of rancidity and have higher melting points (observed in CB) .
- Commercially available products such as “Fattibase” which composed of triglycerides from palm, palm kernel, and coconut oils with self-emulsifying glycerol monostearate and ploy oxylstearate.

1. Suppositories Base

Water-Soluble Bases

- Bases that comprise of glycerol-gelatin or soap base which are used exclusively for laxative or in vaginal products.
- **Examples:** Glycerinated gelatin or Polyethylene glycol mixtures.
- The melting point is over body temperature, which means that they mix with the rectal fluid and they are suitable for application in topical climates.

1. Suppositories Base

Water-Soluble Bases

1. Glycerinated gelatin:

- Used for vaginal suppositories.
- It is suitable for alkaloids, boric acid, and zinc oxide.
- Glycerinated gelatin suppositories are translucent, resilient, gelatinous solids that tend to dissolve or disperse slowly in mucous secretions to provide prolonged release of active ingredients.
- To facilitate administration, glycerinated gelatin suppositories should be dipped in water just before use.

1. Suppositories Base

Water-Soluble Bases

2. Polyethylene glycol mixtures:

- They are chemically stable, non-irritating, miscible with water and mucous secretions.
- Like glycerinated gelatin, they do not melt at body temperature, but dissolve to provide a more prolonged release than CB.
- Certain polyethylene glycol polymers may be used as suppository bases alone but, more commonly, two or more molecular weights mixed in various proportions as needed to yield a finished product of satisfactory hardness and dissolution time.

1. Suppositories Base

Water-Soluble Bases

- **Disadvantages:**

1. They are hygroscopic and therefore attract water, resulting in a painful sensation for the patient.

Solution: Incorporation of at least 20% water and moistening before insertion can help to reduce this problem.

2. Incompatible with many drugs.

3. Exhibit slow release sometimes.

2. Drug

The balance between two important requirements:

- ❑ The drug solubility in the rectal fluid determines the rate of absorption.
- ❑ A certain lipid solubility is required for penetration through the rectal membranes.

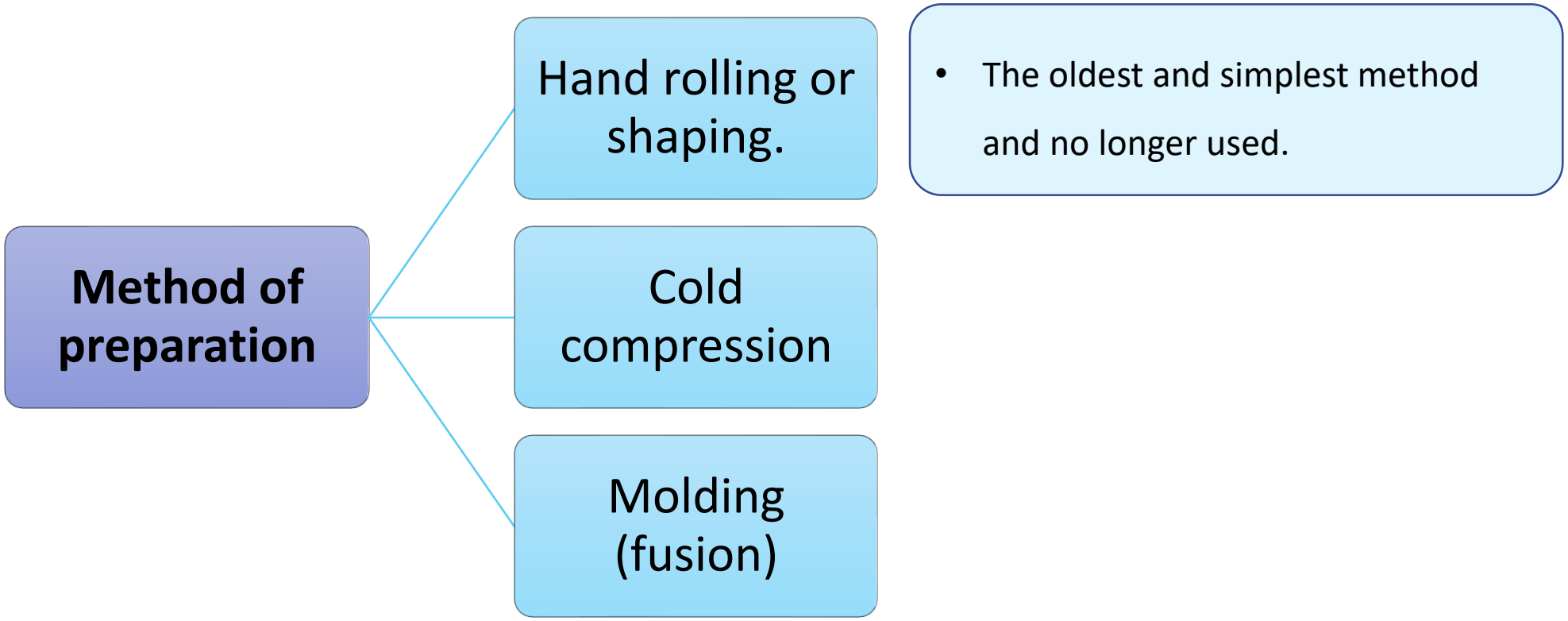
Solubility in fat	Solubility in water	Choice of base
Low	High	Fatty base
High	Low	Aqueous base
Low	Low	indeterminate

- ❑ The particle size should be smaller than approx. 150 µm.

3. Other Ingredients

- Viscosity-increasing additives such as colloidal silicon oxide or aluminium monostearate (1-2%).
- This will create a gel-like system with a slower release rate of the drug from the base.
- Solvents to provide softness and lubricate the suppository mass (e.g. propylene glycol).
- Solubilizers to solubilize or disperse the drug.
- Emulsifiers, solidifying agents, preservatives.. etc.

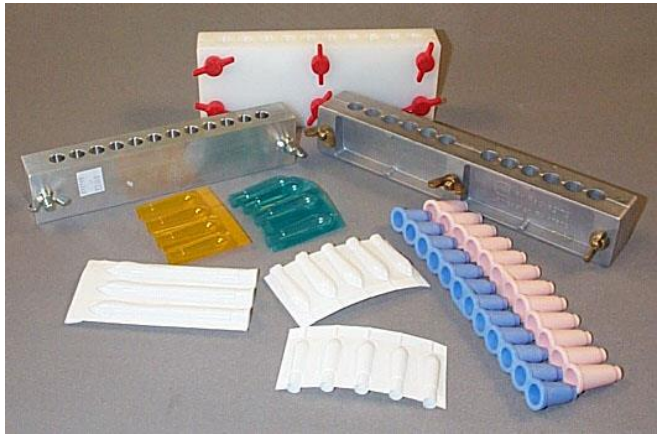
Preparation of Suppositories



Preparation of Suppositories

Cold Compression Method

- Preparing suppositories from a mixed mass of grated suppository base and drugs which is forced into a special compression mold.
- The method requires that the capacity of the molds first be determined by compressing a small amount of the base into the dies and weighing the finished suppositories.
- When active ingredients are added, it is necessary to omit a portion of the suppository base, based on the density factors of the active ingredients.
- The cold compression method is used for thermolabile and insoluble drugs.



Preparation of Suppositories

Molding (Fusion) Method

- The molten mass of base and drug is poured into a lubricated mold kept over ice and made up of plastic/stainless steel, containing two halves that are fixed firmly by a screw.
- The mold is then cooled at room temperature for 10-15 minutes.
- The suppositories, when set, are removed, and each drug is wiped off with a clean cloth and wrapped individually in wax paper.

Preparation of Suppositories

Small-Scale Preparation

Intermediate-Scale Preparation

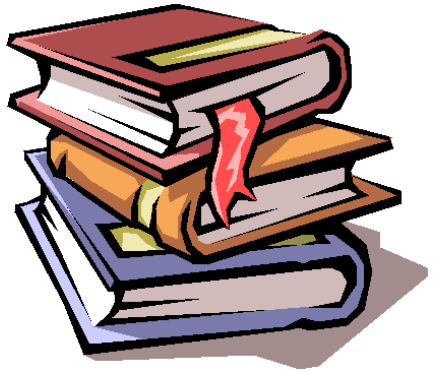
Large-Scale Preparation

Technical Problems During Suppository Production

Problem	Causes	Remedies
• **Rancidity.**	• High water content.	• Optimize water %.
• **Drug crystallization.**	• Water evaporation due to elevated temperature.	• Reduce the heat to the optimal temperature.
• **Brittleness in synthetic fat bases.**	• The temperature difference between the melted base and the mold	• Keep the temperature difference between the melted base and the mold as small as possible. • Use materials that impart plasticity to a fat and make them less brittle such as Tween 80, castor oil, glycerin or propylene glycol

Skin Penetration Enhancers

References



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