

Suppositories and Pessaries



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Chapter Outline

- Introduction
- Importance of rectal, vaginal and urethral routes
- Factors in rectal absorption
- Types of suppositories
- Importance of suppositories as a dosage form
- Suppository bases
- Preparation methods of suppositories
- Packaging and storage
- Determination of displacement value

OBJECTIVES

- After the end of this topic ,students will be able to :
 - Define suppositories and pessaries.
 - Differentiate between suppositories and pessaries.
 - Classify suppositories
 - Advantages & disadvantages of suppositories.
 - Discuss different suppository bases used.
 - Discuss the different method of preparation

Rectal route for drug administration

- The patient is unable to use the oral route (disturbance of GIT, nausea, unconsciousness, post-operation and children, old and mentally disturbed patients).
- The drug is less suited for oral route (causes GI side effects, insufficiently stable at pH of GIT, susceptible to enzymatic degradation, has first-pass effect, with unacceptable taste)

Rectal route for drug administration

- Suppositories may be used for patients in the event it may be **easier to administer** than tablets or syrups.
- Suppositories may also be used when a patient has a **vomiting** tendency, as oral medication can be vomited out.
- Drugs which often cause stomach upset, for example diclofenac sodium (Voltaren) are better tolerated in suppository form.

Drawbacks of rectal route

- Slow and incomplete absorption.
- Development of proctitis (inflammation of the anus and the lining of the rectum)
- Problems with large scale production of suppositories and of achievement of a suitable shelf life
- Demanding stringent storage conditions.

Therapy with the rectal route

- **Local effect:**

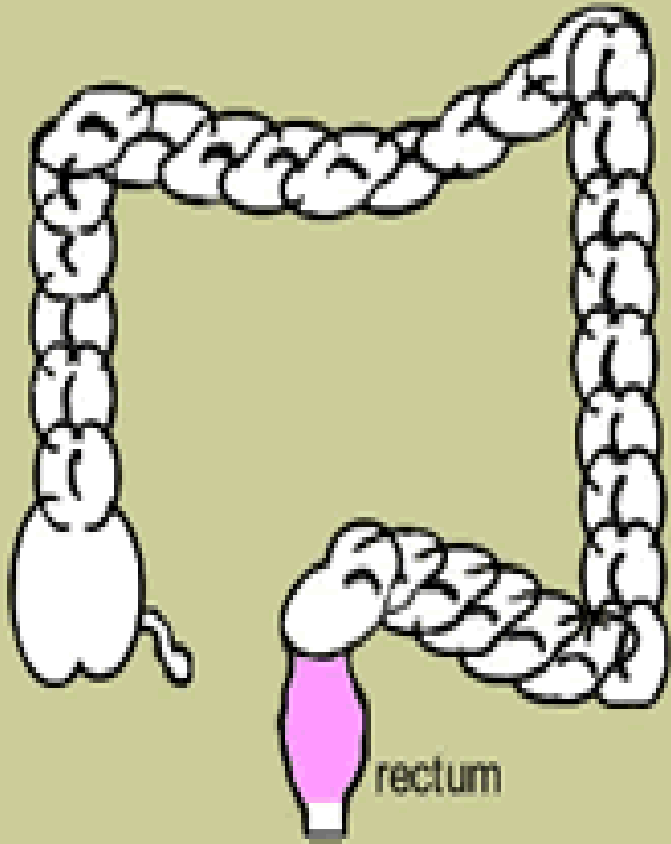
✧ In case of pain, itching and haemorrhoids

✧ locally active drugs include astringents, antiseptics, local anaesthetics, vasoconstrictors, anti-inflammatory compounds, soothing and protective agents and some laxatives.

- **Systemic effect:**

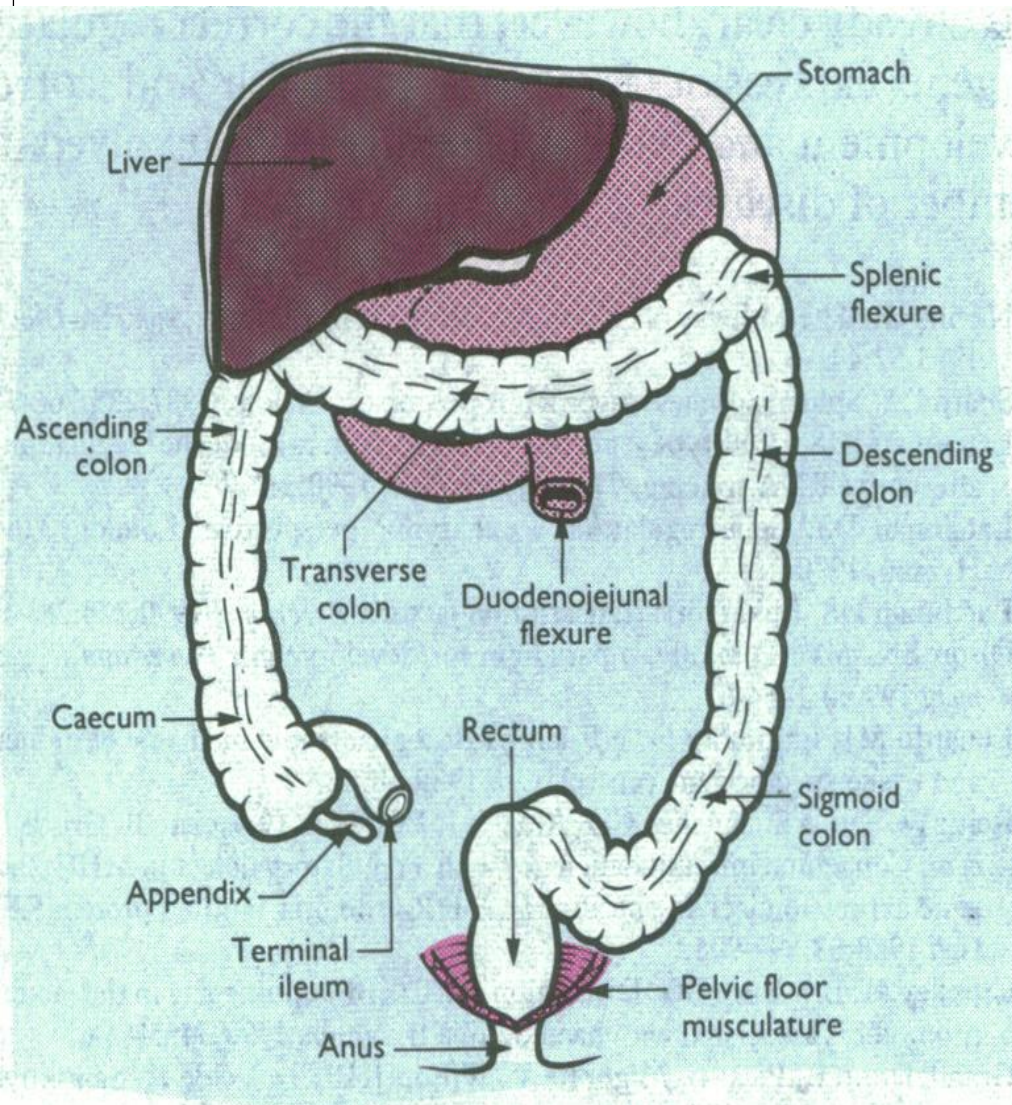
- Anti-asthmatics, anti-rheumatics and analgesics.

Anatomy and Physiology of Rectum



- The rectum is about **15 - 20 cm long**.
- It hooks up with the sigmoid colon to the north and with the anal canal to the south.
- It is a hollow organ with a relatively flat wall surface, **without villi** and with only three major folds, the rectal valves

Anatomy and Physiology of Rectum

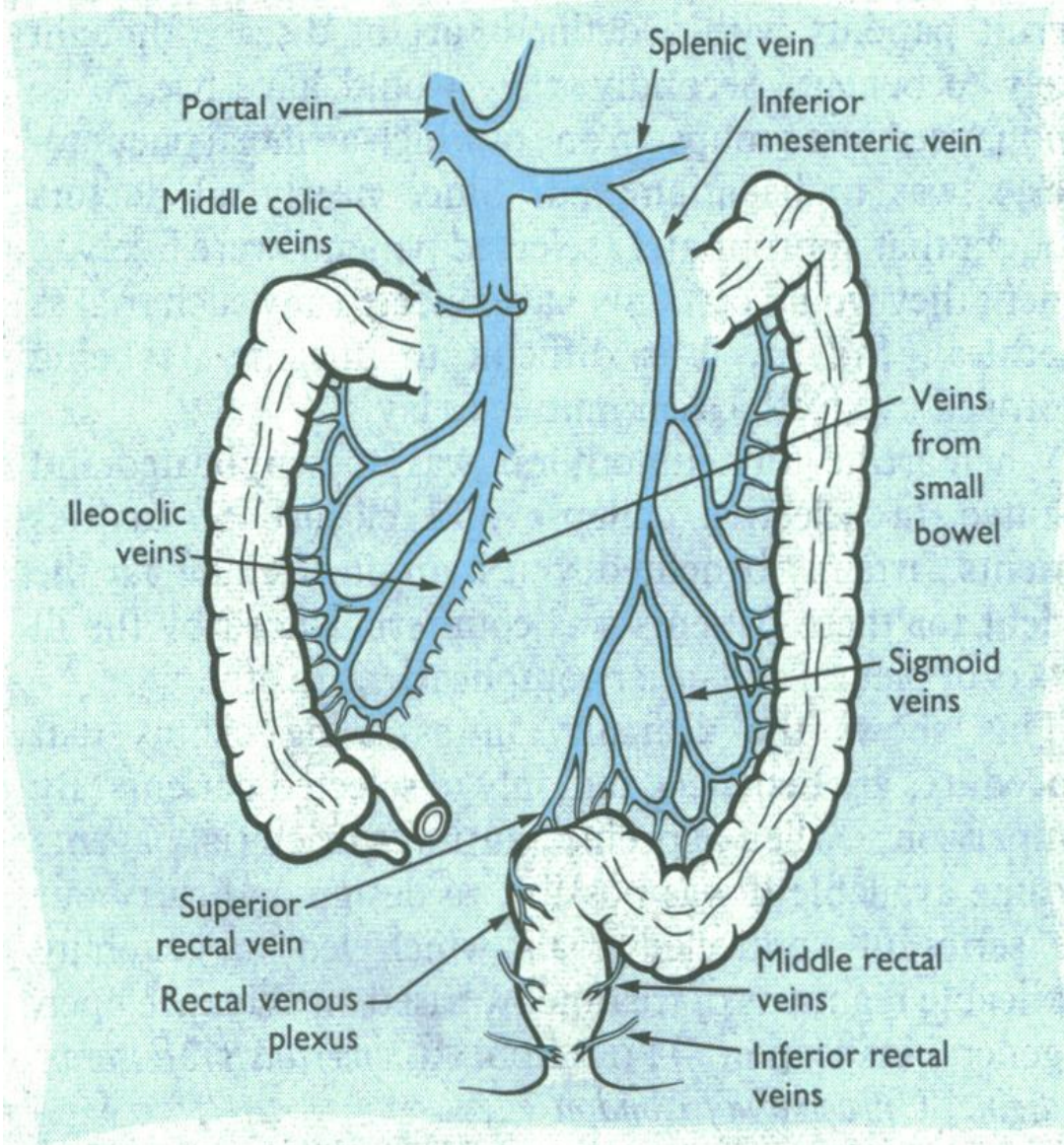


- The terminal 2 to 3 cm of the rectum is called the anal canal.
- The opening of the anal canal to the exterior is called the anus.
- The anus is controlled by an **internal sphincter** of smooth muscle and an **external sphincter** of skeletal muscle.

Anatomy and Physiology of Rectum

- Under normal conditions, the rectum is empty and filling provokes a defecation reflex which under voluntary control.
- The transverse folds in rectum keep stool in place until the person is ready to go to the bathroom.
- Then, stool enters the lower rectum, moves into the anal canal, and then passes through the anus on its way out.
- Rectum contains about **2 to 3 ml of mucous**, which has a **pH of 7.4** and little buffering capacity.

Anatomy and Physiology of Rectum



- The rectal tissues are drained by the inferior, middle and superior **haemorrhoidal veins**, but only the superior vein connects with the hepatic-portal system.

Absorption of drugs from the rectum

- Medicaments absorbed in the lower part of the rectum are delivered directly into the systemic circulation, thus **avoiding any first-pass metabolism**.
- However, it has been found that suppositories can settle high enough in the rectum to allow at least some drug absorption into the superior vein.
- Thus keeping the drug in the **lower part** of the rectum would be advisable.

Absorption of drugs from the rectum

- Insertion of a suppository into the rectum results in a chain of effects leading to the bioavailability of the drug.
- Depending on the character of the base, a suppository will either **dissolve in the rectal fluid** or **melt on the mucous layer**.
- Since the volume of **rectal fluid is so small**, complete dissolution of the base require extra water.

Absorption of drugs from the rectum

- Due to **osmotic effects** of the dissolved base, water is attracted with a painful sensation for the patient.
- Independent on the base type, dissolved drugs in the suppository will diffuse out towards the rectal membrane.
- The process of absorption will be **passive diffusion**.

Physiological factors in rectal absorption

1- Quantity of fluids available

- Very small volume under normal conditions (3ml spread in a layer of approximately 100 μ m thick over the organ).
- Under non-physiological conditions (osmotic attraction of water by water soluble base), the **volume is enlarged**.
- Thus, absorption of slightly soluble drugs (i.e. phenytoin) will be dissolution rate limited.

Physiological factors in rectal absorption

2- Properties of rectal fluids

- Composition, viscosity, pH and surface tension of rectal fluids have great effects on drug bioavailability.

3- Contents of the rectum

- Faecal content

Physiological factors in rectal absorption

4. Motility of the rectum

- The rectal wall may exert a pressure on a suppository present in the lumen by two distinct mechanisms.
- First, the **abdominal organs** may simply press on to the rectum when the body is in upright position.
- This may stimulate spreading and promote absorption.
- Second, the **motility** of the rectal muscle associated with the presence of food in the colon (waves of contractions running over the wall of the colon)

Suppositories

- Suppositories are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve and exert localized or systemic effects.
- Suppositories are medicated, solid bodies of various sizes and shapes suitable for introduction into body cavities for local or systemic effect.

Suppositories

- The medicament is incorporated into a base such as cocoa butter which **melts** at body temperature, or into one such as glycerinated gelatin or PEG which slowly **dissolves** in the mucous secretions.
- Suppositories are suited particularly for producing **local action**, but may also be used to produce a **systemic effect** or to exert a **mechanical effect** to facilitate emptying the lower bowel.

Suppositories

- A suppository is a drug delivery system that is inserted into the rectum (rectal suppository), vagina (vaginal suppository) or urethra (urethral suppository), where it dissolves.

Suppositories as a dosage form

ADVANTAGES:

- Can exert local effect on rectal mucosa.
- Used to promote evacuation of bowel.
- Avoid any gastrointestinal irritation.
- Can be used in unconscious patients .
- Can be used for systemic absorption of drugs and avoid first-pass metabolism

Suppositories as a dosage form

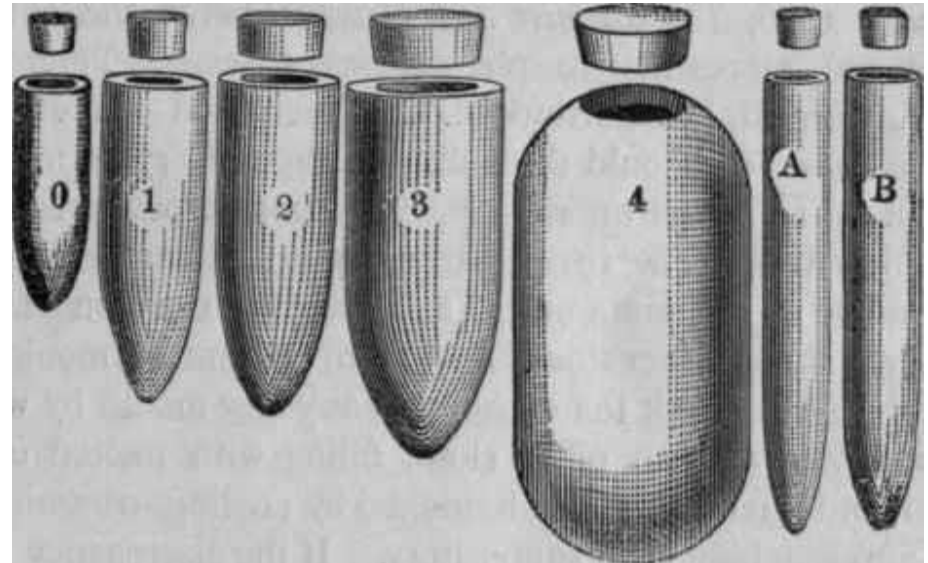
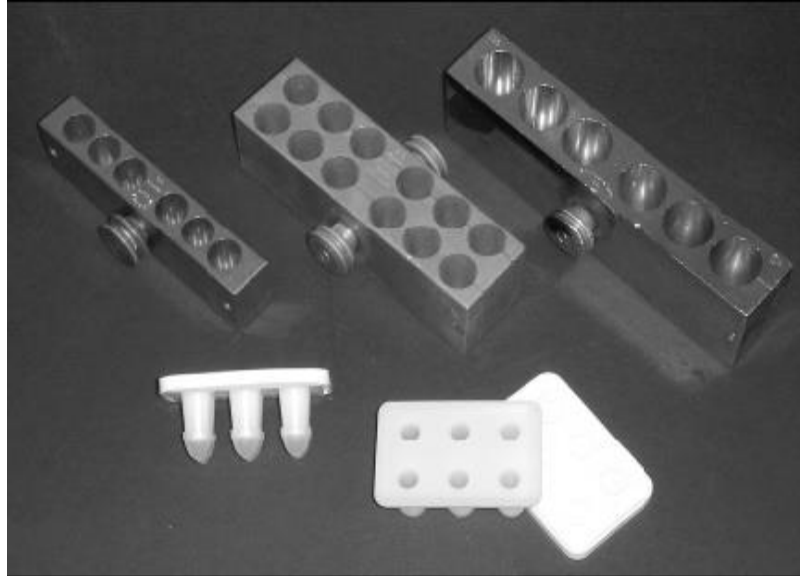
- Babies or old people who cannot swallow oral medication.
- Post operative people who cannot be administered oral medication.
- People suffering from severe nausea or vomiting

Suppositories as a dosage form

DISADVANTAGES

- The problem of patient acceptability.
- Suppositories are not suitable for patients suffering from diarrhea.
- not suitable for drugs that irritate rectal mucosa.
- Incomplete absorption may be obtained because suppository usually promotes evacuation of the bowel.

Shapes of suppositories



Types of suppositories

- Rectal suppositories
- Vaginal suppositories
- Urethral suppositories
- Nasal suppositories
- Ear cones

Rectal suppositories

- Rectal suppositories for adults weigh 2 gm and are torpedo shape.
- Children's suppositories weigh about 1 gm.
- Rectal suppositories are commonly used for:
- **laxative purposes**, with chemicals such as glycerin or bisacodyl
- **treatment of hemorrhoids** by delivering a moisturizer or vasoconstrictor

Rectal suppositories

Rectal administration is a preferred method when:

- An oral drug might be destroyed or diluted by acidic fluids in the stomach,
- An oral drug might be too readily metabolized by the liver and eliminated from the body,
- The patient is unconscious and needs medication,
- Nausea and vomiting or severe acute illness in the GI tract make patient unable to take oral drugs.

Rectal suppositories

- Delivery of many other **systemically-acting** medications, such as promethazine or aspirin.
- General medical administration purposes: the substance crosses the rectal mucosa into the bloodstream; examples include paracetamol (acetaminophen), diclofenac, opiates, and eucalyptol suppositories.
- **Non-laxative** rectal suppositories are to be used **after defecation**, so as not to be expelled before they are fully dissolved and the substance is absorbed.

Mode of insertion of suppositories

- Remove suppository from its package.
- Insert small **tapered end** first with index finger for the full length of the finger.
- May need to be lubricated with a water-soluble gel to ease insertion.
- The use of an **examination glove** or a finger cot can ease insertion by protecting the rectal wall from fingernail.

Vaginal suppositories

- **Pessaries** are a type of suppository intended for vaginal use.
- They have various shapes, usually **ovoid**, with a volume and consistency suitable for insertion into the vagina.
- Vaginal suppositories are commonly used to treat gynecological ailments, including vaginal infections such as candidiasis.

- Vaginal suppositories or Pessaries weigh about **3-5gm** and are molded in **globular or oviform** shape or **compressed** on a tablet press into **conical** shapes.
- The larger size moulds are usually used in the preparation of pessaries such as 4 g and 8 g moulds.
- Pessaries are used almost exclusively for **local medication**, the exception being prostaglandin pessaries that do exert a systemic effect.



- They contain one or more active substances dispersed or dissolved in a suitable bases that may be **soluble** or **dispersible** in water or may **melt** at body temperature.
- Common ingredients for inclusion in pessaries for local action include:
 - antiseptics
 - contraceptive agents
 - local anaesthetics
 - various therapeutic agents to treat trichomonal, bacterial infections.
- Excipients such as diluents, adsorbents, surface-active agents, lubricants, antimicrobial preservatives and coloring matter, may be added.

Vaginal suppositories

- The vaginal route is preferred for:
 - cleansing
 - contraception
 - treatment of infections
- Major disadvantages:
 - Inconvenience
- Vaginal Medications are indicated for:
 - bacterial or fungal infection
 - hormone replacement therapy

Application should follow a specific technique:

1. Begin with an **empty bladder** and washed hands.
2. Open the container and place **dose** in **applicator**.
3. **Lubricate applicator** with water-soluble lubricant if not pre-lubricated.
4. **Lie down**, spread the legs, open the labia with one hand, and insert the applicator about two inches into the vagina with the other hand.
5. Release labia; use free hand to push applicator plunger.
6. Withdraw the applicator and wash the hands.

Urethral suppositories

- The *urethral route* of administration is application of drug by insertion into the urethra
- Urethral delivery may be used to treat
 - incontinence
 - impotence in men
- Disadvantages
 - inconvenience
 - localized pain

Urethral suppositories

- Urethral suppositories called bougies are pencil shape.
- Those intended for males weigh 4 gm each and are 100-150 mm long.
- Female urethral suppositories are 2 gm each and 60-75 mm in length.



Urethral suppositories

- An intraurethral insert containing the prostaglandin alprostadil (a sterile micropellet) , 1.4mm in diameter and 6mm in length, containing the drug and PEG 1450 is available for the treatment of severe erectile dysfunction.
- Inserted 3cm deep into the urethra by the use of a hollow applicator.
- Its use has diminished since the development of oral impotence medications.

Nasal suppositories:

- called nasal bougies or buginaria meant for introduction in to nasal cavity.
- They are prepared with **glycerogelatin** base.
- They weigh about 1 gm and length 9-10 cm.

Ear cones:

- Aurinaria and meant for introduction into ear.
- Rarely used
- **Theobroma oil** is used as base.
- Prepared in urethral bougies mould and cut according to size.

SUPPOSITORY BASE

- Suppositories are drug delivery system where the drugs are incorporated into inert vehicle called suppository base.
- The USP lists the following suppository base:
 - Cocoa butter
 - Cocoa butter substitutes such as vegetable oils modified by esterification, hydrogenation, ...
 - Glycerinated gelatin
 - Mixtures of PEGs of various molecular weights

Ideal Suppository Base

1. Melts at body temperature or dissolves in body fluids.
2. Non-toxic and non-irritant.
3. Compatible with any medicament.
4. Releases any medicament readily.
5. Easily moulded and removed from the mould.
6. Stable to heating above the melting point.
7. Easy to handle.
8. Stable on storage.

Types of suppository bases

- Two types of suppository bases:

1. Fatty Bases

- are designed to melt at body temperature.

2. Water-soluble and water-miscible bases

- are designed to dissolve or disperse within the body fluids.

Suppository Bases

I- Fatty Bases

- designed to melt at body temperature.



A-Theobroma oil (Cocoa butter)

- It is a yellowish-white solid with an odor of chocolate and is a mixture of glyceryl esters of different **unsaturated fatty acids**.

Advantages of fatty bases

- a- A melting range of 30 - 36°C
- b- Readily melted on warming, rapid setting on cooling.
- c- Miscible with many ingredients.
- d- Non-irritating.

Disadvantages fatty bases

a- Polymorphism:

- When melted and cooled it solidifies in different crystalline forms, depending on the temperature of melting, rate of cooling and the size of the mass.
- If melted at not more than 36°C and slowly cooled it forms stable β **crystals** with normal melting point.
- If over-heated then cooled it produce unstable **gamma** crystals which melt at about 15°C or **α crystals** melting at 20°C.
- Cocoa butter must be **slowly melted** over a warm water bath to avoid the formation of the unstable crystalline form.

Disadvantages fatty bases

b- Adherence to the mould:

c- Softening point too low for hot climates.

d- Melting point reduced by soluble ingredients

- Phenol and chloral hydrate have a tendency to lower the melting point of cocoa butter.
- So, solidifying agents like beeswax (4%) may be incorporated to compensate for the softening effect of the added substance.

Disadvantages fatty bases

e- Rancidity on storage

f- Poor water-absorbing ability

- Improved by the addition of emulsifying agents.

g- Leakage from the body

- Seldom used in vaginal suppositories

h- Expensive

B. Synthetic Hard fat

- Obtained from vegetable oil
- As an alternative for theobroma oil
- Their solidifying points are unaffected by overheating
- Resistant to oxidation

Advantages of synthetic Hard Fat

- a- They have good resistance to oxidation because of the lower content of unsaturated fatty acids.
- b- The difference between melting and setting points is small.
 - Hence they set quickly, the risk of sedimentation of suspended ingredients is low.

Advantages of synthetic Hard Fat

- c- Their solidifying points are unaffected by overheating.
- d- They are marketed in a series of grades with different melting point ranges, which can be chosen to suit particular products and climatic condition.
- e- They contain a proportion of **w/o** emulsifying agents, and therefore, their water-absorbing capacities are good.
- f- No mould lubricant is necessary because they contract significantly on cooling.

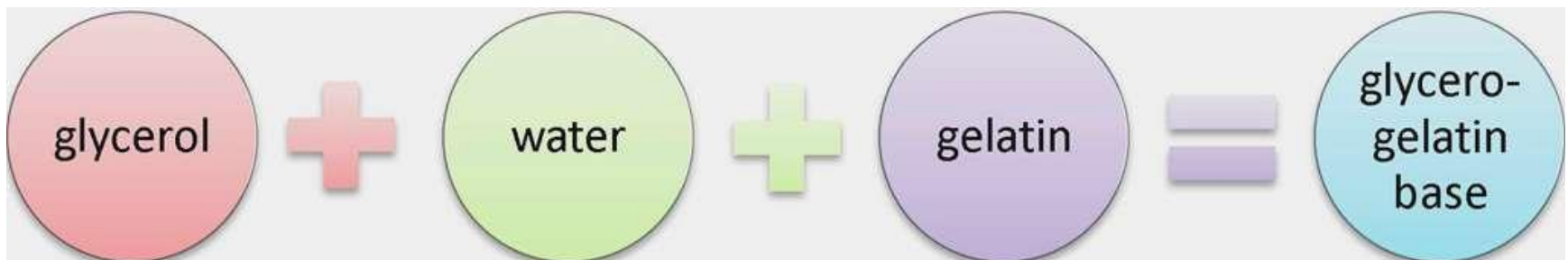
Disadvantages of synthetic Hard Fat :

- a- Brittle if cooled rapidly, avoid refrigeration during preparation.
- b- The melted fats are less viscous than theobroma oil.
 - As a result greater risk of drug particles to sediment during preparation, lack of uniform drug distribution give localized irritancy.

II . Water-soluble and water-miscible bases

- A- Glycero-gelatin base

- are designed to dissolve or disperse within the body fluids.



- Glycerinated gelatin usually is used as a vehicle for vaginal suppositories.
- For rectal use a firmer suppository can be obtained by increasing the gelatin content.
- The commonest is **Glycerol Suppositories Base B.P.**, which has 14% w/w gelatin, and 70% w/w glycerol & water Q.S. to 100%. .
- The **glycero-gelatin base U.S.P.** consisted of 20% w/w gelatin, and 70% w/w glycerol & water Q.S. to 100%.

Disadvantages of Glycerogelatin base

- a- A physiological effect: osmosis occurs during dissolving in the mucous secretions of the rectum, producing a laxative effect.
- b- Can cause rectal irritation due to small amount of liquid present.
- e- Microbial contamination likely.
 - Needs preservative e.g., methylparaben & propylparaben



Disadvantages of Glycerogelatin base

d- Hygroscopic:

- dehydrating effects on the rectal and vaginal mucosa leading to irritation.
- Reduced by: dip the preparation in warm water before insertion
- So, they should be packaged in tight containers.

f- Long preparation time.

- Lubrication, heat treatment

g- Lubrication of the mould is essential.

B- Macrogols (polyethylene glycols):

- Polyethylene glycols are polymers of ethylene oxide and water, prepared to various chain lengths, molecular weights, and physical states.
- The numerical designations refer to the average molecular weights of each of the polymers.
- Polyethylene glycols (PEGs) having average molecular weights of 300, 400, and 600 are clear, colorless liquids, while those with molecular weights of 600-1000 are semisolids

Macrogols

- Those having average molecular weights of greater than 1000 are wax-like, white solids with the hardness increasing with an increase in the molecular weight.
- These polyethylene glycols can be blended together to produce suppository bases with varying: **melting points, dissolution rates** and **physical characteristics**.

Macrogols

- Drug release depends on the base **dissolving** rather than melting.
- Higher proportions of high molecular weight polymers
- release the drug slowly and are also brittle.

Advantages of macrogols

1. The melting point is often around 50°C.

- Can be used in hot climates
- Do not melt in the body but gradually dissolve and disperse so that they **release their medication slowly** and provide **longer action** than fatty base

Advantages of macrogols

2. products which release the drug more readily can be prepared by mixing high polymers with medium and low polymers.
3. No need of lubrication of the mould because they do not stick to the mould.
4. Because of their high molecular weights, solutions of high viscosity are produced
 - Thus leakage is not a serious problem
5. They absorb water well and hence excellent solvent properties.

Disadvantages of macrogols

1. Hygroscopic
 - Problem of irritancy
2. Reduced therapeutic activity
 - Due to good solvent property retention of the drug in the liquefied base may occur.
3. Brittleness
 - Surfactants and plasticizers may reduce this problem
4. Crystal growth of some medicaments
 - The suppository may brittle
 - May cause irritancy

Choice of suppository base

- Solubility of the drug in the vehicle
- Effective release of the drug from base

Other additives

- Antioxidants
- Preservatives: for water soluble bases
- Emulsifying agents
 - Such as emulsifying wax, wool fat ,wool alcohol can be used to facilitate incorporation of aqueous solution
- Hardening agents such as white beeswax in theobroma oil
 - Higher polymer macrogols into low mwt macrogols
 - gelatin for glycerogelatin
- Viscosity modifiers such as, betonite, ...

Reasons for using the additives

1. To help the incorporation of the drug.

- Oily base

- Water soluble/miscible base

2. To improve hydrophilicity

e.g. For cocoa butter-mono and diglycerides

- emulsifying agent

3. To increase the viscosity (η)

- ☞ to improve the η , increase the MP by adding a **hardening agent** such as hard paraffin

- ☞ in presence of phenol and chloral hydrate-bees wax

4. To improve the mechanical strength(MS)

- Is the resistance of a material to deformation under stress.

- For these suppository with water soluble/miscible bases in tropical regions ($T^o > 40^o\text{C}$) loss of water exist.

- To overcome the problem- adding of propylene glycol.

- At room temperature good suppository base can be prepared by mixing PEG 400 (35%) and PEG 4000 (65%).

5. Prevent degradation

- a. Chemical degradation
- b. Microbial degradation

a. Chemical degradation

- o Oxidation-antioxidant
- o Hydrolysis-change solvent (H_2O) by PEG, propylene glycol or glycerol.

NB: During solvent selection, one should optimize both the hydrophilicity and hydrolysis of the preparation.

b. Microbial degradation

- ❖ Pure oil- no need for preservative
- ❖ Witepsol- need preservative.

Displacement value

➤ The volume of a suppository from a particular mould is uniform but its weight will vary because the densities of medicaments usually differ from the density of the base with which the mould was calibrated.

➤ To prepare products accurately, allowance must be made for the change in density of the mass due to added medicament. The most convenient way of making this allowance is to use the displacement value

Definition: displacement value(DV) is the number of parts by weight of the medicament that displaces one part by weight of the base

$$DV = \frac{[drug]_{wt}}{[displaced]_{wt}}$$

Example 1:

RX: wt of six unmedicated suppositories=6g

wt of six suppository containing 40% of zinc oxide= 8.8g

Determine DV of zinc oxide. (Ans ca. 5)

| | |
|----------------------------------|-------|
| Example 2: RX bismuth subgallate | 300mg |
| suppository base | QS |

Prepare 10 suppositories

DV of bismuth subgallate is 3.

Calculate the amount of suppository base required using 1g mould.

(ans=9g)

assignment one:

1. Rx Bismuth Subgallate 300mg
Wetepsol 45, sufficient for 1g mould
Calculate the displacement value

2. Assume the DV of the following compounds is as follow

Hamamelis Dry extract 1.5

Zinc oxide 5

water 1

Calculate amount of base required to prepare 8 suppositories of

Rx Hamamelis Dry extract 200mg

zinc oxide 600mg

water 0.4ml

theobroma oil, sufficient for 2g mould

3. Prepare a suppository containing 100mg of phenobarbital ($DV = 0.81$) using cocoa butter as the base. The weight of the pure cocoa butter suppository is 2.0g. Since 100mg of phenobarbital is to be contained in an approximately 2.0 g suppository, it will be about 5% phenobarbital . What will be the total weight of each suppository?

4. Prepare 12 acetaminophen 300mg suppositories using cocoa butter, where the average weight of the cocoa butter blank is 2g and the average weight of the medicated suppository is 1.8g.

5. Prepare 10 suppositories, each containing 200mg of a drug with a density of 3.0. The suppository base has a density of 0.9 and a prepared blank weighs 2.0g. Calculate required suppository base and the the active drug.

Preparation of suppositories

- Suppositories are prepared by four methods:

I . Hand moulding

- Hand molding is useful when we are preparing a small number of suppositories:
 1. The drug is made into a fine powder.
 2. It is incorporated into the suppository base by kneading with it or by trituration in a mortar.
 3. The kneaded mass is rolled between fingers into rod shaped units.
 4. The rods are cut into pieces and then one end is pointed.

II .Compression molding

- The cold mass of the base containing the drug is compressed into suppositories using a hand operated machine.
- **Advantages:**
 1. It is a simple method.
 2. It gives suppositories that are **more elegant** than hand molded suppositories.
 3. In this method sedimentation of solids in the base is prevented.
 4. Suitable **for heat labile** medicaments.

- **Disadvantages:**

1. Air entrapment may take place.
2. This air may cause weight variation.
3. The drug and/or the base may be oxidized by this air.

III .Pour moulding

- Using a suppository mould which is made of metal or plastic.
- Traditional metal moulds are in two halves which are clamped together with a screw.



Steps in the preparation of suppositories by fatty bases:

1. Calculate the quantity desired
 - Consider DV
 - Usually two more suppositories are prepared

Pour moulding

- Displacement value, DV
- Defined as a number of parts by weight of medicament that displaces one part by weight of the base.
- $DV = \frac{\text{amount of drug added}}{\text{amount of base displaced}}$
- E.g., *Rx Chloral hydrate 60mg*
Theobroma oil ... suffi to fill 1g mould
Prepare 8 suppositories and send 6 suppositories
- DV of Chloral hydrate = 1.5

Pour moulding

2. Prepare the mould

- Cleaning , lubrication
- Mould: made of metal
- Nominal capacity: commonly 1g, 2g, 4g, 8g with respect to the weight of theobroma oil.
- Lubricating the cavities of the mould is helpful in producing elegant suppositories and free from surface depression

Pour moulding

- The lubricant must be different in nature from the suppository base, otherwise it will be become absorbed and will fail to provide a buffer film between the mass &the metal.
- The water soluble lubricant is useful for fatty bases while the oily lubricant is useful for water soluble bases.

Pour moulding

Lubricants for use with suppository bases

Base

- Theobroma oil
- Glycerol-gelatin base

Lubricant

- Soap spirit
- liquid paraffin

No lubricant required

- Synthetic fats
- Macrogols

Pour moulding

3. Prepare the base

- Melting with stirring
- avoid overheating

4. The drug is incorporated in to the molten base.

5. The molten liquid mass is poured into chilled (lubricated if cocoa butter or glycerogelatin is the base) molds.

- Over flowing to allow for contraction on cooling

6. After solidification the cone shaped suppositories are extracted.

IV Automatic Moulding machine:

- All the operations in pour moulding are done by automatic machines.
- Using this machine, up to about 10,000 suppositories per hour can be produced.

Packaging and storage

- Suppositories are usually packed in tin or aluminium, paper or plastic.
- Poorly packed suppositories may give rise to staining, breakage or deformation by melting.
- Both cocoa butter and glycerinated gelatin suppositories stored preferably in a refrigerator.
- Polyethylene glycol suppositories stored at usual room temperature without the requirement of refrigeration.

