UNIT 4

Suppositories

Definition

A **suppository** is a **solid dosage form** intended for **insertion into body orifices** such as the **rectum, vagina, or urethra**, where it **melts, softens, or dissolves** to exert **local or systemic effects**. It is usually composed of one or more **active drugs** dispersed or dissolved in a suitable **base**.

Types of Suppositories (Based on Site of Application)

Type	Site of Use	Shape and Size	Examples
Rectal suppository	Rectum	Cylindrical or conical, 1–2 g	Paracetamol, bisacodyl
Vaginal suppository (Pessary)	Vagina	Oval, globular, or cone-shaped, 3–5 g	Clotrimazole, metronidazole
Urethral suppository (Bougie)	Urethra	Pencil-shaped, 2–4 mm diameter (male), 60 mm long	Antibacterials (e.g., for gonorrhea)
Nasal and ear cones	Nasal cavity or ear	Small cone-shaped	Rare; generally replaced by drops/sprays

Advantages of Suppositories

- Useful for **patients unable to take oral medications** (e.g., vomiting, unconscious)
- Provides **local action** (e.g., hemorrhoids, vaginal infections)
- Avoids **first-pass metabolism** when used rectally
- Less **gastric irritation** compared to oral NSAIDs
- Suitable for **pediatric and geriatric** patients

Disadvantages of Suppositories

- **Patient discomfort** or reluctance
- **Irritation** at site of application in sensitive individuals
- **Variable absorption** due to rectal content, pH, and circulation
- **Storage issues** (some bases melt at room temperature)
- **Short shelf-life** in humid conditions

Types of Bases Used in Suppositories

A suitable base should be **non-toxic**, **non-irritant**, **compatible with drugs**, **stable**, and **able to melt or dissolve** at body temperature.

1. Fatty (Oleaginous) Bases

- **Cocoa butter (Theobroma oil)** – most common natural base
- **Synthetic substitutes**: Witepsol, Fattibase, Hard fat

Properties:

- Melts at body temperature (~30–36°C)
- Provides **smooth texture and release** of drug
- Must be stored in a **cool place**
- Incompatible with some drugs that lower its melting point

Advantages:

- Good patient acceptability
- Non-irritant, emollient effect

Disadvantages:

- Polymorphism (melting point variation)
- Rancidity and microbial growth possible
- Incompatible with water-soluble drugs

2. Water-Soluble and Water-Miscible Bases

- **Glycerinated gelatin**
- **Polyethylene glycols (PEG)**

Properties:

- **Do not melt** but **dissolve slowly** in body fluids
- **Longer drug release time**
- Hygroscopic – can absorb moisture from atmosphere

Glycerinated Gelatin:

- Used for **vaginal and urethral suppositories**
- Composed of **gelatin + glycerin + water**
- Needs **preservatives** and airtight storage

Polyethylene Glycol (PEG):

- Synthetic polymer with various molecular weights
- Non-greasy and **no refrigeration required**
- May cause **irritation to mucosa**

Advantages:

- Stable at room temperature
- Compatible with many drugs
- Non-leaky (suitable for heat-prone environments)

Disadvantages:

- Hygroscopic nature
- May cause mucosal irritation
- Slower drug release than fatty bases

3. Emulsifying Bases

- Macrogol + emulsifying wax
- PEG-based blends

Properties:

- Can accommodate both **hydrophilic and lipophilic drugs**
- Provide **controlled release**
- Common in **modern industrial formulations**

Selection Criteria for Base

Factor	**Preferred Base**
Drug is **lipophilic**	Use **water-soluble base** (e.g., PEG) for better release
Drug is **hydrophilic**	Use **fatty base** (e.g., cocoa butter)
For **fast drug release**	Use **fatty base**
For **sustained release**	Use **PEG base**
For **vaginal application**	Use **glycerinated gelatin**
For **humid climate**	Avoid **glycerinated gelatin**, prefer PEG base

Methods of Preparation of Suppositories

The preparation of suppositories involves incorporating **medicaments into a suitable base**, molding or shaping them for **rectal, vaginal, or urethral** use. The chosen method depends on the **type of base**, **nature of drug**, **dose uniformity**, and **scale of manufacturing**.

The **main goals** in preparation are:

- Uniform distribution of drug
- Proper melting/dissolution behavior
- Smooth finish and stability

Common Methods of Suppository Preparation

Method	Suitable For	Key Features
1. Molding (Fusion) method	All types of suppositories and bases	Most widely used in both small and large scale
2. Compression method	Heat-sensitive drugs, industrial batches	Avoids heat; suitable for drug-brittle formulations
3. Hand rolling and shaping	Extemporaneous, low-tech preparations	Used in pharmacies; not for modern large-scale manufacturing

1. Molding (Fusion) Method

Principle:
The drug is dispersed or dissolved in a **molten suppository base**, poured into molds, and allowed to **cool and solidify**.

Steps:

1. **Preparation of Mold**: Cleaned, lubricated with thin film of oil or liquid paraffin (if required).
2. **Melting the Base**: Fatty bases (e.g., cocoa butter) are melted using a **water bath**, not directly on flame.
3. **Incorporation of Drug**:
    - Drug is either **dissolved** (if soluble) or **finely powdered and levigated** with a portion of molten base (if insoluble).
4. **Mixing**: The drug is thoroughly mixed with the rest of the base.
5. **Pouring into Molds**: Warm molds are filled just above the cavity level to allow contraction.

6. **Cooling and Solidification**: Molds are left to set at room temperature or in a refrigerator.
7. **Finishing**: Excess material is trimmed and suppositories are removed, wrapped, and packed.

Suitable For:

- Cocoa butter
- Glycerinated gelatin
- PEG bases

Advantages:

- Uniform drug distribution
- Good finish and shape
- Widely adaptable for many drug types

Precaution:

- Avoid overheating cocoa butter (above 36°C) to prevent polymorphic transition

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2. Compression Method

Principle:
Involves compressing the base and drug mixture into molds under pressure without heating. Suitable for **heat-sensitive** and **volatile drugs**.

Steps:

1. Base and medicament are **powdered and sieved**
2. Thorough **mixing** to ensure uniformity
3. The mixture is **compressed** using a hand-operated or mechanical **compression mold press**
4. Suppositories are **ejected and polished** if needed

Advantages:

- No heating required
- Suitable for **thermolabile drugs**
- Minimal risk of **drug degradation or evaporation**

Disadvantages:

- Requires **specialized equipment**

- May produce **brittle** suppositories

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3. Hand Rolling and Shaping Method

Principle:
A traditional manual technique used when molds or machines are unavailable.

Steps:

1. A **plastic mass** is prepared by triturating drug with softened base
2. The mixture is **rolled by hand** into cylindrical rods
3. These rods are **cut and shaped** into the desired suppository form

Advantages:

- No equipment required
- Useful for **extemporaneous preparations**

Disadvantages:

- Poor dose uniformity
- Time-consuming and not suitable for mass production

Displacement Value and Its Calculations

In suppository preparation using the **molding (fusion) method**, the **volume of the mold remains constant** whether it's filled with only base or with **base + drug**. However, the **drug** displaces a **certain amount of the base**, and this must be calculated accurately to ensure **uniformity of drug content** in each suppository.

This is where the **Displacement Value (DV)** becomes essential.

Definition of Displacement Value

Displacement Value is defined as:

The **number of parts by weight** of the drug that **displaces one part by weight** of the base.

In simpler terms:

- It tells you **how much of the base is replaced (displaced)** by a **given amount of drug** in the suppository mold.

Why Displacement Value is Important

- Prevents **overfilling** or **underfilling** of molds
- Ensures **accurate dosing** of the medicament
- Essential in **calculation of quantity of base** required per batch

Formula

To calculate the amount of base required for medicated suppositories:

Amount of base required=[Weight of one blank suppository×Number of suppositories]−(Total weight of drug/ Displacement Value)

Another useful version for one suppository:

Base per suppository=Weight of blank suppository−(Drug per suppository/DV)

Worked Example 1:

Problem:
Prepare **6 suppositories**, each weighing **2 g** (blank weight), containing **300 mg of a drug**. The **displacement value of the drug is 3**.
Find the **amount of base** required.

Solution:

- **Total drug** = 300 mg × 6 = 1800 mg = 1.8 g
- **Base displaced** = 1.8 g ÷ 3 = 0.6 g
- **Total weight of suppositories** = 6 × 2 g = 12 g
- **Amount of base required** = 12 g – 0.6 g = **11.4 g**

You'll need **11.4 g of base** and **1.8 g of drug**.

Worked Example 2 (Per Suppository):

Given:

- Weight of blank suppository = 2 g
- Drug per suppository = 400 mg
- Displacement value = 2.5

Calculation:

Base required=2−(0.4/2.5)=2−0.16=1.84 g

Each suppository requires **1.84 g of base** and **400 mg of drug**

General Guidelines

- Displacement values are **drug and base specific**
- Common bases: **Cocoa butter, PEG, glycerinated gelatin**
- Use **accurate weighing and calibration** of molds in real practice

Evaluation of Suppositories

After preparing suppositories, it is essential to evaluate their **quality, stability, and performance** using **pharmaceutical tests**. These tests ensure that suppositories meet the required **physical standards**, **uniformity**, **drug content**, and **release characteristics**, leading to **effective therapeutic action** and **patient acceptability**.

Evaluation is done using both **official (pharmacopoeial)** and **non-official** methods.

1. Physical Evaluation

Parameter	Purpose	Standard / Description
Appearance	Check for uniformity, smooth surface, absence of cracks	Suppositories should be **shiny, smooth**, and free from air bubbles
Weight variation	Ensure uniformity in each unit	Weight difference should be within **±5% for <2g**, **±3% for ≥2g** suppositories
Hardness (Mechanical strength)	Test breakage resistance	Should withstand **light pressure** without crumbling
Melting / Softening point	Ensure it melts at body temperature	Ideal range: **30–36°C for fatty bases**, or **dissolves** for PEG base
Liquefaction time	Time taken to melt at body temperature	Should liquefy within **10–15 minutes** in rectal conditions
Disintegration test	Measures time for complete disintegration in fluid	Performed at **37°C** using **disintegration apparatus**

2. Chemical Evaluation

Parameter	Purpose	Method / Standard
Drug content uniformity	Ensure uniform drug distribution in each unit	Each suppository should contain **85–115%** of label claim
Assay of active ingredient	Confirms actual drug amount present	By suitable analytical method (e.g., UV, HPLC)
pH of aqueous extract	Important for **vaginal/urethral** suppositories	Measured after dissolving in water

3. In-vitro Drug Release Studies

Test	Purpose	Remarks
Dissolution test	Measures the rate and extent of drug release	Performed using modified **dissolution apparatus**
Diffusion studies	Drug diffusion through semipermeable membrane	Simulates **rectal/vaginal mucosal absorption**
In vitro-in vivo correlation	To predict therapeutic efficacy from release data	Helps in **bioequivalence** testing

4. Stability Testing

- **Physical stability**: Evaluate for **melting, discoloration, brittleness** over time
- **Chemical stability**: Check for **degradation** using assay methods
- **Microbial stability**: Especially for **glycerinated gelatin** bases (which support microbial growth)

Conditions:

- Store at **2–8°C** or **below 25°C**, depending on base
- Use **light-resistant, moisture-proof packaging**

Pharmaceutical Incompatibilities

I. Definition

Pharmaceutical incompatibility refers to the **undesirable interaction** between **two or more ingredients** (either active or inactive), when they are combined in a prescription or formulation, leading to an unacceptable **physical, chemical, or therapeutic outcome**.

Such incompatibilities can result in:

- **Change in appearance** (color, odor, consistency)
- **Loss of therapeutic activity**
- **Formation of toxic compounds**
- **Reduced patient compliance**

II. Classification of Pharmaceutical Incompatibilities

Pharmaceutical incompatibilities are classified into:

1. **Physical Incompatibility**

2. **Chemical Incompatibility**
3. **Therapeutic Incompatibility**

III. Types of Incompatibilities

1. Physical Incompatibility

Definition

It occurs when **two or more substances are mixed** and produce **undesirable physical changes** without involving a chemical reaction.

These changes include:

- Precipitation
- Liquefaction
- Color or odor change
- Immiscibility

Causes:

- Insolubility of ingredients
- Inappropriate solvent systems
- Formation of eutectic mixtures
- Volatilization

Examples:

Type	**Example**
Precipitation	Sodium salicylate + Quinine sulphate → precipitation
Immiscibility	Oil and water without an emulsifier → phase separation
Liquefaction	Camphor + Menthol → eutectic mixture liquefies
Volatilization	Menthol and camphor stored in open container → loss due to evaporation

Remedies:

- Use of **suitable emulsifiers or solubilizers**
- **Order of mixing** should be properly followed
- Use of **alternative compatible ingredients**
- **Labeling**: e.g., "Shake well before use"

2. Chemical Incompatibility

Definition

Occurs when a **chemical reaction** takes place between the ingredients in a prescription or formulation, leading to **decomposition, inactivation, or formation of harmful substances**.

Types of Chemical Reactions:

- Oxidation-reduction
- Hydrolysis
- Neutralization
- Double decomposition
- Acid-base reactions

Consequences:

- Loss of active drug
- Formation of toxic or inactive byproducts
- Color/odor changes
- Effervescence or gas formation

Examples:

Reactants	**Type of Reaction**	**Effect**
Tannic acid + Ferric salts	Double decomposition	Forms black ferric tannate precipitate
Sodium bicarbonate + Citric acid	Acid-base reaction	Produces carbon dioxide (effervescence)
Morphine hydrochloride + Sodium hydroxide	Precipitation of free base	Loss of solubility and therapeutic effect
Potassium permanganate + Glycerin	Oxidation-reduction (violent)	Risk of explosion
Aspirin + Sodium hydroxide	Hydrolysis	Produces salicylic acid (irritant) and acetic acid

Remedies:

- **Modify prescription** with stable substitutes
- **Separate incompatible ingredients** (label: "Do not mix")
- Use **buffering agents, antioxidants**, or **preservatives**

- **Dispense freshly** in divided doses if short shelf life

3. Therapeutic Incompatibility

Definition

Occurs when the **combined effect** of two or more drugs administered together results in **undesirable pharmacological outcomes** such as:

- Toxicity
- Reduced efficacy
- Antagonistic or synergistic effects

This is not visible physically but impacts **clinical outcomes**.

Types:

- **Synergism** (enhanced effect): May cause toxicity
- **Antagonism** (opposite effects): Reduces drug action
- **Duplication** (same class): Overdose risk

Examples:

Drugs Involved	**Effect**
Tetracycline + Calcium salts (milk/antacids)	Chelation → Poor absorption of tetracycline
Chloramphenicol + Penicillin	Antagonism (bacteriostatic vs. bactericidal) → Reduced efficacy
Aspirin + Warfarin	Increased bleeding risk due to additive anticoagulant effects
Diuretics + Digoxin	Electrolyte loss → Enhances digoxin toxicity
Metronidazole + Alcohol	Disulfiram-like reaction → Severe nausea and vomiting

Remedies:

- Check **drug-drug interaction references**
- Monitor therapy with **therapeutic drug monitoring (TDM)**
- **Avoid combining incompatible drugs**
- **Adjust dose, frequency**, or **route of administration**