SUPPOSITORIES

Contents to be covered in this topic

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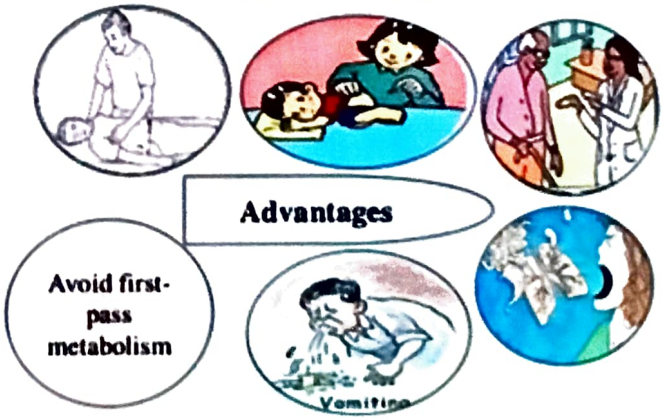
SUPPOSITORIES

❑ INTRODUCTION

- Suppositories are **semisolid dosage form** of various weight and shape
- Medicated for insertion into **body cavity** like **rectum, vagina, and the urethra.**
- They are designated to melt, soften or **dissolve at body temperature.**
- Most suppositories in this group are **used** to **relieve the pain** and **irritation of hemorrhoids.**
- They contain **local anaesthetics** such as **cinchocaine and benzocaine**, astringents such as **bismuth subgallate**

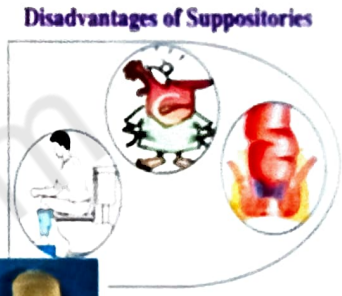
❑ ADVANTAGE OF SUPPOSITORIES

- It **avoid first pass metabolism.**
- **Melt** at **body temperature.**
- It give **localized and systemic effect**
- It is **easy to use** for **pediatric and geriatric patients.**
- **Useful for rapid** and **direct effect in rectum.**
- Useful to **promote evacuation of bowel.**
- Useful for **rapid and direct** effect in **rectum.**
- Useful to **promote evacuation of bowel.**
- Convenient for those **drug causes GIT irritation , vomiting etc.**
- Best for **vaginal and rectum fungal** infection.



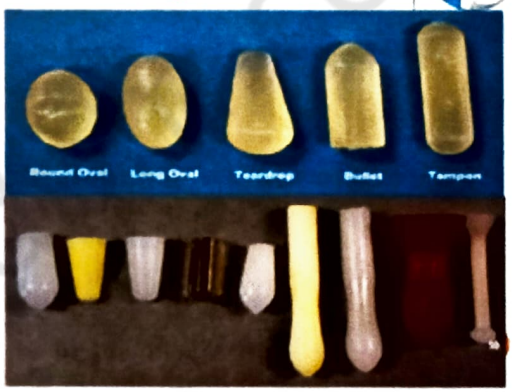
❑ DISADVANTAGE OF SUPPOSITORIES

- Irritant drug can't administered.
- Need to store at low temp.
- Some patients feel embarrassed.
- Preparation is complicated compared to liquid and tablets.
- It can cause irritation in some patients.
- Can't easily prepared and cost-expensive.
- Fluid content of the rectum is much less than that of the small intestine, this may effect dissolution rate, etc.
- Some drug may be degraded by the microbial flora



❑ TYPES OF SUPPOSITORIES

There are 5 types of suppositories according to the route of administration



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

There are 4 types of suppositories in other dosages form

- Tablet Suppositories
- Layered Suppositories
- Coated Suppositories
- Capsule Suppositories

❖ Tablet Suppositories

- This type of tablets prepared by compression like tablets.
- Such type of suppositories used for rectal & vaginal purposes.
- Pessaries tablet suppositories are present in almond like shape.
- Rectal tablets covered with thin layers of materials such as polyethylene glycol for protecting.

❖ Layered Suppositories

- Layered suppositories are **made with different drugs** in different layers to **avoid incompatibility between those drugs**.
- In that type of suppositories are contains different drugs in different layers.
- So that, **incompatibility drugs** can be **separated from each other.**
- Can be **incorporated to control the absorption rate.**

Melting point of different suppository layer

❖ Coated Suppositories

- Coated suppositories **made with free unsaturated fatty acids, polyethylene glycol** etc. for **their smooth lubricating properties.**
- Those materials **controls their disintegration rate**, to **impart lubricant properties** & to **provide protection action during storage.**

❖ Capsule Suppositories

- Capsule suppositories are **made with soft gelatin** in **various sizes and shapes.**
- Soft **gelatin capsules of different shapes** & size are prepared in that type of suppositories.
- In that type of **capsule suppositories** are filled with **liquids, semisolids or solids.**
- These type of capsules are **increasing in popularity.**

❑ SUPPOSITORY BASES

- Suppository bases plays **important role** in **maintaining their shape**, solidity & also play important role when **inserted into the body cavity.**
- There are **large number of bases** used but **Theobroma oil, glycerogelatin** base & **polyethylene glycol** fulfill the above mentioned requirements.

❖ Ideal suppositories base

- It must retain the **shape and size.**
- It should **melt at body temperature.**
- It **should be non-irritant.**
- It should **shrink sufficiently to remove from mould.**
- It should **not interfere in release or absorption of drug.**
- It should **permit incorporation of drug.**
- It should be **compatible with variety of drugs.**
- It should be **physically stable on storage.**
- It should **not be soften or harden on storage.**

❑ TYPES OF SUPPOSITORY BASE

1. Oleaginous (Fatty) Base
2. Aqueous Base/ water soluble/ water miscible base
3. Emulsifying Base/ synthetic base

❖ Oleaginous (Fatty) Base

- ✓ Theobroma Oil or Cocoa butter
- ✓ Emulsified cocoa butter
- ✓ Hydrogenated oils

Theobroma Oil

✓ Theobroma Oil or Cocoa butter

- Cocoa butter is fat obtained from the roasted seed of ***Theobroma cocoa.***
- At **room temperature** it is a **yellowish**, white solid having a faint, **agreeable chocolate like odour.**
- Chemically, it is a triglyceride (combination of glycerin and one or different fatty acids) primarily of oleopalmitostearin and oleodistearine.
- **It melts at 30 – 36°C**

- **Advantages**
  - ✓ Melting just below the **body temperature**
  - ✓ Maintaining its **solidity at usual room temperatures**
  - ✓ Readily **liquefy on heating and solidify on cooling**
- **Disadvantages**
  - ✓ Rancidity
  - ✓ Stick to mould
  - ✓ Leakage from body cavity
  - ✓ Costly
  - ✓ Immiscibility with body fluid
  - ✓ Chloral hydrate or lactic acid liquefy it

EMULSIFIED COCOA BUTTER

✓ **Emulsified Theobroma oil/ Emulsified cocoa butter**

- Emulsified Theobroma oil may be used as a base when large quantities of aqueous solutions are to be incorporated.
- **5% glyceryl monostearate, 10% lenette wax, 2-3% cetyl alcohol & 4% bees wax is recommended for emulsified theobroma oil.**

✓ **Hydrogenated oils**

- Hydrogenated oils are used as a substitute of Theobroma oil.
- E.g. Hydrogenated edible oil, coconut oil, hydrogenated pea oil, stearic acids, palm kernel oil etc.

- **Advantages**
  - ✓ Overheating does not affect the solidifying point.
  - ✓ They are resistant to oxidation.
  - ✓ Lubrication of the mould is not required.
  - ✓ Their emulsifying & water absorbing capacity are good.
- **Disadvantages**
  - ✓ On rapid cooling they become brittle.
  - ✓ When melted they are more fluid than Theobroma oil & result in greater sedimentation of the added substance.

❖ Aqueous Base/ water soluble/ water miscible base

- ✓ Glycero-gelatin base
- ✓ Soap-glycerin suppositories
- ✓ Polyethylene glycols

✓ Glycero-gelatin base

- It is a **mixture of glycerin and water which is made stiff by the addition of gelatin.**
- The suppositories prepared from **glycero-gelatin base are translucent**

To avoid incompatible reactions, the two types of gelatin are used as suppository bases:

I. Type A or **Pharmagel A which is acidic in nature** and used for acidic drugs having **iso-electric point (7-9).**

II. Type B or **Pharmagel B which is alkaline in nature** and used for alkaline drugs having **iso-electric point (4.7 to 5.0)**

➢ Disadvantage

- Gelatin is incompatible with many drugs, such as, tannic acid, ferric chloride, gallic acid etc.
- The suppositories prepared with glycero-gelatin base are hygroscopic and hence require special storage containers.

✓ Soap-glycerin suppositories

- In glycero-gelatin base, the **gelatin is replaced with either curd soap or sodium stearate** which makes the base sufficiently hard to prepare good quality of suppositories.

➢ Disadvantage

- The main disadvantage of this base is that they are **very hygroscopic.** Therefore, the suppositories prepared with this base **must be protected from atmosphere and wrapped in waxed paper or tin foil.**

✓ **Polyethylene glycols**

- Polyethylene glycol polymers are commonly known as carbowaxes or polyglycols or macrogols
- The **physical character of these carbowaxes varies according to the molecular weight**. The macrogols having **molecular weight less than 1000 are liquids** and those **with molecular weight higher than 1000 are wax like solids**

➢ **Advantage**

- They do not allow the bacterial or mould growth to take
- They are non-irritant.
- They are physiologically inert substances.

➢ **Disadvantage**

- They are hygroscopic and hence require special storage conditions to store them.
- They are incompatible with certain drugs like tannins, phenols etc.

❖ **Emulsifying Bases:**

- These are synthetic bases

Number of proprietary synthetic bases are available in the market are

✓ Witepsol
✓ Massa estarinum
✓ Massuppol

✓ **Witepsol**

- They consist of triglycerides of saturated vegetable acid with varying percentage of partial esters.
- The suppositories prepared with witepsol bases should not be cooled rapidly, in order to prevent them from becoming brittle and fracture.

✓ ***Massa estarinum***

- It is a mixture of mono, di- and triglycerides of saturated fatty acids having the formula $C_{11}H_{23}COOH$ to $C_{17}H_{35}COOH$.
- This is also known as **adeps solidus.**
- It is a **white, brittle, almost odourless and tasteless solid.** It has a **M.P. 33.5 to 35.5°C**

✓ **Massuppol**

- It consists of glyceryl esters mainly of **lauric acid to which small amount of glyceryl monostearate has been added to improve its water absorbing capacity**

➢ **Advantages over theobroma oil**

- They solidify rapidly.
- They are non-irritant.
- The lubrication of mould is not required.
- Overheating does not affect the physical properties of the base.

➢ **Disadvantages**

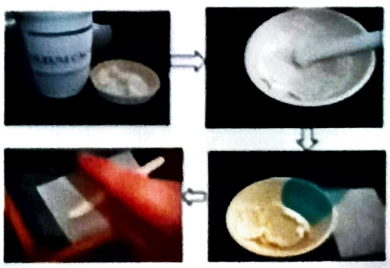
- They should not be cooled rapidly in a refrigerator because they become brittle.
- They are not very viscous on melting, so the medicaments incorporated with the base settle down rapidly.

❑ PREPARATION OF SUPPOSITORIES

❖ Hand molding

- This is the **oldest and simplest method** of preparing suppositories. A **skilled person** is required for the preparation of suppositories.
- It has the advantage of avoiding the necessity of heating the cocoa butter. A plastic-like mass is prepared by triturating grated cocoa butter and active ingredients in a mortar.

Hand Molding



✓ **Process for preparation of hand molding suppositories**

Mix measured quantity of **medicinal** substances with **sufficient quantity of theobroma oil**, triturate & soften with **dilute alcohol** and rub until a **smooth paste is formed.** Add remaining quantity of theobroma oil, when the **mass becomes plastic** by vigorous kneading of the pestle quickly remove **from the mortar with spatula.**

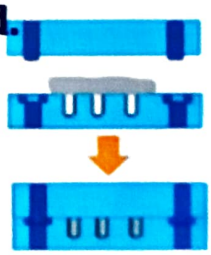
- **Transfer with spatula** to a piece of filter paper and keep in hands during the kneading and rolling procedure.
- **Roll the mass by hands** and immediately **place on a pill tile** and **forms a cylindrical suppository**, **Cut in pieces by spatula** and pack in proper container.

❖ **Compression molding**

- Mix **theobroma oil and drug**
- Mixture is forced into a **mould under pressure**, using a **wheel-operated press**
- Mould is removed, opened and replaced.
- On large-scale cold-compression machines are hydraulically operated by **water-jacketed cooling** and screw fed

❖ **Pour molding**

- Drug is dispersed or dissolved in a **melted suppository base.**
- Pour the mixture into **suppository moulds** and **allow cooling in ice bath**
- Finished suppositories are removed by **opening the mould.**
- Various types and sizes of moulds are available for preparation of suppositories.
- Moulds are made of **aluminum alloys**, **brass or plastic** and are available with from six to several hundred cavities.



POUR MOLDING METHOD PREPARATION OF SUPPOSITORIES

❑ DISPLACEMENT VALUE AND ITS CALCULATION

- "The **quantity** of the drug which **displaces one part** of the base is **known** as **displacement value**."

e.g. Determination of the displacement value of a medicament in Theobroma oil suppositories containing 40% medicament, prepared in 1 gm mould. The weight of 10 suppositories is 14.66 gm.

Solution:

- ✓ Wt. of 10 suppo. Cont. Theobroma oil alone prepared in 1 gm capacity mould = 1 x 10=10 gm.
- ✓ Wt.of 10 suppo. Cont. 40% of medicament = 14.66gm.
- ✓ Amt. of Theobroma oil present = 60/100 x 14.66=8.79 gm
- ✓ Amt. of medicament present = 40/100 x 14.66= 5.86 gm
- ✓ Amt. of Theobroma oil displaced by 5.86 gm of medicament = 10 – 8.79 = 1.20 gm So, Displacement value of medicament = **5.86/1.20 = 5 (Approx.)**

❑ EVALUATION OF SUPPOSITORIES

i. Appearance

- This includes **colour, odour, surface condition** and **shape** of suppositories.
- The suppository when **cut longitudinally** and examined with the **naked eye** the internal and external surfaces of the suppository **should be uniform in appearance.**
- Compliance with the standard indicates satisfactory subdivision and dispersion of suspended material.
- Surface appearance and colour can be **verified usually to assess** absence of **fissuring, absence of fissuring, absence of pitting, absence of exudation, absence of migration of the active ingredients**

II. Uniformity of weight test

- To perform this **20 suppositories are weighed** and **average weight is calculated.**
- **Then each suppository is weighed individually** and weight noted.
- No suppository should deviate from the average weight by more than **5% except that two should not** deviate by **more than 7.5%.**
- **The weight variation may result** if some cavities are **under filled and other are overfilled.**

UNIFORMITY OF WEIGHT

III. Melting Range Test

- This test is also called the **macro melting range test** and is a measure of the **time it takes for the entire suppository to melt** when immersed in a **constant-temperature (37°C) water bath**
- In contrast, the micro melting rang test in the melting range measured in **capillary tubes for the fat base only**
- The apparatus commonly used for measuring the melting range of the entire suppository is a **USP Tablet Disintegration Apparatus.**
- The suppository **melting point apparatus** by **ERWEKA**
- Consists of a **graduated tube** like **glass test chamber.**
- The suppository is completely **immersed in the constant water bath,** and the **time for the entire suppository to melt or disperse** in the surrounding **water is measured.**

IV. Liquefaction or Softening Time Tests of Rectal Suppositories

- It consists of a **U-tube partially submersed in a constant-temperature water bath**
- A constriction on one side **hold the suppository in place in the tube.**
- A glass rod is **placed on top of the suppository,** and the **time for the rod to pass** through to the constriction is **recorded as the softening time.**

- This can be carried out at various temperatures from 35.5 to 37°C, as a quality control check and can also be studied as a measure of physical stability over time.
- A water bath with both cooling and heating elements should be used to assure control with 0.1°C.

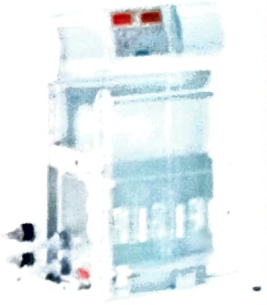
V. Breaking test/Hardness test

- Brittleness of suppositories is a problem for which various solutions have already been described.
- The breaking test is designed as a method for measuring the fragility or brittleness of suppositories.
- The apparatus used for the test consists of a double-wall chamber in which the test suppository is placed.

- Water at 37°c is pumped through the double walls of the chamber, and the suppository contained in the dry inner chamber, supports a disc to which a rod is attached.
- The other end of the rod consists of another disc to which weights are applied.
- The test is conducted by placing 600 g on the platform.
- At 1-min intervals, 200-g weights are added, and the weight at which the suppository collapses is the breaking point, or the force that determines the fragility or brittleness characteristics of the suppository.
- Differently shaped suppositories have different breaking points.
- The desired breaking point of each of these variously shaped suppositories is established as the level that withstands the break forces caused by various types of handling i.e., production, packaging etc.

VI. Dissolution Testing

- Testing for the **rate of in vitro release of drug** substances from suppositories has always posed a difficult problem, owing to melting deformation, and **dispersion in the dissolution medium.**
- Early testing was carried out by simple placement in a **beaker containing a medium.**
- In an effort to control the variation in **mass or medium interface**, various means have been employed, including a wire mesh basket, or a membrane, **to separate the sample chamber from the reservoir**



- **Flow cell apparatus** have been used, **holding the sample in place** with cotton, **wire screening** and most **recently with glass beads.**

PHARMACEUTICAL INCOMPATIBILITIES

Contents to be covered in this topic

- INTRODUCTION
- PHYSICAL INCOMPATIBILITY
- CHEMICAL INCOMPATIBILITIES
- THERAPEUTIC INCOMPATIBILITY

PHARMACEUTICAL INCOMPATIBILITIES

INTRODUCTION

Incompatibilities is the result of prescribing or **mixing two or more substances** which are **antagonist in nature** and an undesirable product is formed which may affect the safety, purpose or appearance of the preparation.

It is usually un intentional. It may occur in-vitro between drugs and other components during preparation, storage or administration.

Incompatibility may be -

(a) Pharmaceutical/Physical Incompatibility

(b) Therapeutic Incompatibility

(c) Chemical Incompatibility

PHYSICAL INCOMPATIBILITY

In this type of incompatibility a **visible physical change** takes place. An **unacceptable, non-uniform, unpalatable** product is formed.

It is a result of **insolubility and immiscibility, Precipitation, liquefaction, adsorption** and **complexation** of solid materials

physical incompatibilities can be corrected by one or more methods:

- **Order of mixing**
- **Alteration of solvents**
- **Change in the form of ingredients**
- **Alteration of volume**
- **Emulsification**
- **Addition of suspending agent**
- **Addition, substitution of therapeutically inactive substances**

Examples of physical incompatibility :

1. IMMISCIBILITY

- **Is the result of the mixture of two or more immiscible liquid or an immiscible solid with a liquid.**
- **Acceptable liquid product can be obtained by emulsification**

Methods of correction of immiscibility can be overcome by:

- **Vigorous shaking / stirring**
- **Emulsification or solubilization**

2. INSOLUBILITY

Liquid preparation with **indiffusible solids** (e.g. Sulphamethoxasole, phenacetin, Zinc oxide, calamine etc.) a **suspending agent is required** to uniform distribution of the solids in the liquid phase

Methods of correction of Insolubility

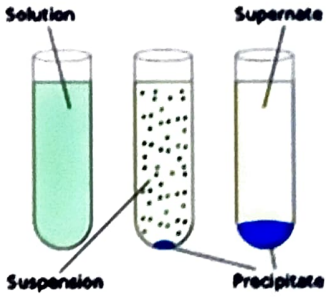
Cosolvency: example, we may use alcohol, propylene glycol, syrups.

Complexation: example, formation of tri-iodide complex, complexation of caffeine with Sodium Benzoate

Hydro trophy: example, Hyoscyamine with tween.

Solubilization: example, Fats soluble vitamins, certain antibiotics.

3. PRECIPITATION



- A solubilized substance may precipitate from solution if a **non-solvent** (i.e. a solvent in which the drug is insoluble) **is added** to the solution.

4. LIQUEFACTION

- Some **low melting point solids sometimes liquefy when mixed together** due to the formation of **eutectic mixture or liberation of water. e.g: Menthol, Thymol, Camphor, Phenol, Naphthol and chloral hydrate** When mixed together forms **eutectic mixtures**
- The **eutectic forming ingredient** may either be **dispensed separately** or these may be mixed separately with enough quantity of adsorbent powder

Methods of rectifying liquefaction :

Use of absorbent like **kaolin, light magnesium carbonate**

Techniques to rectify :

Order of mixing, Alteration of solvent, Change in the form of ingredients, Alteration of volume, Emulsification, Addition of suspending agents, Addition/Substitution/omission of therapeutically inactive substance.

CHEMICAL INCOMPATIBILITIES

- When a **chemical interaction** takes place among the **ingredients of a prescription**
- Such interactions may take place immediately upon **compounding** then these are termed as immediate incompatibilities
- It is due to **oxidation- reduction, acid base hydrolysis or combination reactions.**
- These reactions may be noticed by **effervescence, decomposition, colour change.**
- It may be as a result of chemical interactions between the **ingredients of a prescription** and **a toxic or inactive product** may be formed.

Chemical incompatibilities are of two types:

(a) **Tolerated:** This reaction can be minimized by applying some suitable order of mixing or mixing the solution in dilute form but no change in the active ingredients of the preparation

(b) **Adjusted:** The reaction is **prevented by addition or substitution of one of the reacting substances** with another of equal therapeutic value but does not affect the medicinal value of the preparation.

e.g. of Chemical Incompatibilities: Alkaloidal Incompatibility

Types of Chemical Changes

1. **Oxidation**
2. **Hydrolysis**
3. **Polymerization**
4. **Isomerization**

THERAPEUTIC INCOMPATIBILITY

It may be the result of prescribing certain drugs to the patient with the intention to produce a specific degree of action but the nature or the intensity of the action produced is different from that intended by the prescriber

Therapeutic Incompatibility occurs due to the following reasons:

It may be due to the administration of:

(a) Overdose

(b) Improper or wrong dosage form

(c) Contraindicated drug
(d) Synergistic and antagonistic drugs
(e) Drug interactions

(a) Over dose :

Many therapeutical incompatibility results from **errors in writing the prescription.** The most serious type is **over dose** of a dosage form.

This is the **duty of pharmacist to check the dose** which is **written in the prescription** before **dispensing the medicine to patient**

(b) Wrong dosage form:

There are some drugs which have almost similar names and there are possibilities of dispensing **wrong drug.**

(c) Contraindicated Drugs:

There are certain drugs which may be contraindicated in a particular disease. Penicillin and sulphonamides are not prescribed for those patients who are allergic to it also corticosteroids are never prescribed in peptic ulcer condition.

(d) Drug interaction:

The effect of drug is changed by either prior administration or simultaneous administration of **another drug**

(e) Synergism:

When two drugs are given together the effect of each drug is increased, this is known as synergistic effect. Synergism is usually intentional as the prescriber has given the combination of two drugs which **increases the activity of the drugs.**

(f) Antagonism:

When two drugs are given together and one drug **opposes the pharmacological activity** of another drug it is known as antagonism.