

SUPPOSITORIES

CHAPTER 7(c)

Syllabus:

Factors affecting drug absorption from rectal suppositories, suppository bases, preparation of suppository, packing and storage.

Questions:

1. Define suppositories and displacement value. (98) [4]
 2. Discuss different suppository bases. (98) [4]
 3. Write in brief, the preparation, packing and storage of suppositories (98) [4]
 4. Give the ideal properties of suppository bases.
 5. Discuss the problems encountered in manufacturing of suppositories such as hygroscopicity, incompatibilities, viscosity etc. (96) [8]
 6. Short note on packing of suppositories. (95) [4]
 7. Short notes on suppository bases. (93) [4]
 8. Factors affecting drug absorption from rectal suppositories. (93) [4]
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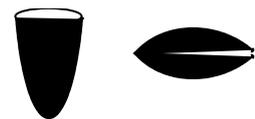
DEFINITION

Definition:

- Suppositories are specially shaped solid dosage form of medicament for insertion into body cavities other than mouth.
- They may be inserted into rectum, vagina or the urethra.
- These products are so formulated that after insertion, they will either melt or dissolve in the cavity fluids to release the medicament.

TYPES OF SUPPOSITORIES

1. Rectal suppositories: These are meant for introduction into the rectum for local and systemic effect.



2. Pessaries: These are meant for introduction into vagina for local action. These are larger than rectal suppositories (3 – 6 gm).



Pear

Cone

Rod

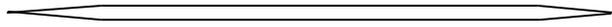
3. Urethral bougies: These are meant for introduction into urethra.



Weight: 2 – 4 gm Length: 2 – 5 inches.

4. Nasal bougies: These are meant for introduction into nasal cavities.

Weight: 1gm Length: 9 – 10 cm



Advantages of rectal suppositories:

(i) *Mechanical action:* The rectal suppositories are extensively used as a mechanical aid to bowel evacuation which produce its action by either irritating the mucous membrane of the rectum (e.g. glycerol and bisacodyl) or by lubricating action or by mechanical lubrication.

(ii) *Local action:* The rectal suppositories may be used for soothing, antiseptic, local anaesthetic action or for astringent effect. Therefore, they may contain

soothing e.g. zinc oxide

local anaesthetic- e.g. cinchocaine, benzocaine

astringents e.g. bismuth subgallate, hamamelis extract and tannic acid

antiinflammatory e.g. hydrocortisone and its acetate.

(iii) *To provide systemic action:* Suppositories are convenient mode of administration of drugs which irritate the gastrointestinal tract, cause vomiting, are destroyed by the hepatic circulation, or are destroyed in the stomach by pH changes, enzymes etc.

Partial bypass: The lower portion of the rectum affords a large absorption surface area from which the soluble substances can absorb and reach the systemic circulation.

e.g. *aminophylline* used in asthmatic and chronic bronchitis.

morphine a powerful analgesic

ergotamine tartarate used to treat migraine

indomethacin and phenyl butazone analgesic and anti-

inflammatory actions.

Systemic treatment by the rectal route is of particular value for

- (a) treating patients who are unconscious, mentally disturbed or unable to tolerate oral medication because of vomiting or pathological conditions of the alimentary tract.
- (b) administering drugs, such as aminophylline, that cause gastric irritation, and
- (c) treating infants.

PROPERTIES OF IDEAL SUPPOSITORY BASE

1. It should melt at rectal temperature (36°) or dissolve or disperse in body fluid. For eutectic mixtures and in tropical climate the melting range of the base should be higher.
2. Release medicaments easily.
3. Shape should remain intact while handling.
4. Non-toxic and non-irritant to sensitive and inflamed mucous membrane.
5. It should be stable on storage i.e. it does not change color, odor, or drug release pattern.
6. Compatible with broad variety of drug and adjuvants.
7. It should shrink so that it comes out easily from the mould without the use of any lubricants.

For fatty bases the following additional specifications are required:

8. "Acid value" is below 0.2
9. "Saponification value" ranges from 200 to 245
10. "Iodine value" is less than 7
11. The interval point and solidification point is small.

SUPPOSITORY BASES

Classification of suppository bases

1. *Fatty bases* – they melt at body temperature.
2. *Water-soluble or water miscible base* – they dissolve or disperse in rectal secretions.
3. *Emulsifying bases* – they emulsifies small amount of aqueous solution of drug.

FATTY BASES

Example: Theobroma oil (Cocoa butter), Synthetic fats.

Theobroma oil (Cocoa butter)

- It is a yellowish-white solid having chocolate flavor.

- It is a mixture of glyceryl esters of stearic, palmitic, oleic and other fatty acids.

Advantages:

- (a) A melting point range of 30 to 36 °C; hence it is solid at normal room temperatures but melts in the body.
- (b) Ready liquefaction on warming and rapid setting on cooling.
- (c) Miscibility with many ingredients.
- (d) Blandness i.e. does not produce irritation.

Disadvantages:

(a) Polymorphism

Cocoa butter has three polymorphs α -crystals (unstable, m.p. 20°C), β -crystals (stable, m.p. 36°C) and γ -crystals (unstable, 15°C).

When melted and cooled it solidifies in different crystalline forms, depending on the temperature of melting, rate of cooling and size of the mass. If melted below 36°C and slowly cooled it forms stable β -crystals with normal melting point, but if over-heated it may produce, on cooling, unstable γ -crystals, which melt at about 15°C, or α -crystals, melting at about 20°C. These unstable forms eventually return to the stable condition but this may take several days and meanwhile, the suppositories may not set at room temperature or, if set by cooling, may remelt in the warmth of the patient's home.

This lowering of the solidification point can also lead to sedimentation of suspended solids. Consequently, great care must be taken to avoid over-heating the base when making theobroma oil suppositories.

(b) Adherence to mould

Because theobroma oil does not contract enough on cooling to loosen the suppositories in the mould, sticking may occur, particularly if the mould is worn. This is prevented by lubricating the mould before use.

(c) Softening point too low for hot climates

To raise the softening point, white beeswax may be added to theobroma oil suppositories intended for use in tropical and subtropical countries.

(d) Melting point reduced by soluble ingredients

Substances, such as chloral hydrate, that dissolve in theobroma oil, may lower its melting point to such an extent that the suppositories are too soft

for use. To restore the melting point, a controlled amount of white beeswax may be added.

(e) Slow deterioration during storage

This is due to oxidation of the unsaturated glycerides.

(f) Poor water absorbing capacity

This fault can be improved by the addition of emulsifying agents.

(g) Leakage from the body

Sometimes melted base escapes from the rectum or vagina. This is most troublesome with pessaries because of their larger size, and therefore, these are rarely made with theobroma oil.

(h) Relatively high cost

Synthetic fats

As a substitute of theobroma oil a number of hydrogenated oils, e.g. hydrogenated edible oil, arachis oil, coconut oil, palm kernel oil, stearic and a mixture of oleic and stearic acids are recommended.

[N.B. Synthetic suppositories bases are by hydrogenation and subsequent heat treatment of vegetable oils such as palm oil and arachis oil. The oils are generally esters of unsaturated fatty acids. Hydrogenation saturates the unsaturated fatty acids and heat treatment splits some of the triglycerides into fatty acids and partial esters (mono- and di-glycerides).]

Advantages of these synthetic fats over theobroma oil:

1. Their solidifying points are unaffected by overheating.
2. They have good resistance to oxidation because their unsaturated fatty acids have been reduced.
3. Their emulsifying and water absorbing capacities are good. [They usually contain a proportion of partial glycerides some of which, e.g. glyceryl monostearate, are w/o emulsifying agents and, therefore, their emulsifying and water absorbing capacity are good.
4. No mould lubricant is required because they contract significantly on cooling.
5. They produce colorless, odourless and elegant suppositories.

Disadvantages:

1. They should not be cooled in refrigerator because they become brittle if cooled quickly. Certain additives e.g. 0.05 % polysorbate80, help to correct this fault.
2. They are more fluid than theobroma oil when melted and at this stage sedimentation rate is greater. Thickeners such as magnesium stearate , bentonite and colloidal silicon dioxide, may be added to reduce this.

WATER SOLUBLE AND WATER MISCIBLE BASES

Glycero-Gelatin base

- This is a mixture of glycerol and water made into a stiff jelly by adding gelatin.
- It is used for the preparation of jellies, suppositories and pessaries. The stiffness of the mass depends upon the proportion of gelatin used which is adjusted according to its use.
- The base being hydrophilic in nature, slowly dissolves in the aqueous secretions and provide a slow continuous release of medicament. Glycerogelatin base is well suited for suppositories containing belladonna extract, boric acid, chloral hydrate, bromides, iodides, iodoform, opium, etc.
- Depending upon the compatibility of the drugs used a suitable type of gelatin is selected for the purpose. Two types of gelatins are used as suppository base
 - (i) Type-A or Pharmagel-A which is made by acid hydrolysis (has isoelectric point between 7 to 9 and on the acid side of the range behaves as a cationic agent, being most effective at pH 7 to 8.) is used for acidic drugs.
 - (ii) Type-B or Pharmagel-B which is prepared by alkaline hydrolysis (having an isoelectric point between 4.7 to 5 and on the alkaline side of the range behaves as an anionic agent, being most effective at pH 7 to 8) is used for alkaline drugs

Disadvantages:

Glycerogelatin base suppositories are less commonly used than the fatty base suppositories because:

- (i) Glycerol has laxative action.
- (ii) They are more difficult to prepare and handle.
- (iii) Their solution time depends on the content and quality of the gelatin and the age of the base.
- (iv) They are hygroscopic, hence must be carefully stored.

(v) Gelatin is incompatible with drugs those precipitate with the protein e.g. tannic acid, ferric chloride, gallic acid, etc.

Soap-Glycerin Suppositories

- In this case gelatin and curd soap or sodium stearate which makes the glycerin sufficiently hard for suppositories and a large quantity of glycerin up to 95% of the mass can be incorporated.
- Further the soap helps in the evacuation of glycerin.
- The soap glycerin suppositories have the disadvantage that they are very hygroscopic, therefore they must be protected from atmosphere and wrapped in waxed paper or tin foil.

Polyethylene glycol bases / Macrogol bases (Carbowaxes)

Depending on their molecular weight they are available in different physical forms.

Examples of Macrogol bases:

	I	II	III	IV
Macrogol 400	-	-	20	-
Macrogol 1000	-	-	-	75
Macrogol 1540	33	33	-	25
Macrogol 4000	47	47	47	-
Macrogol 6000	20	20	-	-
Water				

By choosing a suitable combination a suppository base with the desired characteristics can be prepared.

Advantages:

1. The mixtures generally have a melting point above 42⁰C, hence, does not require cool storage and they are satisfactory for use in hot climate.
2. Because of the high melting point they do not melt in the body cavity, rather they gradually dissolve and disperse, releasing the drug slowly.
3. They do not stick to the wall of the mould since they contract significantly on cooling.

EMULSIFYING BASES

These are synthetic bases and a number of proprietary bases of very good quality are available, few of which are described below:

Witepsol

They consist of triglycerides of saturated vegetable acids (chain length C12 to C18) with varying proportions of partial esters.

Massa Esterium

This is another range of bases, consisting of a mixture of di-, tri- and mono-glycerides of saturated fatty acids with chain lengths of C11 to C17.

Massuppol

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

Advantages of these bases over cocoa butter:

1. Over heating does not alter the physical characteristics.
2. They do not stick to the mould. They do not require previous lubrication of the mould
3. They solidify rapidly.
4. They are less liable to get rancid.
5. They can absorb fairly large amount of aqueous liquids.

FACTORS AFFECTING-ABSORPTION FROM RECTAL SUPPOSITORIES

A. Physiologic factors

The lower hemorrhoidal veins surrounding the colon and rectum directly goes to heart and the upper hemorrhoidal vein connects to liver via portal vein. So more than 50 to 70% of the drug administered rectally were found to directly passing to systemic circulation (i.e. bypassing the liver).

pH of rectal secretion

The principal method of drug absorption from the rectum is by passive diffusion. So a drug that remains mostly in unionized state will be absorbed more readily. Generally weakly basic and weakly acidic drugs remains in unionized state in the pH of rectum (6.8) and hence, absorbed readily than the stronger base or acids.

B. Physicochemical characteristics of the drug

The sequence of events that takes place before absorption in the anorectal area is as follows:

Drug in vehicle → Drug in colon fluids → Absorption through the rectal mucosa

- *Partition coefficient:* Drugs with a high fat to water (K_o/w) partition coefficient are liberated very slowly from the fatty bases. So water soluble salt forms of drugs are more readily absorbed from anorectal area.

- *Rectal fluid volume*: Rectal fluid volumes also vary in different time and in different individuals. This influences the release rate and absorption of drug from suppository bases.
- *Physical state of medicament*: When a drug remains in suspension state in a suppository the drug particles should be very fine, so that the effective surface area is very high and thus dissolution rate is very high. Solution from a suppository will be faster when it melts quickly into a fluid of low viscosity that spreads into thin film over a large area in the rectum. Generally, for *local action* fatty base is suitable and for *systemic action* water-soluble base is better for providing the quick release desirable for systemically active drugs.
- *Presence of surfactants*: Surfactants can both increase or decrease the absorption rate of a drug from anorectal region. Surfactants can reduce the surface tension of the colon fluid → help in washing the rectal mucosa, → new pores for absorption will be opened → absorption is accelerated.

C. Physicochemical characteristics of the base and adjuvants.

- Lower m.p. fatty base + sodium phenobarbitone → absorption rate is faster than higher m.p. fatty base + sod.phenobarbitone.
- High molecular weight PEG bases produces faster absorption than low molecular weight PEG base.
- Fatty bases may be hardened several months after molding, these increase in melting range decrease the drug release.
- Adjuvants in the base changes the rheologic characteristics of the base or may affect the dissolution of the drug.
 - e.g. addition of colloidal silicon oxide to fatty base dramatically changes the rheologic characteristics of the base.
 - e.g. Salicylates were found to improve the rectal absorption of water-soluble antibiotics in lipophilic bases.
- Emulsifying agents such as wool fat, wool alcohols, macrogols, stearates and polysorbates, may be included in the suppository bases to facilitate the incorporation of aqueous solutions. They may cause unpredictable release and absorption of a medicament.
- Large amount of emulsifying agents may cause excessive foaming.
- Strong surface active agent may produce increased absorption of drug and may produce toxic effects.

MANUFACTURING OF SUPPOSITORIES

Moulds

The suppository and pessary moulds are made of metals and have four, six or twelve cavities. By removing a screw, they can be opened longitudinally for lubrication, extraction of the suppositories and cleaning. [N.B. The interior of the mould should never be scrapped or rubbed with abrasive. For cleaning they are immersed in hot water containing detergent, wiped gently with soft cloth and rinsed thoroughly.]

Capacity of moulds: The nominal capacities of the common moulds are 1g, 2g, 4g and 8g.

Calibration

The nominal capacity of a mould varies with the base selected. Each mould should be calibrated before use by preparing a set of suppositories or pessaries using the base alone, weighing the products and taking the mean weight as the true capacity. This procedure is repeated for each base.

Displacement value

The volume of a suppository from a particular mould is uniform but its weight will differ with the density of the base.

Definition

It is the quantity of the drug that displaces one part of the base. e.g. Zinc oxide, $D = 5$.

Calculation of displacement value

Formula for calculation of the amount of base required in each mould

$$\text{Amount of base required for each suppository (gm)} = \text{Capacity of each mould (gm)} - \frac{\text{Dose of drug (gm)}}{\text{Displacement value of the drug}}$$

Lubrication of mould

If the cavities are imperfect, i.e. poorly polished or scratched, it may be difficult to remove the suppositories without damaging their surfaces. So lubrication of the moulds is necessary.

In case of greasy or oily base water soluble lubricants are required.

e.g. For cocoa butter the following lubricant solution formula may be used:

Soft soap	10g
Glycerol	10ml
Alcohol(90%)	50ml

For water soluble /miscible bases oily lubricant may be used. e.g. For glycerogelatin base liquid paraffin or arachis oil may be used as lubricant.

Four methods are used in preparing suppositories:

1. Hand molding [Cold Hand Shaping]

1. Drug is triturated in a mortar into fine powder.
2. Cocoa butter is grated into small particles.
3. Drug is mixed with small portion of cocoa butter in a mortar.
4. One drop fixed vegetable oil is added to give plasticity to the mass.
5. Remainder of the cocoa butter is added by geometric dilution (i.e. by adding the same amount of base as is already in the mortar), triturated with pressure. Heat generated by trituration results in a plastic mass, which is cohesive and ready to roll.
6. The mass is scrapped from the mortar with a spatula and rolled into a ball.
7. An ointment tile is taken, dusted lightly with starch powder, ball is placed on it, rolled with a flat faced spatula to form a cylinder. The cylinder is cut into desired number of pieces with a sharp blade.
8. One end of a suppository is held firmly with a finger and the other end is tapered with the spatula to give the shape of suppository.

2. Compression molding

In this case an instrument known as *compression mould* is used.

1. Drug is powdered and mixed with grated cocoa butter.
2. The mixture is filled into a chilled cylinder. The mixture is pressed within the cylinder by a piston until a pressure is felt.
3. Then the suppositories are expelled from the cylinder.

3. Pour molding (Fusion method)

This is the main method of preparing suppositories.

1. Drug is powdered in a mortar.
2. Carefully grated cocoa butter is taken into a beaker and heated in a water bath. When $2/3^{\text{rd}}$ portion is melted the beaker is taken out of the heat source. The rest of the mass is melted by stirring with a glass rod. [If cocoa butter is heated to clear liquid then unstable α , and γ - crystals will form and the suppositories will remain in melted state at room temperature.]
3. Drug is added into the beaker and stirred thoroughly to mix with the “creamy” base.

4. The “creamy” melted base is then poured into previously lubricated mould.
5. The mould is allowed to congeal, then placed in the refrigerator for 30 minutes to harden (forms stable β -crystal after 24 hours of refrigeration).
6. Mould is taken out from the refrigerator and surface is trimmed off. The mould is opened and the suppositories are expelled out of the mould by gentle pressure with the finger.

4. Automatic molding machine

Two types of molding machines are available: (a) rotary molding machine and (b) straight-line molding machine

Manufacturing cycles in rotary molding machine:

1. Prepared mass is filled in a into a filling hopper where it is continuously mixed and maintained at constant temperature.
2. The suppository molds are lubricated by brushing or spraying lubricant solution.
3. The molten mass is filled in the molds to a slight excess.
4. The mass is *cooled* to solidify and the excess material is *scrapped off* and collected for re-use.
5. In the ejecting section the mold is opened and the suppositories are pushed out by steel rods.
6. The mold is closed, and then moved to the first step of the cycle.

The output of a typical rotary machine ranges from 3500 to 6000 suppositories an hour.

Manufacturing cycles in straight-line molding machine:

Here the cycle is similar to rotary molding machine but the individual molds are carried on a track through a cooling tunnel, where scrape-off and ejection occur.

PACKAGING OF MOLDED SUPPOSITORIES

Objective: The suppositories should be over-wrapped, or they must be placed in a container in such a way that they do not touch each other.

Why packing is required?

Suppositories in contact with one another may fuse with one another or with the container at room temperature.

Packing materials: Suppositories are usually over-wrapped in aluminium foils, paper strip or plastic strips.

Packaging machines

1. *Machine-I:* The chilled-hardened suppositories are placed in a notched turntable and then fed to the packing station, where the foil is unwound from a roll, cut to size, and finally rolled around each suppository.
2. *Machine-II:* The suppositories are enclosed in cellophane or heat-sealed aluminium foils. Plastic may be thermoformed into two packaging halves. Suppository is mechanically placed in one half and the second half of plastic is sealed by heat.

Bulk storage

The individually wrapped suppositories are packaged in slide, folding, or set-up boxes.

Suppositories containing hygroscopic or volatile material are packed in glass or plastic containers.

Many suppositories are not individually over-wrapped. They are placed in sectioned card-board boxes or plastic containers to hold 6 or 12 suppositories.

In-package molding

In this automatic method individual suppository is molded in their wrapping material. Either plastic or aluminium foil/propylene/lacquer laminate are used.

Advantage: If the suppository melts at higher storage temperature their shapes are retained which can be used just by chilling again.

In *plastic* wrapping the plastic is thermoformed into the shape of mould. The molten mass is injected through the top end and top is cooled and sealed.

In *aluminium foil* method two aluminium foils are embossed and sealed to give the shape of a mold and then the mass is injected at the top and then the top is cooled and sealed.

SPECIFIC PROBLEMS IN FORMULATING SUPPOSITORIES

1. Water in suppositories

Water is used as a solvent to incorporate a water-soluble substance in the suppository base. Incorporating water should be avoided for the following reasons.

- (a) Water accelerates the oxidation of fats.
- (b) If the water evaporates the dissolved substances crystallize out.
- (c) In presence of water reactions between various ingredients of suppositories may occur.
- (d) The water may be contaminated with bacteria or fungus.

3. Hygroscopicity

Glycerinated gelatin suppositories lose moisture in dry climates and absorb moisture in high humidity.

Polyethylene glycol bases are also hygroscopic.

4. Incompatibilities

Polyethylene glycol bases are incompatible with silver salts, tannic acid, aminopyrine, quinine, ichthammol, aspirin, benzocaine, iodochlorohydroxyquin, and sulfonamides.

Many chemicals have a tendency to crystallize out of PEG e.g. sodium barbital, salicylic acid and camphor.

5. Viscosity

Viscosity of melted base is low in cocoa butter and high in PEG and glycerinated gelatin. Low viscosity base when melted the suspended particles may sediment very quickly producing nonuniform distribution of drugs.

Remedies:

- (a) The base should be melted at the minimum temperature required to maintain the fluidity of the base.
- (b) The base is constantly stirred in such a way that the particles cannot settle and no air is entrapped in the suppository..
- (c) A base with a narrow melting range closer to rectal temperature is used.
- (d) Inclusion of approximately 2% aluminium monostearate increase the viscosity of the fatty base and also helps in homogeneous suspension of particles.
- (e) Cetyl, stearyl, myristyl alcohol or stearic acid are added to improve the consistency of suppositories.

6. Brittleness

Cocoa butter base is not brittle but synthetic fat bases with high degree of hydrogenation and high stearate containing bases are brittle.

Brittle suppositories produce trouble during manufacture, handling, packaging and during use.

Causes: Rapid chilling (shock cooling) of the melted bases in an extremely cold mold.

Remedies:

(a) The temperature difference between the melted base and mold should be as small as possible.

(b) Addition of small amount of Tween80, castor oil, glycerin or propylene glycol imparts plasticity to a fat and make it less brittle.

7. Volume contraction

When the bases are cooled in the mould volume of some bases may contract.

Volume contraction produces

(a) good mold release facilitating the ejecting from mold.

(b) contraction hole formation at the top: This imperfection can be solved by adding slight excess base over the suppositories and after cooled the excess is scrapped off.

8. Lubricants

Cocoa butter adheres to suppository molds because of very low volume of contraction. Aqueous lubricant may be used to remove the suppositories easily from the molds. They are applied by wiping, brushing or spraying.

The mold surfaces may be coated with teflon to reduce the adhesion of base to mold wall.

9. Rancidity & oxidation

Due to auto oxidation of unsaturated fatty acids present in the base, saturated and unsaturated aldehydes, ketones and acids may formed, which have very strong unpleasant odor – this phenomenon is called rancidification. To prevent this suitable antioxidants like hydroquinone, β -naphthoquinone, α - and β -tocopherols, *gossypol* (present in cotton seed oil), *sesamol* (present in sesame oil) propyl gallate, gallic acid, tannins and tannic acids, ascorbic acid (Vit C.), butylated hydroxyanisole (BHA) and butylated hydroxyanisole (BHA).