Suppositories are **solid bodies** of various weights and shapes, adapted for introduction into the **rectal, vaginal, or urethral** orifice of the human body.

A suppository may act as a **protectant** or palliative to the local tissues at the point of introduction or as a carrier of therapeutic agents for **systemic or local action**.

They usually **melt, soften, or dissolve** at body temperature.
Uses

- **Local** (rectum, vagina, or urethra) or **Systemic** Effect

**Advantages**
- Viable administration route in patients with nausea or vomiting, who are unconscious, severely debilitated, or infants/small children
- Route does not have taste limitations
- Avoid gastric acid (drug degradation) and hepatic first-pass metabolism

**Disadvantages**
- Rectal absorption potentially interrupted by defecation
- Relatively smaller area for absorption (as compared to entire GI tract)
- Less fluid volume may cause problems with drug dissolution or absorption
- Absorption of most drugs is erratic and unpredictable
- Patient’s do not prefer this route due to administration difficulties

**Often suppositories are dosage form of “last resort.”**
Suppository Bases

- **Classes of Suppository Bases**
  - Oleaginous bases (e.g. Cocoa Butter)
  - Cocoa butter substitutes (e.g. Fattibase)
  - Polyethylene Glycol (PEG) bases (e.g. Polybase)
  - Glycerinated Gelatin
  - Surfactant Bases

- **Common, Desired Properties**
  - chemically and physically stable
  - non-toxic, non-sensitizing, and non-irritating
  - expansion and contraction characteristic
  - absorb some water
  - proper viscosity
Cocoa Butter is the fat from the seeds of chocolate beans.

Cocoa Butter suppositories are solid at room temperature (25°C) but when inserted into the body, melt at higher body temperatures (31-34°C).

**Advantages**
- Nonirritating to sensitive membrane tissues
- Excellent emollient
- Available in grated form (saves time)

**Disadvantages**
- May give poor and somewhat erratic release of some drugs
- Store products under refrigeration to avoid softening or melting prior to use.
- *Cocoa butter can very easily be overheated* causing it to form a lower-melting polymorph.

**Melting Procedure (low and slow)**
Cocoa Butter Substitutes (Fattibase)

- Fat-type suppository bases produced from a variety of vegetable oils.
- These products have the **advantages** of Cocoa Butter but with **less** risk of polymorphs.
- Fattibase (or Witepsol) is a commonly used Cocoa Butter Substitutes employed by compounding pharmacists.
  - The base should be heated slowly and evenly to 49–54°C before adding the active ingredients.
    - Remember that Cocoa Butter’s melting point was 34°C, which is far less than the 49–54°C tolerated by Fattibase.
  - However, it should not be heated above 60°C, and the use of microwave ovens for heating the base is not recommended.
  - Fattibase suppositories release well from molds but a light spraying with vegetable oil can be used if needed.
Commonly used example is Polybase

PEG suppository bases are formulated so they do not melt at body temperature, but rather *dissolve in body fluids*.

**Advantages**
- Primarily used for vaginal suppositories
- Can be melted using a microwave
- Can provide more reliable release of drug
- Do not require mold lubrication
- Do not require carefully monitored storage temperatures

**Disadvantages**
- Irritating to body cavity tissues
- Interact with polystyrene, the plastic often used for prescription vials
Selecting a Suppository Base

- Factors to consider
  1. Patient Comfort – fatty-type bases are more comfortable for patients than are PEG bases.
  2. Compatibility and stability – in most cases, fatty bases are less reactive than PEG bases so they have fewer compatibility and stability problems with incorporated therapeutic agents.

- The practical selection of suppository base material depends on:
  - the intended use (systemic versus local effect)
  - the route of administration (rectal, vaginal, or urethral)
    - **Fatty bases are preferred for rectal suppositories**
    - **PEG bases are preferred for vaginal and urethral suppositories**
Compounding Methods

- **Hand Rolling**
  - Advantages
    - Hand-rolled suppositories do not require special calculations.
    - Special equipment is not required for this method.
    - Cocoa butter is the base used for hand-rolled suppositories.
  - Disadvantages
    - Preparing and forming hand-rolled suppositories requires experience and good technique.
    - Hand-rolled suppositories do not have an elegant appearance.

- **Fusion**
  - Advantages
    - This method does not require well-developed manual compounding technique.
    - Suppositories made by fusion have an elegant, professional appearance.
  - Disadvantages
    - Special suppository molds are required to make suppositories by fusion.
    - Caution must be used when incorporating drugs sensitive to heat.
    - Because the components are dosed and measured by weight but compounded by volume, density calculations, mold calibrations, or double-casting procedures are required to give accurate doses.
Suppository Molds

- Plastic, Disposable, “Shells”
- Aluminum/Metal
- Flexible Rubber
Fusion Method – Density & Volume

- Base components and active ingredients are solids and are measured by weight.
- However, the components are melted, combined & poured into suppository mold cavities.
- This means that the dosage unit is created by volume (e.g. the volume of the mold cavity).
- The final amount of drug in a dosage unit therefore depends on three factors:
  - The w/w concentration (%) of active ingredient in the base material
  - The volume of the mixture contained in each mold cavity.
  - The density of the molten mixture.
- Example:
  - Depending on the density of the melted mixture of ingredients, the weight of a suppository formed from a 2 mL cavity can vary.
    - Water, density = 1.0 g/mL × 2 mL = 2 g
    - Cocoa butter, density = 0.86 g/mL × 2 mL = 1.72 g
    - PEG 400, density = 1.125 g/mL × 2 mL = 2.25 g
Density Displacement Factor (DDF)

- When a drug is placed in a suppository base it will displace an amount of base as a function of its density.

- A Density Displacement Factor (DDF) is used to determine how much base a drug will displace.

- DDF Definition: “the weight of drug, in grams, that will displace 1 gram of base”
  - Example: 0.5 g boric acid in cocoa butter, DDF = 1.5
    
    \[
    \frac{1.5 \text{ g BA}}{1 \text{ g CB}} = \frac{0.5 \text{ g BA}}{X \text{ g CB}} = 0.3 \text{ g CB is displaced by 0.5 g of BA}
    \]

- DDF’s will be specific for a drug (and excipient) in a particular base.
  - What if a DDF is not available for a particular drug in a particular base?
    - Double Casting Method of DDF determination
    - Paddock Method of DDF determination
# DDF for common drugs in Cocoa Butter

<table>
<thead>
<tr>
<th>Medication</th>
<th>Factor</th>
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<th>Factor</th>
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<tbody>
<tr>
<td>Alum</td>
<td>1.7</td>
<td>Opium</td>
<td>1.4</td>
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<tr>
<td>Aminophylline</td>
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<td>Paraffin</td>
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<tr>
<td>Aspirin</td>
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<td>Pentobarbital</td>
<td>1.2</td>
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<tr>
<td>Belladonna extract</td>
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<td>Peruvian Balsam</td>
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<td>Benzoic acid</td>
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<td>Phenobarbital</td>
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<tr>
<td>Bismuth salicylate</td>
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<td>Phenol</td>
<td>0.9</td>
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<tr>
<td>Boric acid</td>
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<td>Potassium bromide</td>
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<tr>
<td>Castor oil</td>
<td>1</td>
<td>Procaine</td>
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<tr>
<td>Chloral hydrate</td>
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<td>Quinine hydrochloride</td>
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<tr>
<td>Cocaine hydrochloride</td>
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<td>Resorcinol</td>
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<td>Codeine phosphate</td>
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<td>Salicylic acid</td>
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<td>Digitalis leaf</td>
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<td>Secobarbital sodium</td>
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<td>Diphenhydramine HCl</td>
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<td>Tannic acid</td>
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<tr>
<td>Glycerin</td>
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<td>White wax</td>
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<td>Ichthammol</td>
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<td>Witch hazel fluidextract</td>
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<tr>
<td>Menthol</td>
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<td>Zinc oxide</td>
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<tr>
<td>Morphine hydrochloride</td>
<td>1.6</td>
<td>Zinc sulfate</td>
<td>2.8</td>
</tr>
</tbody>
</table>
DDF – Double Casting Technique

- Determine the average weight of a trimmed suppository from a mold using only base (e.g. cocoa butter).

- The total quantity of drug is mixed with an amount of base that is inadequate to fill the number of cavities.

- The mixture is poured into the mold, filling each cavity only partially.

- Additional blank base is melted and used to fill the remaining portion of the cavities.

- When the suppositories have cooled, the excess base is removed from the top of the mold.

- The suppositories then are removed from the mold, re-melted, and recast to distribute the active ingredient evenly.

- By determining the weights of suppositories at the various steps in the double casting procedure, the density factor can be calculated.
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Information needed to calculate DDF:
- average weight of a blank suppository
- average weight of a drug-containing suppository
- weight of drug in each suppository
Example:
1) Using an aluminum mold, the average weight of six Polybase ONLY suppositories is **2.0 g**
2) Since each suppository needs to contain **0.3 g** of drug,  
   \[ \text{6 sup x 0.3 g/sup} = 1.8 \text{ g} \], Drug Z is added
3) After following the procedure described, the average weight of a medicated suppository is **2.1 g**
4) Thus the weight of the base in the medicated suppository is  
   \[ \text{2.1 g} - \text{0.3 g} = \text{1.8 g} \]
5) The weight of Polybase displaced by Drug Z is  
   \[ \text{2.0 g} - \text{1.8 g} = \text{0.2 g} \]
6) Therefore the DDF factor for Drug Z in Polybase is  
   \[ \frac{0.3 \text{ g Drug Z}}{0.2 \text{ g Polybase}} = 1.5 \]
DDF – Paddock Method

- Determine the average blank weight (A) per suppository using the mold and suppository base of interest.
- Weight the quantity of base necessary for 10 suppositories.
- Weigh 1 g of drug. The weight of drug per suppository (B) is then equal to 1 g/10 suppositories which equals 0.1 g/supp.
- Melt the suppository base and incorporate the drug, mix, pour into mold, cool, trim and remove from mold.
- Weigh the 10 suppositories and determine the average weight (C).
- Determine the Density Factor as follows:
  \[ \text{DF} = \frac{B}{(A - C + B)} \]
- To determine the Replacement Factor (RF), take the weight of the drug per suppository (B) and divide by the Density Factor (DF) determined above.
  \[ \text{RF} = \frac{B}{DF} \]
- Subtract the RF from the blank suppository weight (A) and then multiply by the total number of suppositories to determine the total amount of base needed.
  \[ (A - \text{RF}) \times \# \text{ supp needed} = \text{total base needed} \]
- Multiply the weight of drug per suppository by the number to prepare to obtain the quantity of drug required for the prescription.
  \[ (B) \times \# \text{ supp needed} = \text{total drug needed} \]
Example Rx: Calculations

Rx: Diphenhydramine 12.5 mg rectal supp., Dispense #6

• Information:
  o Use diphenhydramine 50 mg capsules and Fattibase
  o Use plastic shell molds which were calibrated at 1.8 g for Fattibase,
  o Prepare 2 extra suppositories (thus 8 total)
  o DDF for diphenhydramine is 0.8, DDF for excipients is 1

• Calculations:
  1. 8 supp x 1.8 g = 14.4 g total suppository weight
  2. 8 supp x 12.5 mg = 100 mg or 0.1 g diphenhydramine
  3. Will use all of the contents from **two, 50 mg capsules**. The contents of two capsules weigh 380 mg
  4. Determine amount of excipient in capsules, 380 mg – 100 mg = 280 mg or 0.28 g of excipient
  5. 0.8 g D / 1 g FB = 0.1 g D / X g FB = 0.125 g FB is displaced by the drug
  6. 1 g Ex / 1 g FB = 0.28 g Ex / X g FB = 0.28 g FB is displaced by the excipient
  7. Calculate FB to weigh as 14.4 g – 0.125 g (D) – 0.28 g (Ex) = **14 g FB**
Example Rx: Procedure

Rx: Diphenhydramine 12.5 mg rectal supp., Dispense #6

Fusion Method (general steps)

1. Prepare mold
   - lubricate if necessary (aluminum mold), not needed for plastic
2. Prepare base
   - grate or shave into fine, evenly sized particles
3. Weigh ingredients and base
   - open contents of two capsules and weigh 14 g of Fattibase
Example Rx: Procedure

**Fusion Method** (general steps)

4. Melt base
   - water bath, hot plate – microwave not appropriate
5. Incorporate ingredients into base
   - stir in vigorously, ensure homogenously blended
6. Pour molds and allow to set
   - typically molds should be allowed 30 minutes at room temperature before removing
7. Trim excess, wrap (if needed) and dispense
Preparation Guidelines

- **Quality Control**
  - Check and document the following on the compounding record:
    - consistency of weights, shape or physical appearance, color, texture

- **Beyond Use Dating (BUD)**
  - In the absence of stability information, use USP Chapter 795 recommendation:
    - For Nonaqueous dosage forms (including suppositories)
      - The BUD is not later than the time remaining until the earliest expiration date of any API or 90 days (3 months), whichever is earlier.

- **Quantity to Prepare**
  - USP Chapter 795
    - “prepare an excess amount of the total formulation to allow the prescribed amount or quantity to be accurately dispensed”
  - Practically
    - Loss is common during formulation
    - Always prepare excess – base calculations on a *minimum of 2 extra suppositories.*
Preparation Guidelines

- **Drug Labeling**
  - Drug name
  - Weight of drug per suppository
  - Route (e.g. rectal, vaginal)
  - Example: Morphine Sulfate 2.5 mg Rectal Suppository

- **SIG**
  - Clearly indicate the route of administration
  - May need to state preparation information such as “unwrap” or “moisten tip”
  - Example: Unwrap and insert 1 suppository rectally at bedtime.

- **Auxiliary Labels**
  - Include storage warnings
    - Refrigerate, Do Not Refrigerate, Keep Away From Children
  - Include route of administration warnings
    - For Rectal Use Only, For Vaginal Use Only