SUPPOSITORY FORMULATION:
- Suppository base
- Medicinal ingredient
- Shape and size
- Excipients needed for formulation
  - Absorption enhancers

POURING:
- Pouring temperature: has to do with behavior of suppository base upon cooling
- Pouring from a mortar: last suppositories have more drug than the first ones
- Pouring from squeeze bottle: first suppositories have more drugs than last ones

SUPPOSITORY BASES:
- Solid form at room temp. 15-25°C and melts at body temp (for oil-based suppositories)
- Amorphous, smooth, non-irritating vehicle
- Medicinally inert without side effects
- Types:
  - Oleaginous (fatty/oily) bases (lipophilic)
    - Theobroma Oil (cocoa butter) & synthetic triglyceride mixtures
  - Water soluble bases (hydrophilic)

OLEAGINOUS SUPPOSITORY BASES:
- COCOA BUTTER (THEOBROMA OIL):
  - Forms a solid < 30°C and melts at 30-35°C
  - Do not heat > 35° because it’s polymorphic = convert to metastable structure that melts at lower temp (< 25°C)
  - Non-irritating oil which is capable of dissolving certain drugs
  - MP can also be altered by drugs
    - Lower MP: phenols (estradiol, Propolol, diethylstilbestrol, choral hydrate)
    - Raise MP: additives like beeswax and spermaceti

SYNTHETIC TRIGLYCERIDES:
- Hydrogenated vegetable oils
  - Polyglyceryl Suppository Base
  - Fattibase (TGs from palm, palm kernel, coconut oils)
- Wecobee (coconut oil) F5, M, R, and S (various melting points) 33-40°
- Other bases:
  - Dehydag
  - Hydrokote
  - Suppocrir
  - Witepsol

WATER SOLUBLE BASES:
- Contain glycerinated gelatin or the PEG polymers
- Can be used to dissolve a single drug or 2 or more drugs
- May melt at temperatures higher than body temp
- May not require refrigeration
- Useful for prolonged release or delayed release of medication from suppository

POLYETHYLENE GLYCOL POLYMERS:
- Available in a wide range of hardness and melting points
- Does not melt at body temp (can be stored at room temp)
- Can be molded or compressed
- One or more drugs can be formulated into these bases
- PEG combinations:
  - PEG 1450 (30%)/PEG 8000 (70%) = high MP
  - PEG 300 (60%)/PEG 8000 (40%) = med MP
  - PEG 30 (48%)/PEG 6000 (52%)

GLYCERINATED GELATIN:
- Translucent, resilient, gelatinous solids
- Dissolve or disperse in mucous secretions, provides prolonged release of active ingredients with dissolution of suppository
- Keep in air tight container as it can absorb moisture from the air
- Preservative required if prolonged storage (> 30 days)
- Use water or water-based lubricant for administration

ABSORPTION ENHANCERS:
- Increase rectal absorption of active ingredients by enhancing membrane permeability
  - Capric acid, lauric acid, sodium caprate or laurate or cholate or salicylate
  - Sometimes unpredictable absorption increase
- Non-ionic surfactants can be added to oil base suppositories to increase release of lipophilic active substance

EXCIPIENTS:
- Are used as fillers (less costly than bases)
- Can be used as dispersing agents to more evenly spread & homogenize active ingredients
- Used to stabilize the compound
- Act as a preservative

USES:
- When oral administration is difficult (N&V) or drug is incompatible with GIT, or parenterall involves higher risks or barriers
- Nausea, motion sickness, anxiety, and bacterial or fungal infections
- Drugs for systemic treatment where other routes of administration are limited or difficult
  - Children, unconscious ...

FACTORS AFFECTING RECTAL DRUG ABSORPTION:
- Colonic/rectum content: better absorption when rectum is empty (passive diffusion)
- Absorption via lower hemorrhoidal veins: leads directly to inferior vena cava
- pH of rectal fluids: weak acids/bases = better absorbed
- Lipid-water partition coefficient: high = better absorb
- Degree of ionization
- Particle size: smaller particle size is better absorbed

RECTAL DRUG DELIVERY:
- Various levels of acceptability in different countries and cultures (more common in Europe)
- 10-25 mL can be retained reasonably well in rectum
  - Relatively constant environment with reproducible absorption (temp is consistent, pH mostly consistent)
- Avoids first pass effect by liver

SUPPOSITORY ADMINISTRATION: pics on slides 6-8

SUPPOSITORIES: solid medicinal dosage forms formulated and prepared for administration into body cavities
- Rectal, vaginal (pessary), urethral suppositories
- Melt at body temperature or dissolved by mucous or body secretions locally
- Produce a local action, may have systemic absorption and/or mechanical/physical effect
- Available as commercial preparations or compounded

URETHRAL SUPPOSITORY: alprostadil (PGE1) micro-suppository (Muse)
- Erectile dysfunction treatment
  - 125 – 1000 mcg (4 strengths)
- Stimulates adenylyl cyclase, raising cAMP which leads to lower Ca ion and resulting relaxation of smooth muscle increasing arterial blood flow to corpora cavernosa → penile erection
- Onset 5-10 mins; duration 30-60 mins
# Lecture 18

**Pharmaceutics of Suppositories**

## Formulation Decisions:

<table>
<thead>
<tr>
<th>Choice of Dosage Form</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppository</td>
<td>Easy administration</td>
<td>Melting takes times</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mostly suspension</td>
</tr>
<tr>
<td>Enema</td>
<td>No melting process</td>
<td>Packaging more complex</td>
</tr>
<tr>
<td></td>
<td>Mostly solution</td>
<td>Demanding administration</td>
</tr>
<tr>
<td></td>
<td>Larger volume may give faster absorption</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Choice of Base</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty</td>
<td>Hardly any incompatibility</td>
<td>2 compartments → takes more time</td>
</tr>
<tr>
<td>Water</td>
<td>1 compartment → faster</td>
<td>Dissolution of suppository takes more time than the melting of a fatty one</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Choice of Active Substance</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt/free base/free acid</td>
<td>Form not soluble in base (is) often positive for a faster release</td>
<td>Active substance, very badly soluble in rectum fluid, is hardly absorbed</td>
</tr>
<tr>
<td></td>
<td>Best form in combo with type of base has to be chosen based on literature data</td>
<td>Active substance, completely ionized, is hardly absorbed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Choice of Particle Size (for susp)</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty base, active substance, good water soluble</td>
<td>Rate of particle transport to interface determines rate of active substance release</td>
<td>Particles maximal 180 µm, otherwise the preparation will be difficult</td>
</tr>
<tr>
<td></td>
<td>Larger particles have faster transport and therefore a faster release</td>
<td>Particles &gt; 240 µm not optimally spread with the base → slower release</td>
</tr>
<tr>
<td>Fatty base, active substance, poorly water soluble</td>
<td>Extent of interface determines rate of release</td>
<td>Very small particles may irritate the rectal mucosa if the solubility is a little better</td>
</tr>
<tr>
<td></td>
<td>Best choice is a large volume of the dosage form and a small particle size</td>
<td>Ex/ ASA does, paracetamol does not</td>
</tr>
<tr>
<td>Water (soluble) base, active substance, poorly water soluble</td>
<td>Small particles dissolve faster</td>
<td>Particles maximal 180 µm, otherwise the preparation will be difficult</td>
</tr>
<tr>
<td></td>
<td>Larger volume of dosage form → faster absorption</td>
<td></td>
</tr>
</tbody>
</table>

## Other Characteristics:

| Hydroxyl value | Varying the ratio of mono-, di-, tri- glycerides yields varying hydroxyl values |
|               | Higher hydroxyl value results in higher elasticity and higher viscosity |
|               | Suspending substances better when molten |
|               | Less fracturing after cooling |
|               | Low hydroxyl values release drugs faster |
| Acid value    | Lower acid value has less chemical reactivity = results in less irritation to mucous membranes |
|               | Affects ionization of the drug, ionized drugs do not cross membranes and cannot exert effect |
| Iodine value  | Is a measure describing the number of double bonds in an oil or fat |
|               | Large number of double bonds is associated with increased tendency for oxidation (leading to deterioration and loss of effect and may produce odors) |
| Peroxide value| The measure of reactive oxygen in the fat base |
|              | Low peroxide value results in less oxidation of active substances by the base, allowing easily oxidizable drugs like chlorpromazine to be formulated |