Suppositories

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Pharmaceutics 535
Spring 2002
Learning Objectives

- Be able to describe the anatomy and physiology of the rectum, vagina & urethra
- Be able to describe drug delivery to the above mentioned areas
- Be able to describe the different types of suppository bases and their properties
- Be able to manufacture suppositories with the different types of bases
- Put the above together to counsel patients in the use and selection of suppositories
Reading Assignment

- Ansel, Allen & Popovich pp 279-295

Recommended Reading

- Remington Chapter 44 Medicated Topicals
  - Applications
    - Suppositories section only
      - (Same Ch as ointments)
  
- A Practical Guide to Contemporary Pharmacy Practice
  - Judith E. Thompson
  - Ch 23 & 31
Suppositories Outline

- Introduction to suppositories
  - Physiology
    - Rectum, Vagina & Urethra

- Applications
  - Advantages / disadvantages of suppositories

- Suppository bases
  - Base classification
    - Cocoa-butter (Theobroma oil)
    - Hydrophilic suppository bases
    - Compressed tablet suppositories
    - Industrial manufacture

- Compounding
Introduction to Suppositories

- Medicated solid dosage form generally intended:
  - Rectum
  - Vagina
  - Urethra

- Usually vehicles melt or soften at body temp

- 1% of all medications dispensed

- Much more popular in Europe
  - Especially France
Do No Harm

- Many OTC's available for relief of symptoms
- Be very careful!!
  - Many conditions such as colon cancer and other anorectal diseases are very serious
  - You don't want to cover up symptoms when patient should be seeing a doctor!

- Patient counseling can help
Patient Counseling

- Very important!!!

- Must language patient can understand
  - Average reading level of US 7th grade
  - Many patients have swallowed suppositories and foams

- Should be sensitive to patient feelings
  - Often embarrassed
  - Considered an “X-rated” route of delivery
Physiology
Rectum

- Terminal 15-19 cm of large intestine (LI)
- Rectal Fluids -> no buffering capacity
  - 1. 2 - 3 mL
  - pH 6.8
  - Mild environment / drug can change pH
  - LI function absorb H₂O and electrolytes
    - Low S area -> poor absorption compare SI
  - Rectum usually empty of feces
Rectal Blood Circulation

- Main blood supply superior rectal artery
- Blood return 3 blood veins
  - Superior hemorrhoidal vein
  - Middle hemorrhoidal vein
  - Inferior hemorrhoidal vein
Rectal Blood Circulation

Inferior Vena Cava

Common Iliac Vein

Superior Hemorrhoidal

Middle Hemorrhoidal

Inferior Hemorrhoidal

To Portal System

Inferior Mesenteric Vein
Suppositories

Too High
Too Low
Just Right

Too Low
Rectal Blood Circulation cont

- Middle & inferior hemorrhoidal veins
  - Iliac vein -> inferior vena cava

- Superior hemorrhoidal vein
  - Inferior mesenteric -> Hepatic portal -> Liver

- Middle and inferior
  - Drug goes directly into systemic circulation
  - No first pass metabolism by liver
  - Drug avoids stomach and digestive enzymes
  - Patient counseling -> don't place too high in rectum
    - Unless medical need
Vagina

- Fibromuscular tub about - 7.5 cm long

Vaginal Blood Circulation
- Blood supply vaginal artery (branch of iliac)
- Blood return avoids the hepatic portal system
  - Typically targeted drug administration

Vaginal fluids
- Origin in cervix
- Protective mucus
  - Complex mixture of proteins and polysaccharides
- Low pH 3 \(<- (3.5 - 4.2) -> 6\)
- Prepuberal & post-menopause
  - neutral to slightly alkaline
Urethra

- Tube
  - Males 20 cm
  - Females 4 cm
- Poorly perfused by blood
Applications
Targeted Delivery

- Concentrate drug at site of action
- Reduce side effects
Advantages of Suppositories

- Self administration
- Avoidance of oral and parenteral routes
  - Avoid first pass metabolism
  - Protect drug from harsh conditions in stomach
  - Drug causes nausea and vomiting
  - Oral intake restricted before surgery
    - Patient suffering from severe vomiting
- Can be targeted delivery system
  - Localized action reduced systemic distribution
  - Rectum vagina & urethra poor blood flow
    - Get to site of action with lower dose
    - Reducing systemic toxicity
Disadvantages of Suppositories

- Mucosal irritation
  - Eg: indomethacin can cause rashes

- Patient compliance

- Erratic and undesired absorption
  - Placement too high -> first pass metabolism
  - Installation may trigger defecation reaction
    - expel product

- GI state affects absorption
  - Diarrhea & disease states affect absorption
Disadvantages of Suppositories

- May get absorption when don't want
  - e.g. Estrogen creams
    - ↑ absorbed into circulation  ↑ Side effects
- High cost of manufacture
  - Special formulation
  - Special packaging
- Lack of comparative data
  - Not well researched area
  - Company avoid financial risk
- Can melt at ambient temperatures
  - e.g., Baltimore in the summer
Suppositories

- Rectal
  - 4 gm adult
  - 1 gm child
Suppositories

- **Urethral**
  - male 4 gm 100 – 150 mm
  - Female 60 – 75 mm
  - 5 mm diameter
Suppositories

- Vaginal
  - 3 – 5 gm
Examples

- **Progesterone vaginal suppositories**
  - F < 10%
    - Poor absorption and high 1st pass metabolism
    - Lessen the possibility of miscarriage
      - luteal phase defect
      - *In vitro* fertilization (IVF) -> uterine lining development

- **NPO – preoperative maintenance therapy**
  - Aminophylline / theophylline Suppositories

- **Miconazole Vaginal Suppositories**
  - Fungus resides on mucosal membranes
  - i.e., outside the body, need high PO dose
Examples Cont.

- Acetaminophen
- Aminophylline
- Aspirin
- Belladonna and Opium
- Bisacodyl
- Chlora Hydrate
- Chlorpromazine
- Clindamycin
- Dinoprostone
- Ergotamine Tartrate & Caffeine
- Glycerin
- Hydrocortisone
- Hydromorphine
- Indomethacin
- Mesalamine
- Methocarbamol & Aspirin
- Miconazole
- Morphine Sulfate
- Nonoxynol 9
- Oxymorphone
- Pentobarbital
- Prochlorperazine
- Promethazine
- Propoxyphene and Aspirin
- Senna
- Sulfanilamide
- Terconazole
- Thiethylperazine
- Trimethobenzamide
- Nystatin Vaginal
Suppository Bases
Suppository Bases

- Ideal base
  - Melts, dissolves, or disperses at 37°C
  - Nonirritating
  - Physically stable -> manufacture & storage
  - Chemically stable & inert
    - No color change
    - Compatible with drugs
  - Convenient to handle -> break or melt
  - High viscosity when melted
    - Doesn't leak from rectum or vagina
Base Classification

- **Oleaginous**
  - Cocoa-butter
  - Cocoa-butter substitutes

- **Water soluble (Hydrophilic Bases)**
  - Polyethylene - glycol mixtures
  - Glycerated gelatin

- **Water dispersible (Won't cover)**
  - Polyethylene-glycol derivations
  - Cocoa-butter substitutes with surfactants

- **Non-base**
  - Tablets
  - Soft gelatin capsules
Drug Release

- Oleaginous
  - Melts
  - Spreads

- Hydrophilic
  - Dissolves in fluids
  - Diffuses from fluids

H₂O  H₂O
Drug Release Cont.

- Drug release rate
  - If $K \gg \gg \gg$ drug won’t partition out of base
  - Water (i.e. rectal fluids)

$$K = \frac{Oil}{Water} : \text{e.g.} \frac{.1}{.0001} = 1000$$
Drug Release Cont.

- Factors controlling release rate

<table>
<thead>
<tr>
<th>Drug Sol</th>
<th>Vehicle Oleaginous</th>
<th>Vehicle Aqueous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil Rate -&gt;</td>
<td>Slow Partitioning</td>
<td>Moderate Drug in aq.</td>
</tr>
<tr>
<td>Water Rate -&gt;</td>
<td>Rapid Partitioning</td>
<td>Rapid – slow Drug in aq.</td>
</tr>
</tbody>
</table>
Drug Release Cont.

- **Particle Size**
  - 50 μm limit irritation
  - S/V ratio ↑ dissolution rate ↑
  - Affect drug sedimentation when molding
Cocoa-butter (Theobroma oil)

- Most widely used base for Rx
  - Innocuous
  - Bland
  - Nonreactive
  - Melts at body temperature

- Disadvantages
  - Fatty acids can become rancid
  - Melt in warm weather
  - Liquefy when certain drugs are incorporated
  - Variable properties (natural product)
Cocoa-butter Composition

- Obtained from roasted seed
  - of Theobroma Cacao

- Primarily triglyceride
  - Oleopalmitostearin
  - Oleodistearin

- Yellowish-white solid

- Brittle fat

- Smells and tastes like chocolate
  - Melting point 30-35 °C

- Stored in cool, dry, light protected
Polymorphic Forms

- Polymorphism (Greek: Many - shapes)
- Different crystal structures same chemical
- Common example: Diamond and graphite
  - Both made of Carbon
  - Diamond hardest material
  - Graphite can't scratch paper
- Different crystal structure
  - Different properties
- Formulation problem
  - Same chemical different properties
Thermodynamics

- One form most stable for given set of conditions
  - Example
    - Diamond unstable at room temperature
    - Graphite more stable at room temp
    - High temp diamond more stable
    - Diamond metastable form at room temp
    - Metastable:
      - Thermodynamically unstable -> some degree of kinetic stability
Thermodynamics & Kinetics

- Room Temperature

![Diagram of energy state transition from graphite to diamond with activation energy $E_a$]

- Thermodynamic
- Kinetic
Boltzmann Distribution

Frequency / Probability

Kinetic Energy

$E_a$ $E'_a$
Thermodynamics Cont.

- Most stable low energy crystal
  - Higher Energy Barrier: Solid -> liquid
  - Highest melting point

- Least stable highest energy crystal
  - Can be big problem
  - Highest melting/softening point
    - i.e., Soften/liquid at Room Temperature

- Coca Butter - 4 polymorphic forms
  - $\alpha$, $\beta'$, $\beta$, $\gamma$
Thermodynamics & Kinetics

- Solid to liquid (melt) conversion

![Diagram showing the transition from one state to another involving energy and state changes.](image-url)
Manufacture Method

- Mfg. conditions produces a particular polymorph

- Must control melt to get right polymorph!
  - Temperature
  - Rate of cooling
    - Rapid cooling locks in metastable form
  - Agitation

- E.g.
  - Heat to $T > 36 \degree C$ & rapid chill below $0 \degree C$
    - Suppository melts or softens at room temp.
Polymorphic Properties

- **α** Melting point 24 °C
  - *Rapid* cooling of liquid to 0 °C

- **γ** Melting point 18 °C
  - *Rapid* cooling of 20 °C liquid
    - e.g., pouring into cold mold

- **β’** Melting point 28 to 31 °C
  - Crystallizes from *Stirred* liquid at 18-23 °C
  - β’ -> β: 1-4 days depending upon conditions

- **β** Melting point 34 to 35 °C
  - Stable form
    - All forms convert to β couple in days to a week
    - Won't work if need to fill Rx
Polymorphic Properties

Energy

α
β'
β
γ

22 °C
28 °C
34.5 °C
18 °C
How to Compound?

- Don't heat above 34.5 °C for long time

Why?
- Need β seed crystals to get β form
- Heat enough to remove α, β', but keep β
- Heat enough β still present act as seed
  - ie don't totally melt before pouring
- Prolonged heating -> no seed crystals
  - i.e., if turns to clear liquid you have problems!

Tricks
- Add seed crystals from stock
- Temper at 28 to 30 °C
  - ie store at 28 to 30 °C
Cocoa Butter Substitutes

- Cocoa butter is bad for high speed manufacture

- Cocoa butter replacements
  - Mixtures of synthetic or natural vegetable oils
  - Triglycerides of natural saturated fatty acids
  - Wax
  - Fatty alcohols C10-C18

- e.g.
  - Cotmar, Dehydag, Wecobee, Witepsol & Fattibase
Purification of cocoa butter

- Complex mixture of Primarily triglycerides
  - Oleopalmitostearin
  - Oleodistearin

- Break cocoa butter apart
  - Remove undesirable components
    - Get more uniform properties

- Steps in purification
  - Split glycerin from fatty acids
  - Remaining fatty acids separated by distillation
  - Undesirable fatty acids are removed
  - Then mixed back together
  - Reattached to glycerin
Hydrophilic: Glycerinated Gelatin

- **Glycerinated Gelatin**
  - Mixture glycerin and gelatin
    - Ratio glycerin/gelatin/H₂O -> duration of action
  - Oldest type

- **Example**
  - USP 24
    - Purified H₂O 10 gm
    - Glycerin 70 gm
    - Gelatin 20 gm

- **Vaginal suppositories (Above Rx used for)**
  - Local application of antimicrobials
Glycerinated Gelatin Cont.

- Glycerin hygroscopic protect from H₂O
  - Patient counseling leave in package
    - Will support mold and bacterial growth
    - Can use preservative
      - Propylparaben 0.02% & Methylparaben 0.18%

Not as good for rectal delivery
- Absorb H₂O from mucosal membranes
- Wet before use to:
  - Avoid/reduce “stinging”
  - Faster dissolution
Hydrophilic Bases PEG

- **Polyethylene glycols**
  - \( \text{HOCH}_2(\text{CH}_2-\text{O-CH}_2)_n\text{CH}_2\text{OH} \)
  - Properties change with MW
  - Liquid 200-600 MW
  - Wax-like solids . MW \( > 1000 \)

- **Will not support mold growth**

- **Packaged in tightly closed containers**
  - Absorbs \( \text{H}_2\text{O} \).
  - Can store without refrigeration

- **Labeling**
  - Moistened with water before inserting
    - Avoid/reduce "stinging"
    - Faster dissolution
PEG Cont.

- **Example**
  - |       | Base 1 | Base 2 |
  - | PEG-1000 | 96%    | 75%    |
  - | PEG-4000 | 4%     | 25%    |

- **Base 1**
  - Low melting (refrigerate in summer)
  - Rapid drug release

- **Base 2**
  - Higher melting
  - Slower drug release
Compressed Tablets

- Not common for rectal suppositories
  - Low moisture environment

- Advantages
  - Becoming more popular for vaginal use
  - Easier to manufacture
  - More stable
    - Heat storage & chemical reaction
  - Doesn't melt and run out
Compounding Suppositories
Rx Note

- Systemic Absorption
  - Suppositories prone to erratic absorption
    - i.e., formulation is critical
  - Use commercial products where available!

- Local Action
  - Not as critical
    - Most bases hold drug in contact with target tissue
Base Selection

- **Vehicle influences drug release!**
  - Cocoa butter immiscible with body fluids
    - Inhibits diffusion of fat-soluble drugs
    - Ionized drugs partition more readily
  - **Water-miscible bases**
    - Can dissolve very slowly -> retarding release

- **Systemic absorption**
  - Generally:
    - Ionized \(\uparrow\) bioavailability
    - Nonionized \(\downarrow\) bioavailability
    - e.g., Codeine phosphate or sulfate is better in cocoa butter than Codeine
Base Selection Cont.

- **Oleaginous vehicles**
  - Less irritation of rectum
  - Less popular in vaginal preparations
    - Nonabsorbable residue

- **Hydrophilic vehicles**
  - Less popular rectally
    - Slow dissolution
  - Vehicle -> relatively slowly cleared vaginally
    - Less likely to leak (where no sphincter muscles)
Base Selection Cont.

- **Chemical Stability**
  - Fatty Bases > PEG

- **Some drugs lower melting point**
  - Volatile oils, creosote, phenol, chloral hydrate
  - White wax or cetyl ester raises T-melt
    - Note too much wax
      - T-melts > 37 °C
Base Selection Cont.

- Cocoa butter has no emulsifier
  - Low water uptake 20-30 gm H₂O/100 gm
  - Tween 61 5-10% increases water absorption

- Hydrophilic drugs can precipitate
  - Tween 61 helps solubilize hydrophilic drugs

- Surfactants
  - ↑ bioavailability
    - Breakup suppository -> faster release
    - Disperse drug better
Preparation of Suppositories

- Non-tablet

- Hand rolling and shaping

- Fusion -> Molding from a melt

- Compression molding
  - Not commonly done
Hand Rolling & Shaping

- Advantages
  - No equipment
  - No special calculations
  - No heat

- Disadvantages
  - Difficult to manufacture
  - They’re not pretty
Hand molding

- Simplest & oldest method
- Only use cocoa butter (theobroma oil)

Procedure
- Grate base
- Active ingredients finely powdered or dissolved in alcohol, mixed with wool fat to help incorporation with base
- Kneaded active ingredients into base with mortar and pestle
- Roll Mass into cylindrical rod on pill tile
- Cut rod to desired length; adjusted by slicing
- Wrap individually in 3 x 3 inch foil squares
Fusion

- **Advantages**
  - Elegant appearance
  - Don’t need good hands

- **Disadvantages**
  - Heat
  - Equipment: need molds, etc.
  - Special Calculations
Molding From a Melt

- Steps
  - Melt base
  - Incorporating other ingredients and drug
  - Pouring the melt into mold
  - Allowing the melt to congeal
  - Remove from mold
Molds

- Stainless steel
- Aluminum
- Brass
- Plastic

- High speed molding machine
  - 3500-1000/hour
Mold Lubrication

- Solidification -> adhere to molds
  - Low volume contraction
  - Must use lubricant for mold release
    - Glycerinated gelatin; usually necessary

- Mineral oil
Dose Calculation

- **Physician**
  - Gives dose for patient

- **Pharmacists**
  - Determine amount of base necessary for dose

- **Methods**
  - Density Displacement
  - Double Pour
Mold Calibration

- Determine the volume of each cell in mold
  - Pour in base & solidify
  - Weigh base from each cell
  - Put in beaker & melt to get volume
  - Calculate weight and volume of each cell

- Different bases will have different \( \rho \)'s

- e.g. (assume 2 mL cavity)

<table>
<thead>
<tr>
<th>Material</th>
<th>( \rho ) (g/mL)</th>
<th>Mass (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>1.0</td>
<td>2</td>
</tr>
<tr>
<td>Cocoa Butter</td>
<td>0.86</td>
<td>1.72</td>
</tr>
<tr>
<td>PEG 400</td>
<td>1.125</td>
<td>2.26</td>
</tr>
</tbody>
</table>
Density Factors

Dose Calculation

1) Calibrate mold
2) Calculate amt. Drug
3) Calculate total suppository weight
   - drug + base
4) Calculate base needed by difference
   - Use “Density Factors” to calculate amt. of base displaced by drug
## Density Factors – Cocoa Butter

1 gm of cocoa butter = x gm of drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>1.3</td>
</tr>
<tr>
<td>Barbital</td>
<td>1.2</td>
</tr>
<tr>
<td>Bismuth salicylate</td>
<td>4.5</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>1.3</td>
</tr>
<tr>
<td>Cocaine HCl</td>
<td>1.3</td>
</tr>
<tr>
<td>Codeine phosphate</td>
<td>1.1</td>
</tr>
<tr>
<td>Diphenhydramine HCl</td>
<td>1.3</td>
</tr>
<tr>
<td>Morphine HCl</td>
<td>1.6</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>1.2</td>
</tr>
<tr>
<td>Zinc Oxide</td>
<td>4.0</td>
</tr>
</tbody>
</table>
e.g. Calculation

- **Rx**
  - Aspirin 100 mg
  - Cocoa Butter q.s.
  - M & ft. Suppositories #6
  - Sig: I supp pr q4-6 hours prn pain and fever

- **Calculations (make for 2 extra)**
  - Mold calibration 2 g/cavity
  - Aspirin $\Rightarrow$ 8 X 100 mg = 800 mg
  - 8 X 2 g = 16 gm
  - 0.8 g Aspirin X (1 g CB/1.3 Aspirin) = 0.615
  - Base $\Rightarrow$ 16 g – 0.615 g = 15.38 g
Double Pour Method
- Mix drug & fraction of base
- QS with base
- Scrape off excess & remelt/mix
Disposable Molds

- Pour directly into wrapping material
- Don't worry about melting upon shipping
- Don't need to refrigerate
- Don't need to cool before removal from mold
Disposable Molds
Beyond-Use Dating

- **Product Stability**
  - Expiration Date – Manufacturer
    - In original packaging
  - Beyond-Use Dating - Rx

- **USP 24 NF19 <795>**
  - In the absence of stability information
  - Nonsterile compounded drug preparations
    - Packaged in tight, light-resistant containers
    - Stored at controlled room temperature
Beyond-Use Dating Cont.

- For Nonaqueous Liquids and Solids
  - Where the manufactured drug product is the source of active ingredient
    - The beyond-use date is not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier
  - Where a USP or NF substance is the source of active ingredient
    - The beyond-use date is not later than 6 months.