Rectal and Vaginal Drug Delivery

Dr. Elkeeb

Rectal Drug Delivery

- When oral administration is not feasible or desirable.
- Rectal dosage form is the best choice for active agents that are poorly absorbed in the upper gastrointestinal (GI) tract and unstable to proteolytic enzymes.

Advantages of Rectal Drug Delivery

1. Potential for Better Absorption than oral drugs
2. Not affected by acid, less enzymatic effect.
3. Not affected by gastric emptying.
4. Limited first pass effect...
5. Rapid systemic effect possible (solution)
6. Rectal serves as an alternative to oral administration when patients are:
   1. Prone to nausea
   2. Vomiting
   3. Convulsions
   4. Patient might be unconscious

Disadvantages

- Defecation decreases absorption.
- Micro-organisms may degrade some drugs.
- Patient acceptability (varies by country).
- Cost: Suppositories are more expensive.

Anatomy of the rectum

- Unlike the small intestine and upper colon, the vasculature draining the rectal cavity does not totally direct the blood supply to the liver.
- Drugs absorbed in the inferior and middle rectal veins that drain the lower part of the rectum will be delivered preferentially to the systemic circulation, bypassing the liver and avoiding first-pass metabolism.

- Villi and microvilli are not present in the rectum.
- Sufficient surface area for drug absorption.
- Lack of motility (except for defecation).
Factors of drug absorption from rectal suppositories.

1. Physiological Factors:
2. Physicochemical factors

Physiological Factors

1. Circulation Route.
2. pH and lack of buffering capacity of rectal fluids.
3. Colonic content.

From pages 369-370 in the Ansel’s Pharmaceutical Dosage form. Read to discuss in class

Physicochemical Factors

1. Lipid water solubility.
2. Particle size.

From pages 370-371 in the Ansel’s Pharmaceutical Dosage form, read to discuss in class.

SUPPOSITORIES

Definition

• Suppositories are solid dosage form intended to be inserted into body orifices such as the rectum, vagina or urethra.
• They contain one or more active ingredient that are dispersed in a suitable base and molded into a suitable shape for insertion.
• After insertion they melt or soften at body temperature and release the active ingredient.

Formulations: Suppositories

• Rectal suppositories: cylindrical and may be tapered at one or both ends.
  — Shape: Torpedo, bullet shaped
  — Weight: 1g (children) to 2g (adult)
• Vaginal suppositories (pessaries):
  — Shape: globular or oval
  — Weight: 5g
• Urethral suppositories (bougies):
  — Shape: slender pencil shaped
  — Weight:
    • Male urethral suppositories 4g
    • Female urethral suppositories are 2g and half the length
Suppository Bases

- Type of bases:
  - fatty bases (low-melting)
  - water-soluble bases (dissolving/melting)
- Lipophillic drugs - water-soluble bases
- Hydrophillic drugs - fatty bases

An Ideal Suppository Base

1. Nontoxic and non irritating to membranes.
2. Compatible with a variety of drugs.
3. Melting or dissolving in rectal fluids.
4. Stable on storage, should not bind or interfere with the release and absorption of drug substances.

Oleaginous Base

- They used to be the most frequently used suppository base.

Examples:
1. Cocoa Butter
2. Theobroma oil

Cocoa butter melts between 30°C and 36°C making it an ideal suppository base melting just below body temperature and maintaining solidity at room temperature. It satisfies the requirement of an ideal suppository base.

Disadvantage

1. Possibility of adherence to the mold during compounding.
2. Poor water absorbing capacity.
3. Low softening point due to hot climates.
4. Deterioration during storage.
5. Leakage from the body.
6. Reduced melting point due to addition of other substances such as phenols.
7. Polymorphism.
Polymorphism

- **What is Polymorphism?**
- Occurs due to high proportion of unsaturated triglycerides.
- Occurs due to varying degrees of heating and cooling and condition during process.
- Different forms of polymorphs have different melting point and drug release rates.

Crystal Forms

- α crystals: occur due to quick chilling of melted base resulting in a metastable crystal with a melting point lower than the normal for cocoa butter (24°C). *Why is this a problem?*
- β crystals: with time the α crystal form will revert to the stable form β with melting point higher than room temperature. *Where is the problem? How can we insure we achieve a stable β crystals with normal melting point when we compound suppositories?*
- γ crystal: occurs due to pouring of a cool cocoa butter into a container that was cooled at deep freeze temperature. Melting point is 18°C.

To overcome problems with Cocoa Butter

<table>
<thead>
<tr>
<th>Problem</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to the mold</td>
<td>Lubrication</td>
</tr>
<tr>
<td>Poor water absorbing capacity</td>
<td>Addition of emulsifying agents.</td>
</tr>
<tr>
<td>Low softening point</td>
<td>Beeswax are added to raise the softening point in hot climates.</td>
</tr>
<tr>
<td>Low melting point due to addition of substances e.g phenols</td>
<td>Beeswax are added</td>
</tr>
<tr>
<td>Polymorphism</td>
<td>Heating and cooling gradually.</td>
</tr>
</tbody>
</table>

Synthetic Fats bases

1. Fattibase:
2. Wecobee:
3. Witepsol:
   - Their solidifying points not affected by over heating no polymorphism problem.
   - Have good resistance to oxidation thus more stable during storage.
   - High softening point grades great for hot climates.
   - Their problem is that they are more brittle than cocoa butter. Can be avoided by not placing in freezer and during compounding temperature of the mold should be close to the temperature of the melted base.

Glycerinated gelatin

1. Gelatin (20%) + glycerin (70%) + water or solution of drug (10%).
2. Most commonly used in vaginal suppositories Also is used for urethral. With this formula Gelatin (20%) + glycerin (60%) + water or solution of drug (20%).
3. Slower to soften thus providing prolonged local action i.e slower release.
4. Mixes well with physiological fluids.
Disadvantage

1. They are hygroscopic:
   1. So they tend to absorb moisture and have to be protected from atmospheric moisture.
   2. Have dehydrating effect (base draws water from mucous membranes) thus irritating tissues upon insertion/contact. (especially those that don’t have at least 20% water).
   3. To overcome this problem it is advised that the suppository is moistened with water prior to insertion to minimize this effect.

PEG based Suppositories

- They do not melt but rather dissolve slowly at body temperature.
- Using a mixture of PEG with higher melting point than the body temperature allows for
  - Slower release of the drug from the base once inserted.
  - Convenient storage without the need for refrigeration.
  - No risk of melting in hot climates.
  - No leakage from the body orifice since they mix with body fluids upon dissolution.

Drug Release Rates

<table>
<thead>
<tr>
<th>Drug: Base Characteristics</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Oil soluble drug: oily base</td>
<td>Slow Release</td>
</tr>
<tr>
<td>Water soluble drug: Oily base</td>
<td>Rapid Release</td>
</tr>
<tr>
<td>Oil soluble drug: Water miscible base</td>
<td>Moderate Release</td>
</tr>
<tr>
<td>Water-miscible Drug: Water-miscible base</td>
<td>Moderate release</td>
</tr>
</tbody>
</table>

Preparation Of Suppositories

1. **Molding or Fusion**: (Melt and Pour method)
2. **Hand Rolling and shaping**.
3. **Compression**: similar to hand rolling and shaping but instead of hand rolling the mixed mass is forced into a special mold.

Molding

1. Melt the base.
2. Incorporate drug.
3. Pour the melt into molds.
4. Allow to cool and congeal.
5. Remove from mold (when using metal molds)

Molds

1. Reusable Plastic molds.
3. Disposable plastic molds.
   
   - Lubrication of molds is necessary when using metal molds. To facilitate clean and easy removal of the molded suppositories.
Lubricants

- The lubricant must be of the opposite nature to the suppository base i.e.
  1. When the suppository base is fatty, the lubricant is glycerin.
  2. When the base is aqueous, the lubricant is liquid paraffin/mineral oil.

Calibration of Mold

- Due to difference in densities the weight of Cocoa butter suppositories will be different from the weight of glycerogelatin suppositories prepared by the same mold.
  1. Prepare suppositories using the base alone and weigh them and average weight of each suppository is recorded.
  2. Also the volume of the mold can be determined, suppository base is melted in a calibrated beaker and the volume of the melt is determined.

Examples of Suppositories

- Indication: Ulcerative colitis/Dose: 10-100 mg 1-2 times/day for 2-3 weeks http://drugster.info/drug/medicament/13077/
- Indication: Nausea/vomiting/Dose: 12.5-25 mg PR every 4-6 hours Max: 50 mg/dose http://www.healthsquare.com/drugs/224/
- Indication: Analgesic and antipyretic/Dose: 325-650 mg every 4-6 hours Max: 4 g/day http://drugster.info/dru
ges/15377

Dose Replacement (Density Calculations)

- A problem that arises is the density difference between the base and the drug.
- When the amount of drug is very low e.g. under 100 mg for a 2g suppository, the effect of the density is negligible and we need not take it into account.
- We will discuss during the lecture if time permitting or during the workshop.

Examples of Suppositories II

- Indication: Relief of constipation/Dose: <5 years: 5 mg in a single dose 1 year: 10 mg
  Max: 60 mg/day http://drugster.info/drug/medicament/2226/
- Indication: Analgesic and antipruritic/Dose: 10-20 mg every 4-6 hours Max: 6 g/day http://drugster.info/drug/medicament 2226/
Rectal and Vaginal Drug Delivery

Administration

1. Wash hands with soap and water.
2. If the suppository feels soft, chill (with wrapper - fringe or under cold water for a few minutes.
3. Use a disposable glove, if desired.
4. Remove the entire wrapper.
5. Moisten the suppository by application of one or two drops of water.
6. Advise patient to lay on their side, raise their knees to chest and insert suppository, tapered end first, without breaking.
7. Advise patient to try not to defecate for 1 hour.

Other Dosage Forms

Solutions, Suspensions, & Enemas

- Less application - contrast media and imaging agents to lower GI
- Absorption faster than from suppositories

Gels, foams or ointments

- Better retention than solid
- Local use e.g. hemorrhoids and lower bowel inflammation
- Faster effect than suppositories

Examples of Solutions, Suspensions & Enemas

- Diazepam rectal gel for Seizures
  Dose: 0.2 mg/kg PR x1
  Max: 1x/4-12hrs.
  http://www.healthsquare.com/drugs/ Diazepam_rectal_gel_for_Seizures.htm

Gels, Foams & Ointments

- Lansoprazole rectal gel for Ulcers
  Indication: Ulcerative colitis/rectal/anal inflammation/burning
  Dose: 10-150 mg 1-2 times/day for 2-3 weeks
  http://www.rxlist.com/lansoprazole-drug.htm

Introduction

- Local therapy
  - contraceptives, antifungals, antimicrobials, cleansers, deodorants & lubricants.
  - tablets, capsules, creams, suppositories, foams, films, solutions, ointments, and gels
  - Used for many years
- Recently value for systemic delivery recognized
  - bypasses liver.
  - less metabolic enzymes than GIT.
  - initially female hormones.

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some material from Dr. Pather’s Handouts

11/5/2015

PHAR 632
**Anatomy & Physiology**

- Greater similarity to buccal mucosa than to skin
- Vaginal surface is ~60 cm²
- pH of fluids 4.5 to 5.5 (reproductive age)
- Acidity is maintained by lactobacilli

**Path to General Circulation**

- Vagina
  - Perineum venous plexus
  - Pudendal vein
  - Inferior vena cava
  - Systemic circulation (bypassing the liver)

**Advantages**

- Absorption not affected by GI disturbances.
- Avoidance of first-pass metabolism.
- 1 self-administered dosage form ➔ drug supply continuously for weeks.
- Local effect - lower hormone dose.
- Low enzymatic activity in the vaginal area.

**Disadvantages**

- Thickness of the vaginal epithelium and the pH vary with age, hormonal activity, and menstrual cycle
- Systemic absorption can be erratic and unpredictable
- Formulation may leak or slip
- Local irritation
- Coital interference
- Patient’s reluctance to use this route

**Absorption Pathways & Delivery Systems**

- Pathways
  - Transcellular
  - Paracellular
  - Receptor Mediated Endocytosis (RME)
- Delivery Systems
  - Tablets, Suppositories(pessaries), Creams, Ointments, Gels and Foams
  - Vaginal rings - contraceptives and hormones

**Vagifem**

- Estradiol for treatment atrophic vaginitis
- Mucoadhesive & slow release
Pessaries

- Also called “suppositories” or “ovules”
- Melting or dissolving to release the drug

Creams and Ointments

- Generally used to provide local action.
- Spermicides, antibacterial drugs, hormones, and drugs used for cervical ripening.
- May be messy to use and uncomfortable.
- Supplied with a plastic applicator.

Gels and Foams

- Generally used to provide local action.
- Spermicides, antibacterial drugs, hormones, and drugs used for cervical ripening.
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Rings

- Commonly used
  - Femring™
  - Estring™
  - NuvaRing™

Advantages of Rings

1. Not messy to use.
2. Flexible, nonirritating.
3. Consistent release for an extended period.
Disadvantages

1. Does not protect against sexually transmitted infections, including HIV/AIDS.

Reservoir-type Ring Design

- Drug located in center core
- Polymeric membrane coat
- Drug release - diffusion
- Release modified by changing
  - thickness of the polymer coat, or
  - diameter of the core

Femring® (estradiol)

- Atrophic vaginitis & vasomotor symptoms
- Dosing: 0.05mg per day intravaginally
- Ring left in place for 3 months

Estring® (estradiol)

- Atrophic vaginitis.
- Silicone polymers
- Dosing: 7.5 µg daily for 90 days (2 mg total drug)

NuvaRing®

- Ethinyl estradiol/etonogestrel – Contraception
- Inserted and left in place for 3 weeks
- Removed
- New ring inserted 7 days after removal (even if bleeding is not complete)
- Inserted at approx. same time of day

Some material from Dr. Pather’s Handouts