Rectal and Vaginal Drug Delivery

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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

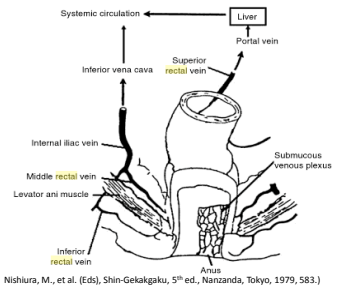
Advantages of Rectal Drug Delivery

1. Potential for Better Absorption than oral drugs
   1. Not affected by acid, less enzymatic effect.
   2. Not affected by gastric emptying.
   3. Not affected by food.
   4. Limited first pass effect..
   5. Rapid systemic effect possible (solution)
2. 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



Nishiura, M., et al. (Eds), Shin-Gekakgaku, 5th ed., Nanzanda, Tokyo, 1979, 583.)

- ✧ 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.

Anatomy of the rectum

- 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 oviform
  - Weight: 5g
- Urethral suppositories (bougies):
  - Shape: slender pencil shaped
  - Weight:
    - male urethral suppositories 4g
    - Female urethral suppositories are 2g and half the length

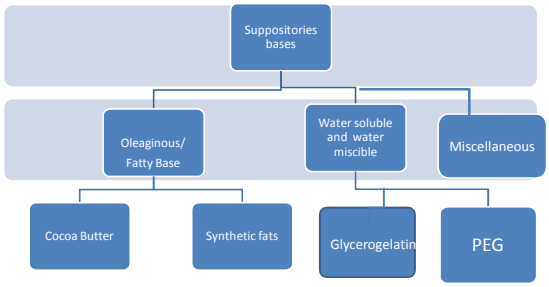
Suppository Bases

- Type of bases:
  - fatty bases (low-melting)
  - water-soluble bases (dissolving/ melting)
- Lipophilic drugs - water-soluble bases
- Hydrophilic 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.

Suppositories Bases



OLEAGINOUS OR FATTY BASES

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 makes 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. **Polymorphisim.**

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 (24C). 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.
- ϒ crystal: occurs due to pouring of a cool cocoa butter into a container that was cooled at deep freez temperature. Melting point is 18C.

  Where is the problem?

  How can we insure we achieve a stable β crystals with normal melting point when we compound suppositories?

To overcome problems with Cocoa Butter

Problem	Solution
Adherence to the mold	Lubrication
Poor water absorbing capacity	Addition of emulsifying agents.
Low softening point	Beeswax are added to raise the softening point in hot climates.
Low melting point due to addition of substances e.g phenols	Beeswax are added
Polymorphisim	heating and cooling gradually.

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.

WATER SOLUBLE AND WATER MISCIBLE BASES

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

Drug: Base Characteristics	Drug Release Rates
Oil soluble drug : oily base	Slow Release
Water soluble drug: Oily base	Rapid Release
Oil soluble drug: Water miscible base	Moderate Release
Water –miscible Drug: Water –miscible base.	Moderate release

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.
2. Metal: stainless steel, aluminum, brass.
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.

Molds

Google images

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.

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

Indication: Nausea/vomiting
Dose: 12.5-25 mg PR every 4-6 hours. Max: 50 mg/dose
http://www.healthsquare.com/drugs/120394.htm

Indication: pain/fever
Dose: 325-650 mg every 4-6 hours or 1000 mg 3-4 times/day; do **not** exceed 4 g/day
http://rx-s.net/images/tables/acep.php

Indication: Ulcerative colitis/Dose: 10-100 mg 1-2 times/day for 2-3 weeks
http://www.gwlabs.com/usa/prescriptionproductshydrocortisoneacetatesuppositories.htm

Examples of Suppositories II

Indication: Relief of constipation
Dose: <2 years: 5 mg as a single dose
>2 years: 10 mg
http://drugster.info/drug/medicament/13077/

Indication: Active ulcerative proctitis
Dose: Insert one 1000 mg suppository in rectum daily at bedtime; retained for at least 1-3 hours to achieve maximum benefit
http://drugster.info/drug/medicament/2224/

Indication: Analgesic and antipyretic
Dose: 300-600 mg every 4-6 hours
Max: 4 g/day
http://drugster.info/drug/medicament/224/

Administration

1. Wash hands with soap and water.
2. If the suppository feels soft, chill (with wrapper - fridge 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 soln
- Local use e.g. hemorrhoids and lower bowel inflammation
- Faster effect than suppositories

Examples of Solutions, Suspensions & Enemas

Indication: Hyperkalemia
Dose: 30-50 g PR every 6 hours.
http://www.healthsquare.com/drugs/120394.htm

Indication: Ulcerative colitis
Dose: Insert one 1000 mg suppository in rectum daily at bedtime; retained for at least 1-3 hours to achieve maximum benefit
http://www.healthsquare.com/drugs/120394.htm

Indication: Constipation
Dose: Use 1 bottle PR daily as needed
http://www.healthsquare.com/drugs/120394.htm

Gels, Foams & Ointments

Indication: Ulcerative colitis/hemorrhoidal inflammation/itching
Dose: Rectal: 10-100 mg 1-2 times/day for 2-3 weeks
http://www.rxzone.us/product.cfm/rx/Proctozone-Hc-Cream-25-1-oz-571612.html

Diazepam rectal gel for Seizures
Dose: 0.2 mg/kg PR x1
Max: 1 tx/5days, 5 tx/month. May repeat dose x1 in 4-12hrs.
http://www.rxlist.com/diastat-drug.htm

VAGINAL DRUG DELIVERY

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.

Anatomy & Physiology

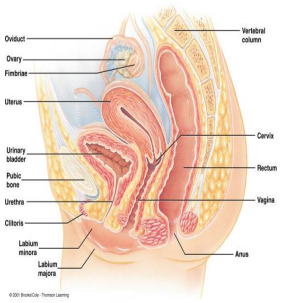


Image from: http://www.getceusnow.com/female.jpg

- Greater similarity to buccal mucosa than to skin
- Vaginal surface is ~60cm^2
- 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

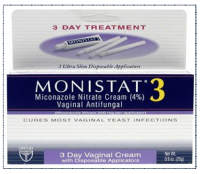
Image from: http://www.vagifemhcp.com/Content/images/zoomedia/hormone-therapy/flash_vagifem_home.jpg

Pessaries

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

http://www.medicineandmore.com/images/1111244L.jpg http://www.prestoimages.net/store20/rd648/648_pd2008329_th1.jpg

Creams and Ointments



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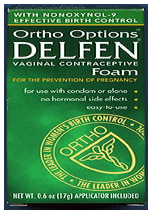
http://images.healthpricer.com/medicine_cabinet_images/large/11805000/11807993.jpg

Gels and Foams

http://www.drugstore.com/popups/largerphoto/default.asp?pid=362365&catid=184078&size=300&fm=29888&fmp1=362365&fmp2=1



http://www.uky.edu/Pharmacy/faculty/kuhn/formulary/group4/delfen.jpg

Creams, Ointments, Gels, and Foams

- 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.

Rings

- Commonly used
  - Femring®
  - Estring®
  - NuvaRing®

http://images.medscape.com/pi/features/drugdirectory/octupdate/A2150360.jpg

https://members.kaiserpermanente.org/kpweb/image/feature/026drugcy/drugphotos/WC162010.JPG

http://www.matemiteens.com/wp-content/uploads/2011/04/nuvaring.jpg

Advantages of Rings

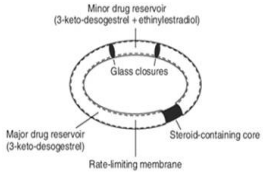
1. Not messy to use.
2. Flexible, nonirritating.
3. Consistent release for an extended period.

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



http://www.pharmainfo.net/files/images/stories/article_images/StructuralComponentsOfContraceptiveVaginalRing.jpg

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

http://drugster.info/img/drug/nuvaring-16799_2.jpg