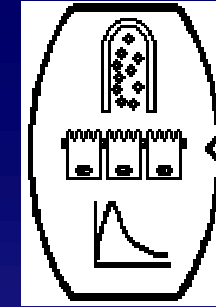
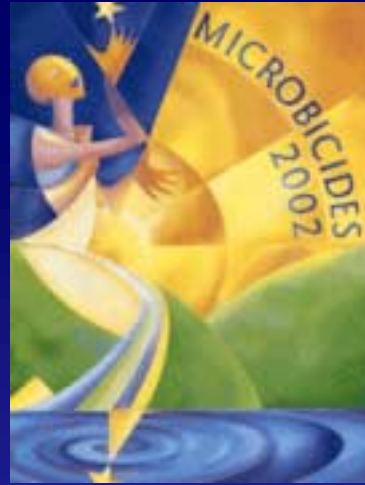




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FTB

Formulation aspects of vaginal microbicides

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Outline

- **Physiological** considerations with respect to vaginal drug delivery and drug absorption
- **Formulation** factors affecting vaginal drug delivery
- Overview of **formulation strategies**



Physiological considerations

1. Vaginal fluids → Drug Dissolution

- Transudation, cervical fluid (mucus), secretion from Bartholin's glands
- 1.55g/8hr ; maximal at ovulation
- Contains antimicrobial substances

2. Vaginal pH → Drug Ionization

4.0 - 5.0, *f(menstrual cycle; life cycle)*

Cellular glycogen or carbohydrates → Lactic acid



Physiological considerations

3. Enzyme activity \Rightarrow Drug Stability

Lower than GI tract

Protease, β -glucuronidase, acid phosphatase, alkaline phosphatase, esterase: *f(menstrual cycle; life cycle)*

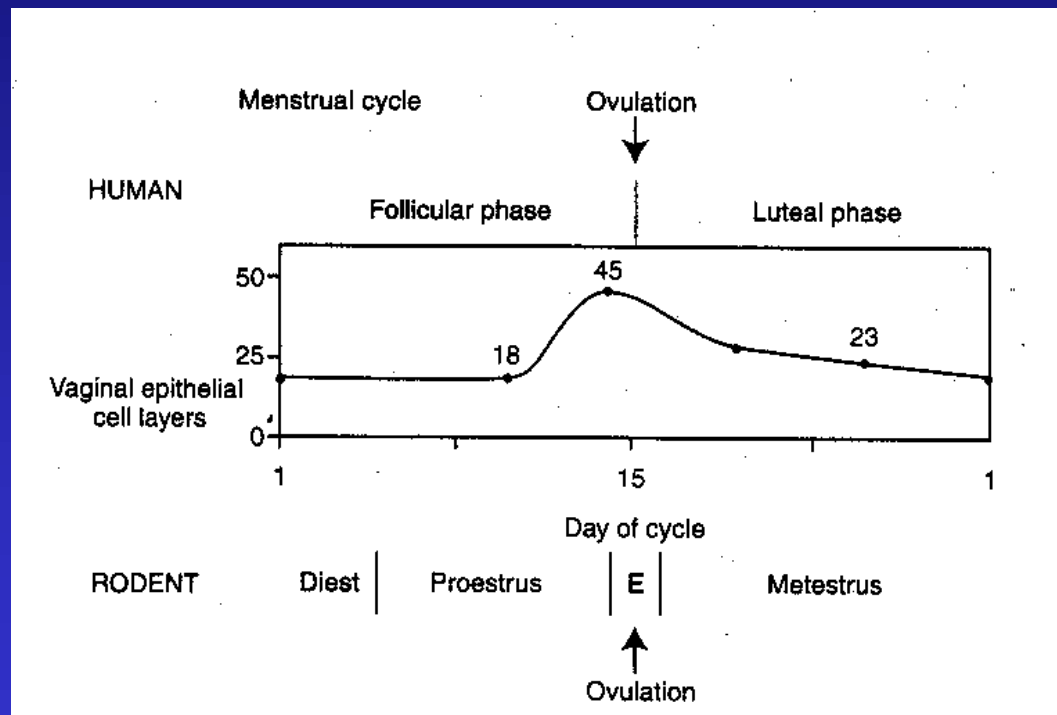
4. Transport routes \Rightarrow Drug Absorption

Cyclic changes in vaginal epithelium alter transcellular and paracellular drug uptake



Physiological considerations

Cyclic changes in vaginal epithelium



Hydrophilic drugs:
increased absorption
possibilities during
luteal phase



Physiological considerations

- *Salicylic acid (Na⁺ salt)*
 - Proestrus: 29% absorbed
 - Diestrus: 66% absorbed
- *Vidaribine*
 - 5 to 100 times higher permeability coefficient during diestrus
- *Penicilline*
 - Therapeutic blood levels when administered at the end of menstrual cycle and during menopause

Large fluctuations in absorption, depending on particular stage of menstrual cycle



Formulation factors

- Physicochemical factors associated with the **drug**
 - Solubility / dissolution rate
 - Ionization characteristics
 - Chemical structure
 - Size
 - Self-association, aggregation
 - Chemical stability

*Pharmaceutical
and
biological availability*



Formulation factors

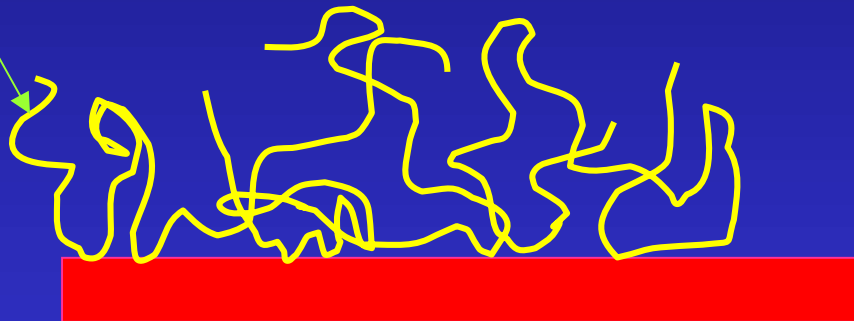
- Factors associated with the **dosage form**
 - Compatible with daily activities; ease of administration
 - Drug release from the dosage form
 - *Limited amount of fluid !*
 - Drug and excipient concentration
 - Effective area of contact (*vaginal cavity: $\sim 60\text{cm}^2$*)
 - *Hydrophilicity; spreadability; viscosity*
 - Residence time : *bio-adhesion and phase change polymers*



Formulation factors

- *Bio-adhesion* as a means to prolong residence time

Polymer



Mucosal or non-mucosal surface

Mechanisms involved (?):

Electronic
Adsorption
Wetting
Diffusion

Type of interaction:

Covalent
Hydrogen bonding
Electrostatic
Hydrophobic
Van der Waals



Formulation factors

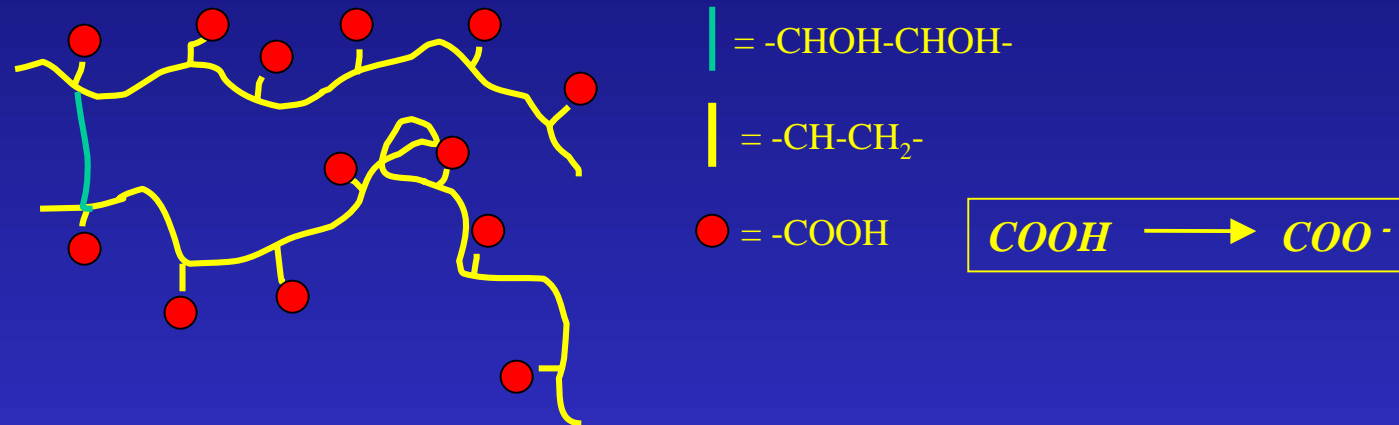
- **Bio-adhesion:** selection of polymers
 - Non-ionic or charged polymers (natural mucin: \ominus)
 - Molecular weight and chain flexibility
 - Crosslinked (water insoluble) or non-crosslinked





Formulation factors

- **Bioadhesion:** Polycarbophil



Other polymers:

Carbopol; Na⁺-CMC; Na⁺- Alginate (*COOH/COO⁻*)

Hyaluronate, HPMC, HPC (*OH*)

Chitosan (*R₃N⁺*)



Formulation factors

- *Phase change* as a means to prolong residence time

Fluid like behaviour



External stimuli

Temperature

pH

Specific ions (Ca^{++})

Solid like behaviour

*Example: poly (N-isopropylamide); Poloxamer 407[®]
Smart-Gel[®] (Poloxamer + PAA)*



Formulation strategies

Semi-solids

gels, creams,...

- + Prolonged residence, inexpensive, ease of manufacture, spreadability
- Messy, frequent applications, difficult to remove, preservative

Tablets

- + Ease of insertion
- More expensive, frequent applications, spreadability

Pessaries / suppositories

- + Ease of insertion, relatively inexpensive
- Frequent applications, poor retention in vagina, spreadability
- ! Can accommodate drugs in solution, emulsion or in suspension

For Controlled Release purpose: microspheres and intravaginal rings (expensive and high tech)



General conclusion

Formulation of a vaginal microbicide is a concerted action that combines knowledge about the drug substance (specific), vaginal physiology (general), and desired properties of the delivery system.