Vaginal preparations
Constitutive excipients
Bioavailability

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Introduction

- Vagina: potential route of drug administration
- Less common route of administration than rectal
- Mainly drugs with local effect (some with systemic effect)
- Local effect:
  - antiinflammatory drugs: clotrimazole, miconazole, clindamycin
- Systemic effect:
  - steroids – progesterone, estrogen, prostaglandins,
  - anticancer drugs
Anatomy of vagina

- multilayer epithel
- production of transudate – cervical mucus fluid 0.3 – 1 ml
  - thick and sticky outside ovulation
  - thin, watery during ovulation
- After ovulation: production of the fluid decreases and cervix is closed with mucus seal
• Permeability of mucous membrane depends on the menstrual cycle

• Acid pH: 3,8 – 4,4 – lactic acid (glycogen in the sloughed cells is metabolized to lactic acid)

• Changes if:
  ▫ Lack of estrogen
  ▫ Intravaginal application of antibiotics
  ▫ During inflammation
  ▫ Diabetes
  ▫ Microorganism and their metabolites

• In these cases pH 6 – 6,7 – it can influence drug release
Absorption of drug

- Blood is transported from vaginal plexus into vena superior – it avoids first pass effect in liver
- Drug absorption depends on chem.-phys. properties of the drug:
  - Lipophility
  - Ionisation
  - Mr
  - Interaction drug-vaginal membrane
1. **drug dissolution** - in vaginal transudate
   - Abundance of the transudate – drug is drain away, contact between vaginal wall and the drug is not long enough -> bioadhesive excipients (cellulose and polyacryl derivates)
   - Mucoadhesion = interaction of hydrophile polymer with mucous surface
2. **membrane penetration**
Absorption mechanism

- **Transcellular**: via concentration diffusion through the cells
- **Paracellular** – via tight junctions
- **Vesicular or receptor mediated transport**
Advantages of vaginal delivery

- Easy administration
- Reduction of side effects
- Great permeation area with high vascularisation
- Relative low enzymatic activity
- Partially avoidance of hepatic first pass effect
- Prolonged effective plasmatic concentration in endometrium
- Local effect – lower doses of drugs, slower absorption, systemic distribution and lower toxicity
Advantages of vaginal delivery

- Vomiting, stomach and small intestine irritation,
- Prevention of enzymatic degradation in GIT
- Drug delivery can be stopped by removing dosage form (vaginal rings)
- Rapid drug absorption
- BA of small drug molecules is good
- BA of larger molecules can be improved by absorption enhancers
- Possible self-medication
Drawbacks of vaginal delivery

- Genital hygiene issues
- Menstrual-cycle associated vaginal changes
- Coitus interference
- Local side-effects
- Variable drug permeability
Vaginal preparations - Vaginalia

- Definition PhEur 10: Vaginal preparations are liquid, semi-solid or solid preparations intended for administration to the vagina usually in order to obtain a local effect.
- They may contain 1 or more active substances in a suitable basis.
- When appropriate, containers for vaginal preparations comply with the requirements for material used for the manufacture of containers (3.1 and subsections) and containers (3.2 and subsections).
Categories of vaginal preparations (PhEur 10)

1. Pessaries
2. Vaginal tablets
3. Vaginal capsules
4. Vaginal solutions, emulsions and suspensions
5. Tablets for vaginal solutions and suspensions
6. Semi-solid vaginal preparations
7. Vaginal foams
8. Medicated vaginal tampons
1. Pessaries (Globuli vaginales, Suppositoria vagianlia, Ovuli)

- Def. Ph.Eur. 10: Pessaries are solid, single-dose preparations. They have various shapes, usually ovoid, with a volume and consistency suitable for insertion into the vagina.
- They contain 1 or more active substances dispersed or dissolved in a suitable basis that may be soluble or dispersible in water or may melt at body temperature.
• Excipients such as:
  ▫ diluents,
  ▫ adsorbents,
  ▫ surface-active agents,
  ▫ lubricants,
  ▫ antimicrobial preservatives and
colouring matter authorised by the competent authority
may be added if necessary
• Production: Pessaries – prepared by moulding measures taken to ensure a suitable and controlled particle size of the active substance(s)
• Active substance(s) are previously ground and sieved through a suitable sieve
• Medicated mass, sufficiently liquefied by heating, is poured into suitable moulds
• Pessaries solidifies on cooling
• Excipients:
  ▫ hard fat,
  ▫ macrogols, (combination of liquid with solid)
  ▫ coca butter,
  ▫ gelatinous mixtures consisting for ex. of gelatin, water and glycerol (10 – 20 % of gelatin, 60 – 70 % glycerol, and water) – suitable for drug soluble in hydrophile solvent
  ▫ Moulding forms: 3 or 4 g
iccebridge prototypes. Volume is constant at 3 mL across all five shapes. Samples were prepared with konne-carrageen.
• A suitable tests is carried out to demonstrate the appropriate release of the active substance(s) from pessaries intended for prolonged local action
• Tests: Disintegration (2.9.2) - all pessaries except those intended for prolonged local action
• Examine the state of the pessaries after 60 min

• Most common dosage form of vaginal preparations
• Drugs for cervical ripening prior to childbirth and local delivery of drugs
2. Vaginal tablets (Tabulettae vaginales)

• Def. Ph.Eur.10: Vaginal tablets are solid, single-dose preparations. They generally conform to the definitions of uncoated or film-coated tablets given in the monograph *Tablets*

• Production: a suitable test is carried out to demonstrate the appropriate release of the active substance(s) from vaginal tablets intended for prolonged local action
• Shape and size should be different from peroral tablets
• Excipients should be soluble in water
• **Lubricants** are: lactose, saccharose, glucose, modified starches, sorbitol and manitol
• Talc is not recommended
• Preparation of effervescent tablets:
  ▫ Excess of tartaric, citric or alginic acid is needed to maintain acidic pH in vagina
  ▫ Carbonates and hydrogen carbonates are essential
  ▫ Surfactants – to create a stable foam
• Test **Disintegration (2.9.2)**
• for all vaginal tablets except those intended for prolonged local action (special method for vaginal tablets)
• Examine the state of the tablets after 30 min
3. Vaginal capsules (Capsulae vaginales)

- Def. Ph.Eur.10: Vaginal capsules (shell pessaries) are solid, single-dose preparations. They are generally similar to soft capsules as defined in monograph *Capsules*, differing only in their shape and size.
- Vaginal capsules have various shapes, usually ovoid.
- They are smooth and have a uniform external appearance.
• Production: a suitable test is carried out to demonstrate the appropriate release of the active substance(s) from vaginal capsules intended for prolonged action
• Tests: Disintegration (2.9.2):
• for all vaginal capsules except those intended for prolonged local action
• Examine the state of the capsules after 30 min
4. Vaginal solutions, emulsions and suspensions

- **Def. Ph.Eur.10**: Vaginal solutions, emulsions and suspensions are liquid preparations intended for a local effect, for irrigation or for diagnostic purposes.
- Supplied in single-dose containers. The container is adapted to deliver the preparation to the vagina or it is accompanied by a suitable applicator.
• May contain excipients, for example to:
  ▫ adjust the viscosity of the preparation,
  ▫ adjust or stabilize pH
  ▫ increase the solubility of the active substance(s)
  ▫ stabilize the preparation

• These substances do not adversely affect the intended medical action or, at the concentrations used, cause undue local irritation
• Vaginal emulsions may show evidence of phase separation but are readily redispersed on shaking.
• Vaginal suspensions may show a sediment that is readily dispersible on shaking to give a suspension that remains sufficiently stable to enable a homogenous preparation to be delivered.
• Production: in the manufacture of vaginal suspensions measures are taken to ensure a suitable and controlled particle size with regard to the intended use

• Vaginal douches, solutions – for irrigation, cleansing of vagina
5. Tablets for vaginal solutions and suspensions

- Def. Ph.Eur.10: Tablets intended for the preparation of vaginal solutions and suspensions are single-dose preparations that are dissolved or dispersed in water at the time of administration.
- They may contain excipients to facilitate dissolution or dispersion or to prevent caking.
- Apart from the test for disintegration, tablets for vaginal solutions or suspensions conform with the definition for Tablets.
- After dissolution or dispersion, they comply with the requirements for vaginal solution or vaginal suspension, as appropriate.
• Tests: **Disintegration (2.9.1)** - tablets for vaginal solutions or suspensions disintegrate within 3 min, using water R at 15-25 °C as the liquid medium

• Labelling: the label states:
  ▫ The method of preparation of the vaginal solution or suspension
  ▫ The conditions and duration of storage of the solution or suspension after constitution
6. Semi-solid vaginal preparations

- Def. Ph.Eur.10: Semi-solid vaginal preparations are ointments, creams or gels
- They are often supplied in single-dose containers. The container is provided with a suitable applicator
- They comply with the requirements of the monograph *Semi-solid preparations for cutaneous application*
Topical vaginal preparations:

• for infections (ex: nystatin, clotrimazole, miconazole, clindamycin, sulfonamides)
• vaginitis,
• conditions of endometrial atrophy
• contraceptives (ex: progesterone, dinestrol)

• Mainly applied by applicators
How to Apply Vaginal Cream

1. Wash your hands
2. Squeeze the cream from the tube into the applicator
3. Lie with your knees drawn toward you
4. Insert the applicator into your vagina and press the applicator plunger downward
5. If the applicator is reusable, wash it with mild soap and warm water
7. Vaginal foams (Spumae vaginales)

- Def. Ph.Eur.10: Vaginal foams comply with the requirements of the monograph *Medicated foams*
- They are intended for the application on the mucous membrane of the vagina

- They consist of a big volume of gas dispersed in the liquid
- They contain 1 or more active substances, surfactants to create foam and other excipients. Foam is usually created during application from the pressurized container equipped with the valve and push button
• Aerosols foams containing estrogenic substances and contraceptive agents
• Container has plunger which apply the foam in the vagina
• Povidone-iodine vaginal foams
• Novel approaches: bioadhesive foams
8. Medicated vaginal tampons (Tampona vaginalia medicata)

- Def. Ph.Eur.10: Medicated vaginal tampons are solid, single-dose preparations intended to be inserted in the vagina for a limited time.
- They comply with the requirements of the monograph *Medicated tampons*.
- active substance(s) suspended in the base with other excipients is absorbed in textil hydrophile material.
30 pcs/lot
Controlled release vaginal drug delivery

**Advantaged:**
- Prolonged release
- Minimal systemic side effects
- Increase of bioavailability
- Smaller dose compared with oral route
- Hepatic FPM can be avoided
1. Vaginal rings

- Circular ring type drug delivery devices designed to release the drug in a controlled fashion after insertion in the vagina
- Advantages:
  - user controlled,
  - no daily intake of pills,
  - continuous delivery of low dose steroids
• 5.5 cm diameter with a circular cross section (diameter 4-9 mm) and the ring is inserted in the vagina

• **Simple rings:**
  
  • Drug is homogenously dispersed within polymeric ring
  
  • Drug at the surface of the ring is released faster than drug in the inner layer of the ring
  
  • Sometimes, drugs in the outermost layer provide an initial burst release
To obtain a constant release of a drug:

A) Reservoir type:

- Drug is located within the central core that is surrounded by a drug-free silicon layer that acts as rate controlling membrane for drug diffusion.
- In a single ring it is possible to have several cores of different drugs (administration of several drugs from the same device).
• The rate of drug release can be modified by changing the core diameter or thickness of the no medicated coating

• Material: polymer:
  ▫ Poly(dimethylsiloxane) or silicone
  ▫ Ethylene vinyl acetate
  ▫ Styrene butadiene block copolymer
B) Matrix type
- Drug is homogenously dispersed through the polymer matrix

C) Sandwich type:
- Consist of a narrow drug containing layer located between non-medicated impervious central core and non-medicated outer rate controlling band
- Small and constant release of the drug
Vaginal rings are used for:
- Contraceptives (rings are placed in the vagina for 21 days + 7 days ring-free period)
- Hormone replacement therapy
2. Local progesterone release

- From various polymers
- Cervical ripening and induction of labor
- Contraceptive device: intrauterine device IUD:
  - 1. contraceptive metals: metal device + polypropylene plastic device in shape of number 7, copper is released by a combination of ionization and chelation from a copper wire wrapped around the vertical limb
  - 2. steroid hormones: a reservoir system of progesterone (release of progesterone is almost constant for 1 year)
Types of IUDs; An IUD in Position

Copper T 380A

(b)
3. Vaginal inserts

- Contain flat rectangular polymeric slab enclosed in a pouch of knitted polyester removal system
- The buff coloured semi-transparent hydrogel slab contains drug
- The retrieval system is in the shape of long knitted tape that is used to retrieve the slab
- CERVIDIL
DESIGNED FOR CERVICAL RIPENING

Easy to insert and remove¹:

CERVIDIL is a thin, flat, polymeric slab which is rectangular in shape with rounded corners contained within the pouch of an off-white knitted polyester retrieval system.

Dinoprostone-infused insert is placed in the posterior fornix of the vagina.

Long tape retrieval system allows CERVIDIL to be easily removed anytime.

Controlled release of dinoprostone from insert slab for up to 12 hours.
4. Bioadhesive delivery systems

- **Disadvantages of conventional vaginal formulations:**
  - Low retention to the vaginal epithelium
  - Leakage and messiness

- **Advantages of bioadhesive vaginal delivery systems:**
  - Formulation are readily localized in the region of application thus improving BA of drugs
  - Provide intimate contact of the formulation with the underlying absorption surface. It allows modification of tissue permeability for absorption of macromolecules (as proteins)
  - It permits continuous and prolonged residence of the dosage forms at the site of application
  - It reduce side effects due to avoidance of repeated administration of the drug
Low production cost
Avoidance of aqueous or organic solvents
Ease of self-administration with no need to use applicators
Gel-like consistency in the activated state
Avoidance of local irritation
Rapid bioadhesion
Prolonged residence time in the vaginal cavity even in absence of physiological secretions
Extended dosing interval
Improved chemical and physical activity
MUCOADHESIVE POLYMERS:

- Synthetic and natural polymers
- Polymers capable of forming hydrogels:
  - Polyacrylates
  - Polycarbophil
  - Chitosan
  - Cellulose derivates (HEC, HPC and HPMC)
  - Hyaluronic acid derivates
  - Pectin
  - Tragacanth
  - Carrageenan
  - Sodium alginate
  - Thyolated polymers
- Bioadhesive properties are ensured by polyacrylic acid-based polymers = Carbomers (many are commercially available)
- **Principle:** The water insoluble polymer swells in vagina and form bioadhesive gel on vagina layer
• Classification of mucoadhesive vaginal drug delivery systems:
  ▫ Mucoadhesive gels
  ▫ Mucoadhesive Tablets
  ▫ Mucoadhesive films
  ▫ Emulsion type Mucoadhesive systems
  ▫ Mucoadhesive pessaries or suppositories
  ▫ Bioadhesive Vaginal foams
1. Mucoadhesive vaginal gels
   - Most widely used mucoadhesive vag. del. syst.
   - Prolonged contact between the active substance and the vaginal mucosa
   - Gradual release of the active substance over time
   - Hydrating and lubricating action
   Ex: Crinone gel
2. Mucoadhesive vaginal tablets

- Polymers: polycarbophil, cellulose ethers, chitosan and polyvinylpyrrolidinone
- Matrix mixture comprise active substance and excipients
- Drug diffusion through the swollen polymer and progressive erosion/dissolution of the matrix
bioadhesive effervescent vaginal tablets
Ex: ketokonazole
Release of the active substance is controlled by:
  ▫ Changing polymer type (Carbopol, HPMC or HPC)
  ▫ Polymer concentration
  ▫ Effervescent content (acts as disintegrating agent)
3. Mucoadhesive vaginal films

- Sheets (of 220 – 240 µm thickness) often of square shape (5 x 5 cm), colourless, soft, homogenous surface
- Film is made of a precursor composition containing a water-soluble or water-swellable thermoplastic polymer (HPC and/or PEO) and a bioadhesive polymer
- + active substance, preservative, buffering agent, antioxidant, super-disintegrable or absorbent, flavorant, colorant, water-insoluble polymer, organic acid, surfactant, film modifier and/or cross-linking agent
• Polymer: HPMC, gelatin, alginic acid sodium salt, pectin, collagen, poloxamer, carbopol, microcrystalline cellulose, polyacrylic acid, PEG and polypropylene glycol
• Film: controllable rate of gelling, swelling and degradation
• pH-responsive films: biocompatible, hydrophilic polymer, positively charged at a low pH and assumes a neutral form at a higher pH
4. Emulsion type mucoadhesive vaginal systems
   • Emulsion of neutral pH, w/o type
   • Water soluble inner phase contains an active agent
   • Size of particles 0.1-100 μm
5. Mucoadhesive vaginal suppositories
   Consist of:
   ▫ Hydrophilic polymers: sodium carboxymethyl cellulose, polyacrylates
   ▫ Pessary/suppository base
   ▫ Water (30% g/g)
   ▫ Active substance
6. Bioadhesive vaginal foams
- o/w emulsion foams
- w/o emulsion foams
- Petrolatum based foam
- Waterless hydrophilic foam
- Oily foam
- Suspension foam

- Mixture of hypromellose and carbopol
- Sodium carboxymethylcellulose and HEC pressurized in aluminium monoblock containers
Evaluation of vaginal formulations

In-vitro studies:

• Release:
  ▫ By membrane diffusion studies
  ▫ Microbiological methods
  ▫ Vaginal dissolution test

• The bioadhesive strength
  ▫ Measuring of tensile strength or shear stress required to separate the formulation from the vaginal mucosa
  ▫ Disintegration or dissolution test
  ▫ Uniformity of content or mass
• **In vivo studies:**

• **Bioavailability tests:**
  ▫ Monitoring quantities of systematically absorbed materials (e.g. proteins)
  ▫ Measuring the pharmacological activity
  ▫ Analysis of vaginal lavage

• **Methods:**
  ▫ Gamma scintigraphy – assess distribution, spreading and retention of vaginal formulation
  ▫ Colposcopy – for direct in vivo visualization and analysis
Tests according to Ph.Eur. 10

1. Uniformity of dosage units
2. Uniformity of content
3. Uniformity of mass
4. Dissolution test
1. Uniformity of dosage units (2.9.40)

- For liquid and semi-solid single-dose vaginal preparations
- Solid-single dose vaginal preparations comply with the test or, where justified and authorised, with the test for uniformity of content
- Herbal drugs and herbal drug preparations present in the dosage form are not subject to the provisions of this paragraph
2. Uniformity of content (2.9.6)

- Solid single-dose vaginal preparations with a content of active substance less than 2 mg or less than 2 % of the total mass comply with the test A (vaginal tablets)
- Or test B (pessaries, vaginal capsules)
• If the preparation contains more than 1 active substance, this requirement applies only to those substances that correspond to the above conditions.

• Is based on the assay of the individual contents of active substance(s) of a number of single-dose units to determine whether the individual contents are within limits set with reference to the average content of the sample.
3. Uniformity of mass (2.9.5)

- Solid single-dose vaginal preparations comply with the test
- If the test for uniformity of content is prescribed for all active substances, the test for uniformity of mass is not required
• Technique: weigh individually 20 units taken at random, for single-dose preparations presented in individual container, the contents of 20 units, and determine the average mass

• Not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation shown in table 2.9.5.-1 and none deviates by more than twice that percentage
Table 2.9.5.-1

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Average mass</th>
<th>deviation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets (uncoated and film-coated)</td>
<td>≥ 80 mg</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>80-250 mg</td>
<td>7,5</td>
</tr>
<tr>
<td></td>
<td>≤ 250 mg</td>
<td>5</td>
</tr>
<tr>
<td>Capsules, granules (uncoated, single-dose), powders (single-dose)</td>
<td>≤ 300 mg</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>≥ 300 mg</td>
<td>7,5</td>
</tr>
<tr>
<td>Powders for parenteral administration (single-dose)</td>
<td>≥ 40 mg</td>
<td></td>
</tr>
<tr>
<td>Suppositories and pessaries</td>
<td>Všetky hmotnosti</td>
<td>5</td>
</tr>
<tr>
<td>Powders for eye-drops and eye lotiones (single-dose)</td>
<td>≥ 300 mg</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>≥ 300 mg</td>
<td>7,5</td>
</tr>
</tbody>
</table>
4. Dissolution

- A suitable test may be carried out to demonstrate the appropriate release of the active substance(s) from solid single-dose vaginal prep., for example 2.9.3. Dissolution test for dosage forms or in 2.9.42 Dissolution test for lipophilic solid dosage forms.
- When a dissolution test is prescribed, a disintegration test may not be required.
Thank you for the attention