PRINCIPLES AND SYSTEMS OF DRUG DELIVERY · SEMINARS 21–23

Local cavities: eye, ear, vagina, uterus and rectum

Educational program “Pharmacy” · 4th year · Al-Farabi Kazakh National University

Why eye drops work poorly

7 µL

Tear volume; a drop is 25–50 µL and mostly overflows

~1 µL/min

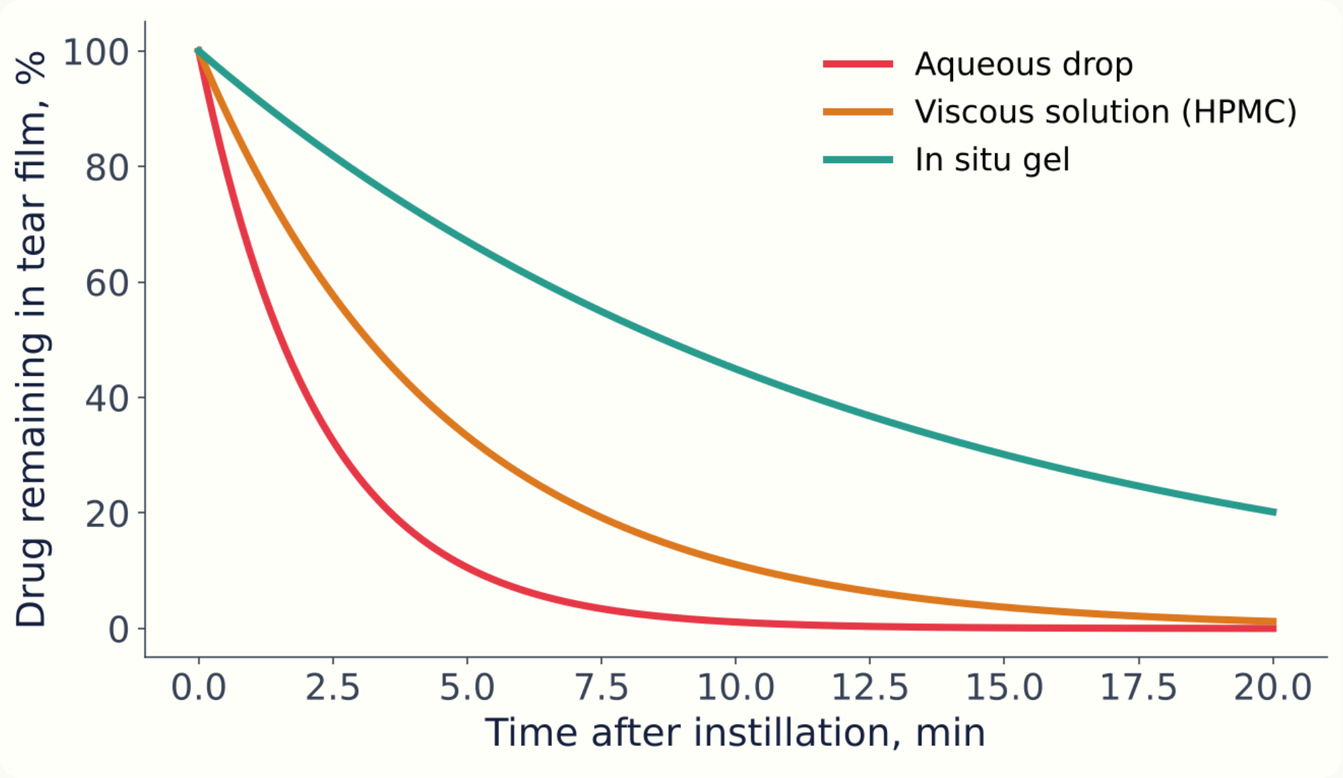
Tear turnover plus nasolacrimal drainage

< 5%

Of the dose enters the eye; the rest reaches the blood

Barriers: tear film, cornea (lipophilic epithelium + hydrophilic stroma), conjunctiva, blood–retinal barrier for the back of the eye.

Viscosity and in situ gels slow precorneal loss



Ion-activated: gellan gum (Timoptic-XE)

Temperature: poloxamer 407

pH: carbomer, cellulose acetate phthalate

Controlled ocular delivery systems

System	Example	Feature
Insert	Ocusert (1974), Dextenza	Pilocarpine 7 days; dexamethasone in tear duct 30 days
Nanoemulsion	Ikervis, Restasis	Cyclosporine for dry eye; cationic droplets adhere longer
Drug-eluting lens	Acuvue Theravision	Ketotifen; FDA 2022
Intravitreal implant	Ozurdex, Iluvien	PLGA ~6 months; non-degradable up to 36 months
Intracameral	Durysta, iDose TR	Glaucoma without daily drops
Refillable port	Susvimo	Ranibizumab refilled every 24 weeks

Otic delivery

External ear

Drops for otitis externa (ciprofloxacin + dexamethasone)

Middle ear

Otiprio: ciprofloxacin in poloxamer 407, one dose during tube surgery (FDA 2015)

Inner ear

Intratympanic steroids, gentamicin; entry via round window membrane

Poloxamer 407 is liquid when cold and gels at body temperature, holding the drug against the round window. Loss: Eustachian tube.

The vagina as a route of administration

Advantages

- Large, well-vascularised surface
- Avoids hepatic first pass
- Long-term devices possible (rings)
- Local therapy: infections, atrophy

Variables

- pH 3.8–4.5 (lactobacilli)
- Epithelium thickness changes with cycle and age
- Fluid volume small; leakage
- Acceptability, cultural factors

Vaginal rings: polymer reservoirs and matrices

Ring	Drugs	Polymer	Use
NuvaRing	Etonogestrel + ethinylestradiol	EVA reservoir	3 weeks in, 1 week out
Annovera	Segesterone acetate + EE	Silicone	Reusable for 1 year
Estring	Estradiol, low dose	Silicone reservoir	Local atrophy, 90 days
Dapivirine ring	Dapivirine (NNRTI)	Silicone matrix	HIV prevention, monthly

Same design rules as implants: reservoir → near zero order; matrix → declining release.

Seminar 22 · Malcolm et al., J Control Release 2016;241:57–70; product information; WHO 2021 recommendation (dapivirine ring)

Intrauterine contraception: hormonal and non-hormonal

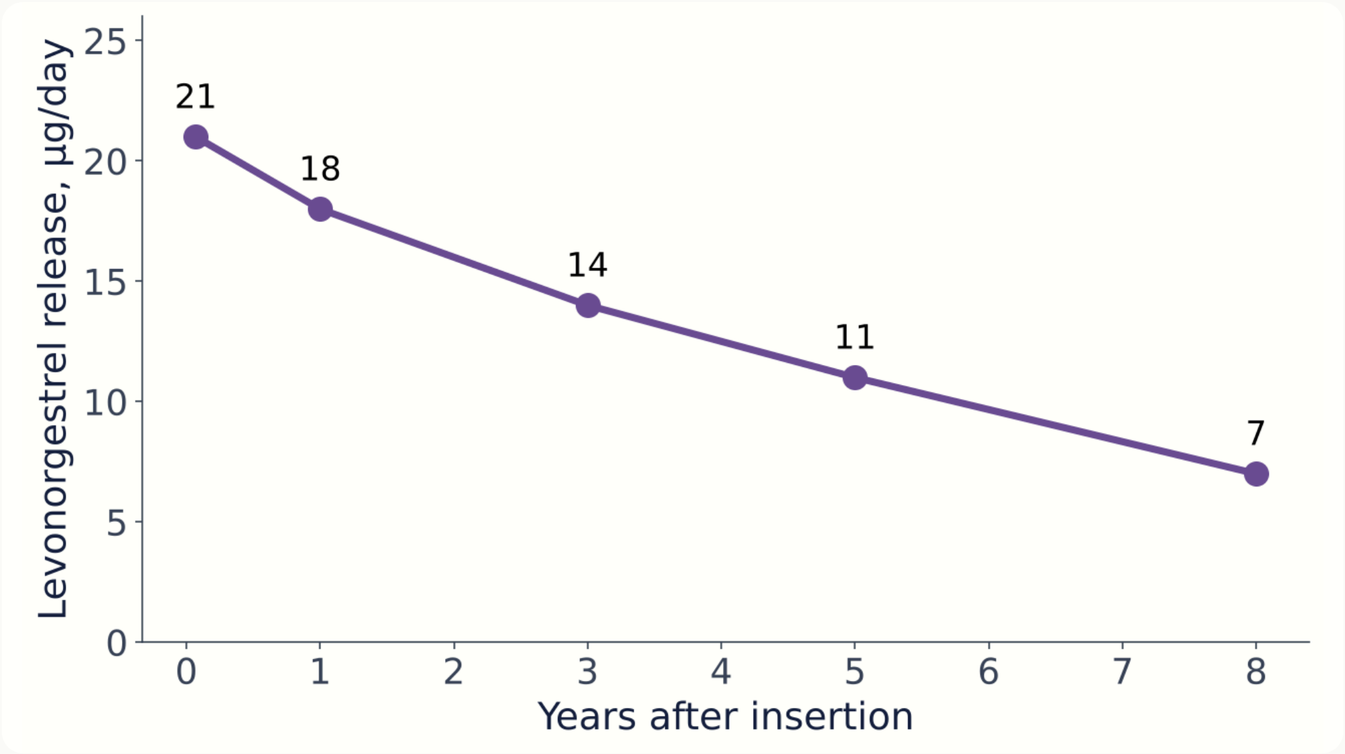
Levonorgestrel IUS

- T-frame + PDMS reservoir with 52 mg LNG
- Thickens cervical mucus, thins endometrium
- Up to 8 years (Mirena); smaller doses for 3–5 years
- Also treats heavy menstrual bleeding

Copper IUD

- Copper wire releases Cu^{2+} ions
- Toxic to sperm, inflammatory reaction
- Up to 10 years (TCu380A)
- Emergency contraception within 5 days

Levonorgestrel release from the IUS over 8 years

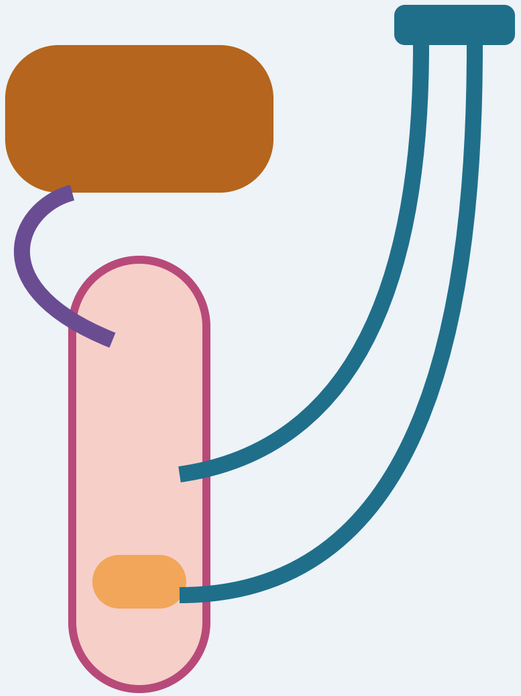


21 → 7 µg/day: gradual decline as the reservoir empties

Still effective: the uterus is the target, so tiny doses are enough

Oral LNG pill: 150 µg/day

Rectal absorption: a partial bypass of the liver



Upper rectum → superior rectal vein → portal vein → **liver**

Lower rectum → middle and inferior veins → vena cava, **no first pass**

Suppository placed low avoids part of the first-pass effect

Suppositories: bases and factors affecting absorption

Bases

- **Fatty** (cocoa butter, hard fat): melt at 34–37 °C
- **Water-soluble** (PEG, glycerinated gelatin): dissolve in rectal fluid
- Drug–base partition decides release

Factors

- Only ~1–3 mL rectal fluid, pH ~7.5
- Particle size of suspended drug
- Depth of insertion (first pass)
- Defecation, patient acceptance

Rule: a lipophilic drug in a water-soluble base, or a hydrophilic drug in a fatty base, releases best.

Questions for discussion

1. Why does a second eye drop given immediately add little drug?
2. How does an in situ gel change precorneal residence?
3. Why does the LNG-IUS work with 20 µg/day while the pill needs 150 µg?
4. Compare a reservoir ring and a matrix ring.
5. Why can rectal bioavailability exceed oral bioavailability?
6. Which suppository base suits a lipophilic drug?

References

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