PharmacoLearn

MPH102T Drug Delivery System, M.Pharm Semester 1

Unit 4: Ocular Drug Delivery Systems

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4.1 Why ocular delivery is difficult

The eye is protected so well that most of an eye drop never reaches its target. Less than about 5 percent of an instilled dose typically enters the eye; the rest is drained or absorbed into the blood through the nose. Understanding the barriers is the whole unit, because every ocular delivery technology is an answer to one of them.

4.2 Barriers of drug permeation

- **Tear film and tear turnover:** the precorneal tear film is only a few microlitres, the cul de sac holds about 30 microlitres at most while a commercial drop is 25 to 50 microlitres, so much of the drop spills or drains at once. Tear turnover (about 1 microlitre per minute, faster with reflex tearing from irritation) washes the drug away within minutes.
- **Nasolacrimal drainage:** solution drains through the puncta into the nose, where the drug is absorbed into the systemic circulation across the nasal mucosa without first pass protection. This is why eye drops can cause systemic side effects: timolol eye drops can slow the heart and constrict airways in sensitive patients.
- **The cornea:** the main route into the anterior chamber and a three layer barrier in series: the lipophilic epithelium (with tight junctions), the hydrophilic stroma (about 90 percent of corneal thickness), and the lipophilic endothelium. A drug must therefore be both water soluble enough to cross the stroma and lipid soluble enough to cross the epithelium: an intermediate partition coefficient, log P roughly 1 to 3, performs best. Ionised drug crosses poorly.
- **The conjunctiva and sclera:** the conjunctiva is leakier than the cornea and rich in blood vessels, so drug absorbed there is largely lost to the blood (non productive absorption), though the conjunctival and scleral route is genuinely useful for larger molecules aiming at tissues behind the eye.
- **Blood ocular barriers:** the blood aqueous barrier (tight junctions of the iris and ciliary vessels) and the blood retinal barrier (retinal pigment epithelium and retinal vessel endothelium) block entry from the blood into the eye, which is why systemic dosing barely treats intraocular disease and why local delivery dominates eye therapy.
- **Efflux and metabolism:** transporters and enzymes in the cornea and iris ciliary body remove or break down part of what does enter.

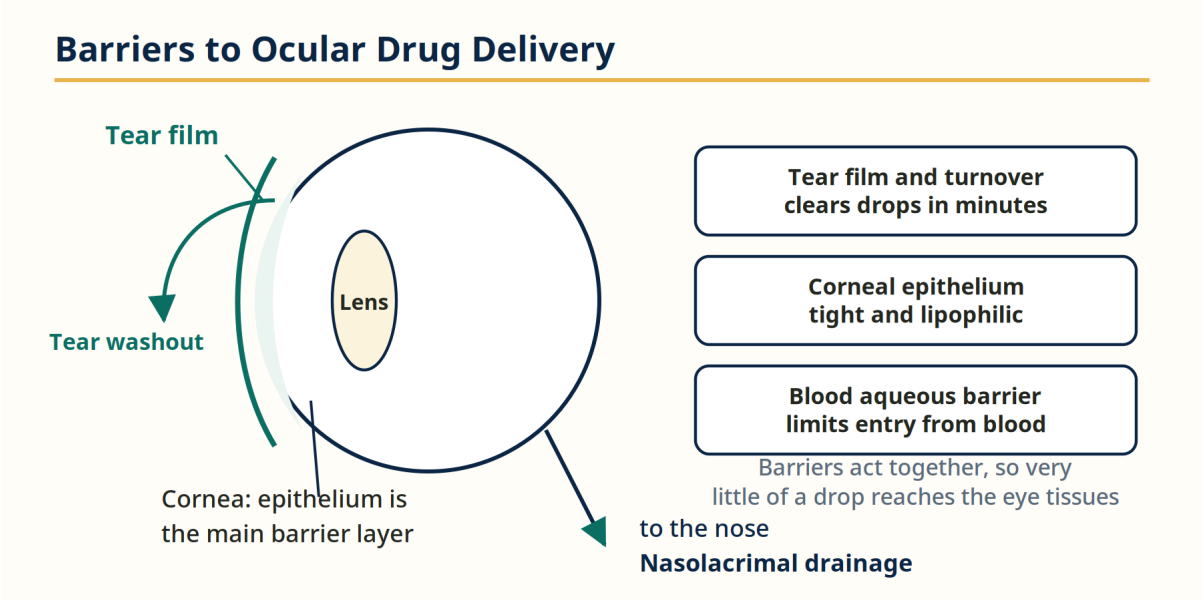

Figure: The barriers of the eye act together: tear washout, the corneal epithelium, drainage and the blood aqueous barrier.

4.3 Methods to overcome the barriers

- **Increasing residence time:** viscosity enhancers (HPMC, polyvinyl alcohol, carbomers) slow drainage; in situ gelling systems are solutions that gel on the eye with temperature (poloxamers), pH (carbopol) or ions in tears (gellan gum, alginate); mucoadhesive polymers grip the mucin of the tear film.
- **Particulate and carrier systems:** liposomes, nanoparticles, nanosuspensions and dendrimers prolong contact, protect the drug and can carry it across the cornea; cyclodextrins keep poorly soluble drugs in solution at the corneal surface without irritation.
- **Ocular inserts and devices:** soluble and insoluble inserts placed in the cul de sac release drug over hours to days. The classic example is the Ocusert, a membrane controlled pilocarpine reservoir that released a set amount per hour for a week, replacing four times daily drops. Collagen shields, drug eluting contact lenses and punctal plugs (which also block the drainage route physically) are the modern relatives.
- **Prodrugs:** a lipophilic ester form crosses the cornea and enzymes inside convert it to the active drug: dipivefrin (a prodrug of adrenaline) and the prostaglandin analogues such as latanoprost (an isopropyl ester prodrug) are the standard teaching examples.
- **Permeation enhancers and physical methods:** preservatives such as benzalkonium chloride loosen epithelial junctions (an effect balanced against their toxicity); research methods include iontophoresis (small electric current drives ionised drug), microneedles and ultrasound for delivery to the back of the eye.
- **Invasive routes for the posterior segment:** intravitreal injections (anti VEGF agents for wet macular degeneration are the biggest example), periocular and subretinal routes, and sustained implants (biodegradable and non biodegradable implants releasing steroid or antiviral drug over months) bypass every surface barrier at the cost of procedure risk.

4.4 Formulation and evaluation of ophthalmic dosage forms (key concepts)

Formulation musts for eye preparations: sterility (a non negotiable requirement; aseptic manufacture or sterilisation, single dose units where possible), isotonicity close to tears (about 0.9 percent sodium chloride equivalent; the eye tolerates a small range), pH near tear pH 7.4 within comfort limits (about 6.5 to 7.8 preferred; buffers are kept weak so tears can restore pH), freedom from particulate matter, controlled

viscosity (high enough to stay, low enough to not blur vision or feel sticky), and a preservative system for multidose containers chosen to balance antimicrobial cover against corneal toxicity.

Evaluation: sterility testing, clarity and particulate inspection, pH, osmolality and viscosity measurement, drug content and in vitro release for inserts and gels, preservative efficacy testing for multidose packs, and irritation assessment historically by the Draize test and now increasingly by in vitro alternatives. For delivery systems specifically, residence and pharmacokinetic studies (drug levels in aqueous humour or tears over time) prove that the barrier strategy actually worked.

Barrier	What it does to the dose	Main formulation answers
Tear turnover and drainage	Removes most of the dose in minutes	Viscosity enhancers, in situ gels, inserts, punctal occlusion
Corneal epithelium and stroma	Blocks very lipophilic and very hydrophilic drugs	Balanced log P design, prodrugs, carriers, cyclodextrins
Conjunctival blood flow	Steals drug into systemic circulation	Target corneal route, reduce dose volume, controlled release
Blood retinal barrier	Stops systemic drugs reaching the retina	Intravitreal injection and implants, periocular routes