Drug Delivery Systems

Ocular Drug Delivery

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Ocular Drug Delivery

- Many eye diseases if **left untreated** can result in severe morbidity (including **blindness**) having a significant impact on patient quality of life.

- The **front** of the eye is **accessible**, and conditions affecting it can be treated by simple **topical eye drops**.

- The **back of the eye** is treated as an entirely **separate** ocular region, and more **advanced** delivery systems including intraocular **injections** and **implants** that can provide sustained drug release **over 2 years**, such as (steroids, antibiotics and antivirals).

❑ Anatomy and physiology of the eye:

A. Outer layer of the eye:

- The outer layer of the eye consists of two segments of a sphere: **Sclera and Cornea**.

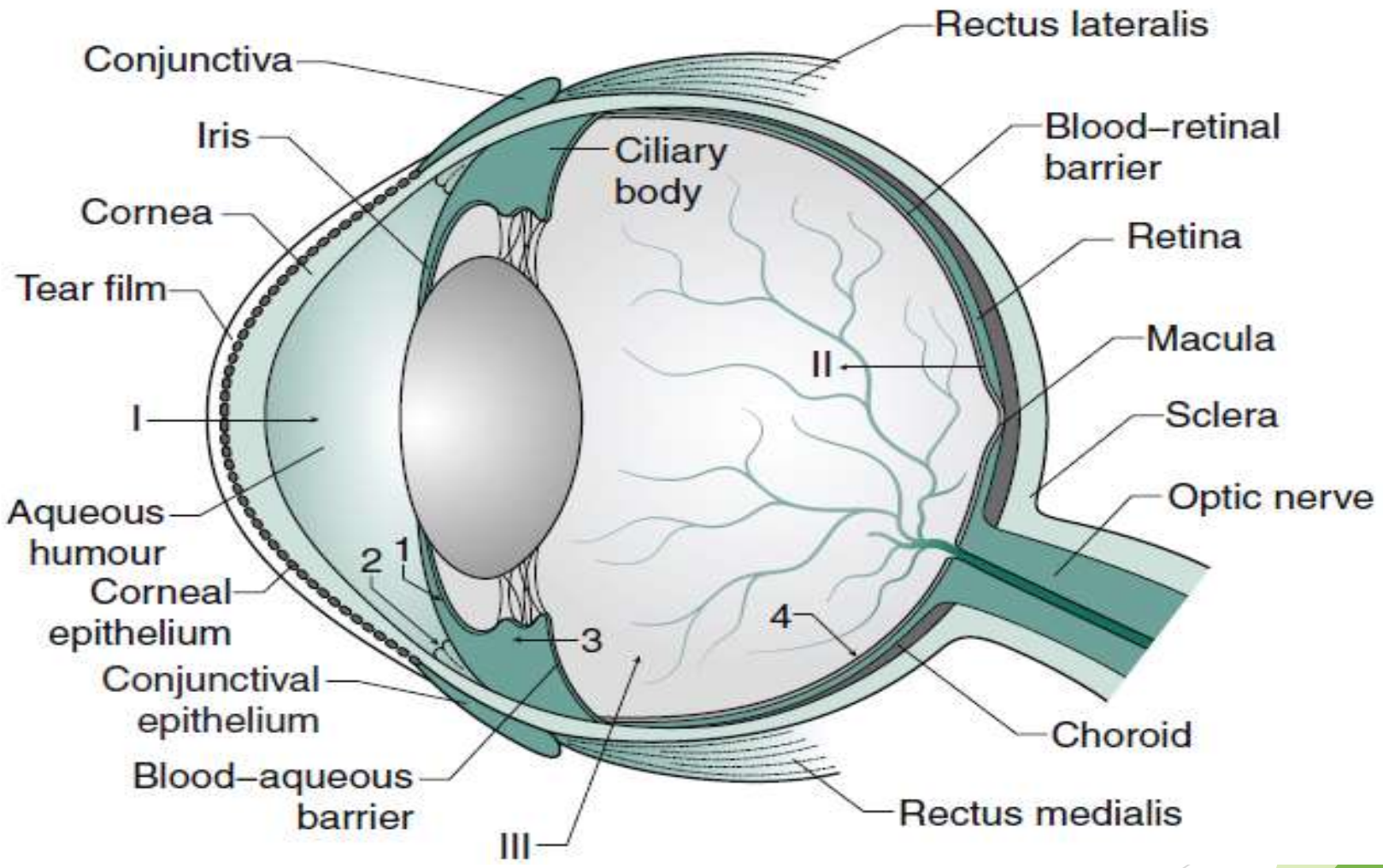
1. The sclera:

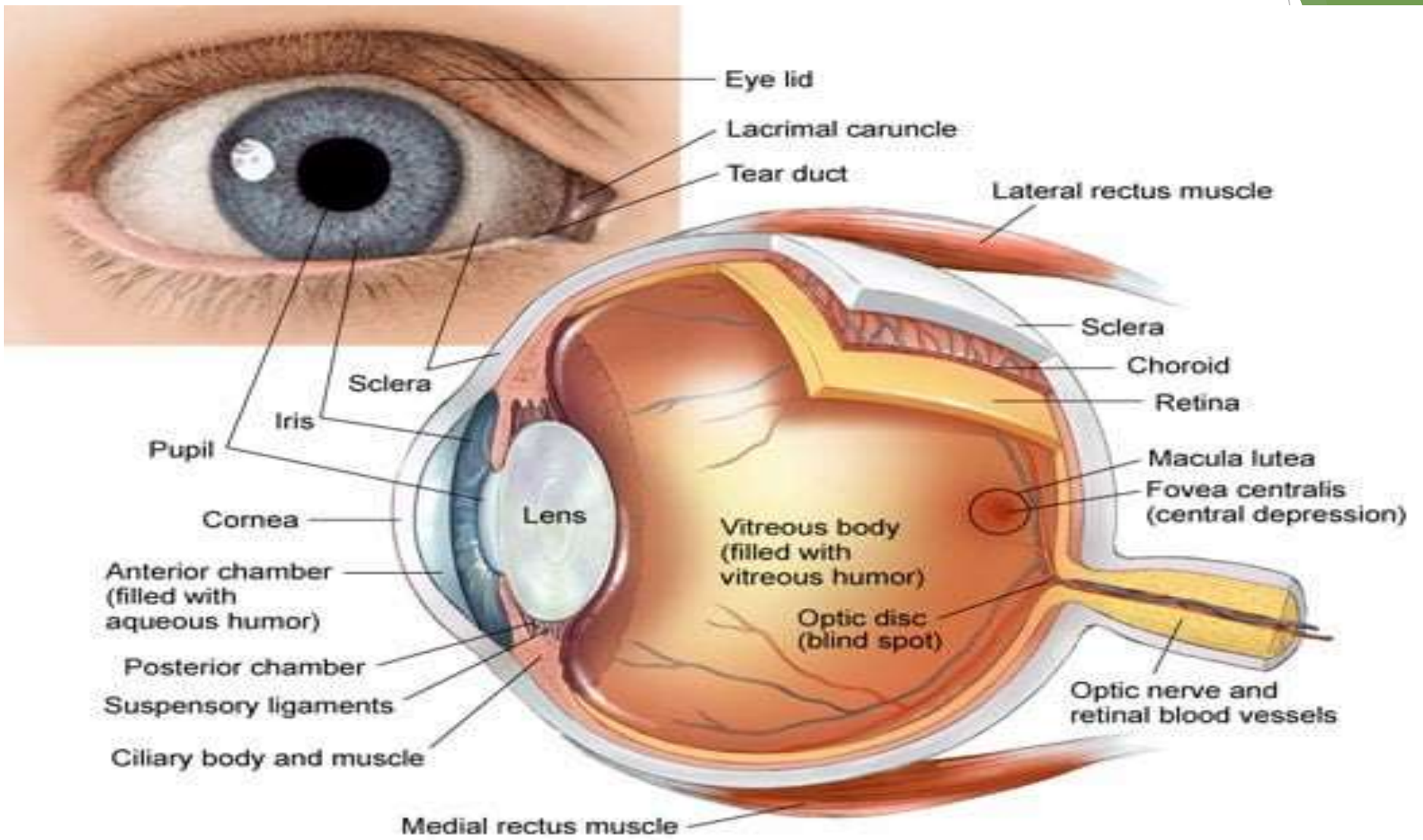
- Forms the posterior **five-sixths** of the eyeball.
- Appears as the **white, opaque** part of the eye.
- Composed of **tough fibrous tissue.**
- Functions

i. **Protects** the eye from internal and external forces.

ii. Maintains **the shape** of the globe.

- **Episclera** is the outermost layer; rich in **blood supply.**
- **Conjunctiva**: Thin, transparent membrane **covers** the **visible sclera** and lines the **inner eyelids**.
- **Optic nerve** exits through the posterior sclera.


Conjunctiva
Iris
Cornea
Tear film
I
Aqueous humour
Corneal epithelium
Conjunctival epithelium
Blood–aqueous barrier
III
2
1
3
Ciliary body
Rectus lateralis
Blood–retinal barrier
Retina
II
Macula
Sclera
Optic nerve
4
Choroid
Rectus medialis


Eye lid
Lacrimal caruncle
Tear duct
Lateral rectus muscle
Sclera
Choroid
Retina
Macula lutea
Fovea centralis
(central depression)
Sclera
Iris
Pupil
Cornea
Lens
Vitreous body
(filled with
vitreous humor)
Anterior chamber
(filled with
aqueous humor)
Optic disc
(blind spot)
Posterior chamber
Suspensory ligaments
Ciliary body and muscle
Optic nerve and
retinal blood vessels
Medial rectus muscle
Right Eye (viewed from above)

2. The cornea:

- Forms the anterior **one-sixth** of the eyeball.
- Transparent and located in **front of the iris and pupil**.
- Densely **innervated**, especially by sensory nerves.
- **Avascular** in the central region.
- Blood supply present at the **corneoscleral limbus** (The junction between the cornea and sclera.
- Functions

i. Refracts and **transmits light** to the lens and retina.
ii. Provides protection **against infection and mechanical injury**.

- **Precorneal tear film**: The cornea and conjunctiva are **covered by a tear film**, produced mainly by the lacrimal gland.

i. **Lubricates** the ocular surface

ii. Protects against **chemicals, microorganisms** and airborne particles.

B. Middle layer of the eye:

- The middle layer consists of: Iris, Ciliary body and Choroid.

1. Ciliary Body

- Ring-shaped structure extending from the iris to the choroid.
- Functions:

i. **Ciliary muscle contraction** allows the lens to become **more convex** (**accommodation**).

ii. Produces **aqueous humour and vitreous humour**.

2. The iris:

- Thin, fragile diaphragm located in front of the lens.
- Separates **anterior chamber and Posterior chamber**.
- Iris color is determined by the amount of **melanin**.

- **Muscles**:

i. **Circular constrictor** muscles.
ii. **Radial dilator** muscles.

- Functions:

i. Regulates **pupil size.**
ii. Controls the **amount of light** reaching the retina.

3. The choroid:

- Highly **vascular** layer.
- Located **between the retina and sclera**.

- Functions:

i. Supplies **oxygen and nutrients** to the outer retina.

ii. Provides a **dark background** to improve image quality on the retina.

C. The inner layer of the eye:

- The **retina** is the **innermost** layer of the eye and consists of a complex network of **neurons** responsible for **light detection and processing.**

- Layers of the Retina:

i. Neural Retina:

- Surrounding the **vitreous cavity**.
- Responsible for **receiving and processing light signals.**

ii. Retinal Pigment Epithelium (RPE):

- Forms the **outer** retinal layer.
- Lies adjacent to the choroid and sclera.

❑ Chambers of the eye:

- The eye contains three main chambers: **Anterior chamber, Posterior chamber and Vitreous cavity.**

1) Aqueous humour:

- Fills the **anterior and posterior** chambers.
- Clear, colorless, watery fluid.
- Contains **electrolytes, organic solutes, growth factors, and proteins**.
- Produced by the ciliary body epithelium and flows into the anterior chamber.
- Functions: **Nourishes non-vascularized** tissues, especially **corneal endothelium and lens.**
- Aqueous humor outflow pathways:

i. Conventional pathway:

➢ Through trabecular meshwork → Into Schlemm's canal → Episcleral veins.

ii. Unconventional pathway:

➢ Through the **sclera** and downstream tissues.

- **Obstruction** of aqueous humor **drainage** → Fluid accumulation → ↑ **Intraocular pressure** → Glaucoma and optic nerve damage.

- **Trabecular Meshwork**

➢ Extracellular matrix, forms a **porous** structure for **aqueous humour flow** → Drains into **Schlemm's canal**.

2) Vitreous Cavity

➢ Accounts for approximately **80%** of eye volume, **pH is 7.5**, viscosity is **2-4** times that of water **(Due to sodium hyaluronate)** → Contains **vitreous humour**.

➢ Composition: 98% water, 2% solids **(collagen type II, Hyaluronic acid).**

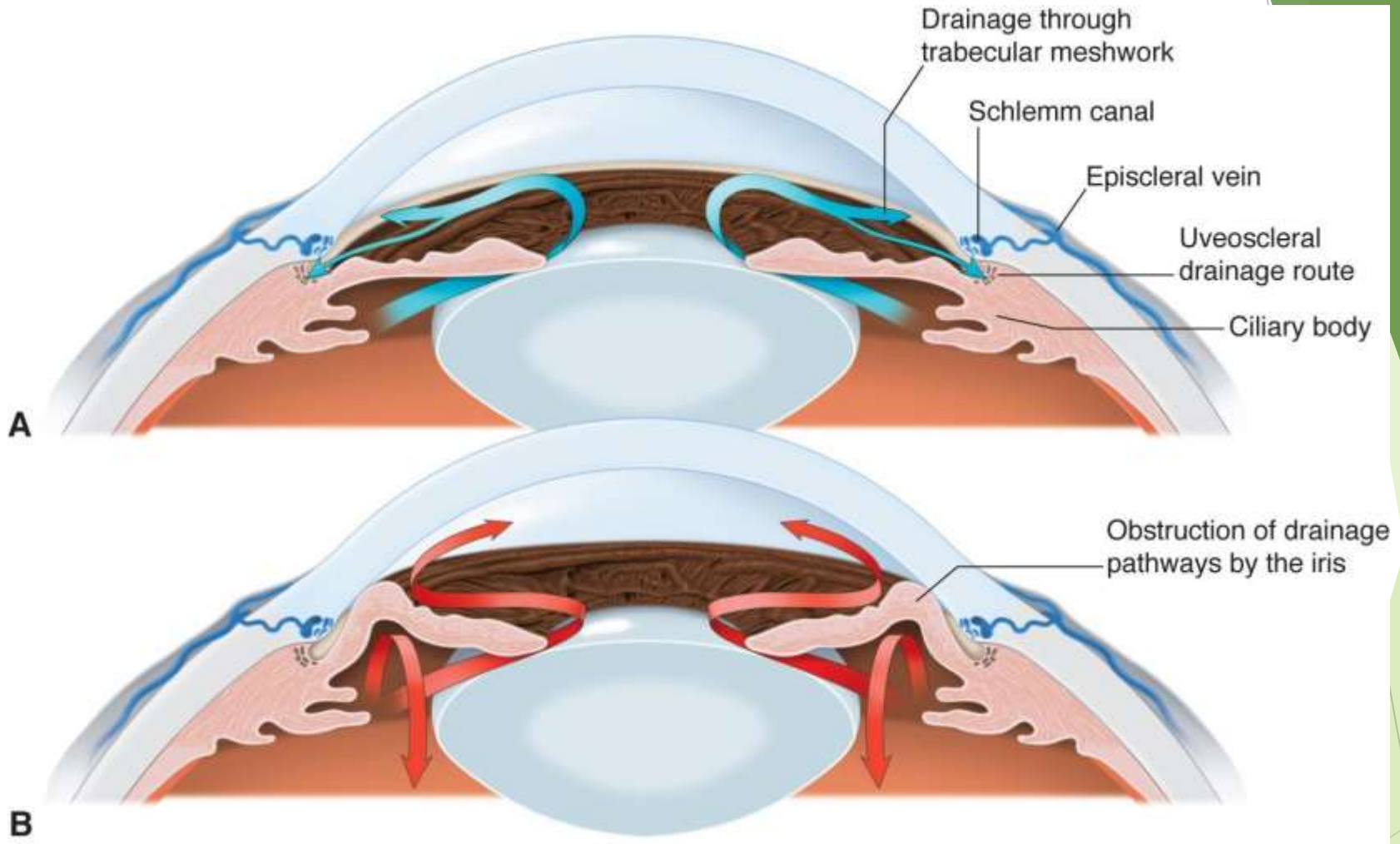


Fig. A: Conventional pathway for aqueous humour drainage.
Fig. B: Obstruction of aqueous humour drainage.

❑ Ocular drug delivery routes and elimination pathways:

- The major **routes** of drug entry in ocular drug delivery can be summarized as follows:

i. Corneal Route (Topical Delivery)

- Primary route for **topically** administered ocular drugs.
- **Drugs penetrate the cornea to reach the aqueous humour.**
- Most relevant for **eye drops.**

ii. Intravitreal Route

- Direct drug delivery **into the vitreous humour.**
- **Bypasses** ocular barriers.
- Used to **target the back of the eye** (e.g., retina, choroid).

- The main barrier for ocular drug delivery in the eye is the **"Blood-Retinal Barrier"**

i. Composed of: **{Retinal pigment epithelium (RPE) and Retinal capillary endothelium}.**
ii. Restricts drug entry from the **systemic circulation**.
iii. Major limitation for drug delivery **to the posterior segment.**

- **Drug Elimination from the Ocular Surface:**

➢ After topical administration, drugs may be eliminated via:

i. Tear turnover.
ii. Nasolacrimal drainage.
iii. Absorption into conjunctival blood vessels → Leads to systemic clearance.

- **Drug Elimination from Intraocular Compartments**
- Once a drug enters the aqueous humour or posterior segment, elimination can occur through:

i. Uveoscleral Pathway:
- Transfer from aqueous humour into **systemic uveoscleral circulation**.

ii. Trabecular Outflow Pathway:
- Drainage from aqueous humour via: **Trabecular meshwork → Schlemm's canal**.

iii. Anterior Diffusion:
- Movement of drug from **vitreous humour into the anterior chamber.**

iv. Posterior Elimination
- Drug transport **across** the **blood-retinal barrier** → **Entry into systemic circulation**.

❑ **Some common ocular conditions and pharmacological interventions:**

i. **Dry eye syndrome**: Dry eye is a common disease which occurs when either the **tear volume is inadequate** or when tears are of **poor quality** (poorly lubricating).

ii. **Cataract:** The **opacity of the lens**, results from **denaturation of the lens protein**. Age-related cataracts, are the most common cause of treatable blindness worldwide.

iii. **Glaucoma**: Group of diseases in which there is a specific **optic nerve damage**, resulting in a characteristic pattern of **visual field loss.**

iv. **Endophthalmitis** is an **inflammatory condition** of the internal layers of the eye. Can be **infectious or non-infectious.**

a) Infectious Endophthalmitis

- Common Causes:

i. **Ocular surgery** (most frequent)

ii. Penetrating **ocular trauma** (when a foreign body is retained).

- Causative microorganisms:

i. Postoperative Endophthalmitis:

- **Gram-positive bacteria** (90%), including: Staphylococcus epidermidis, **S. aureus** and Streptococcus species.

ii. Post-Traumatic Endophthalmitis:

- S. Species and Bacillus species.

b) Non-Infectious Endophthalmitis

- Possible causes:

i. **Impurities** in intraocular injections.
ii. Drug or **excipient aggregation** (e.g. endotoxins and silicone oil precipitates).

- Treatment:

i. **Antibiotics** and anti-inflammatory agents administered (periorbital, intraocular or parenteral).
ii. Surgical intervention: **Vitrectomy** (**removal of infected vitreous humour**).

❑ Topical ophthalmic preparations:

- Topical ophthalmic preparations include solutions, suspensions, ointments/gels and the newer dispersion systems.
- Designing effective ocular formulations requires understanding **ocular tolerance and protective mechanisms:**

i. Tear film defense: Tears contain **lysozymes and immunoglobulins** → Provide anti-infective protection, however, may act as a **barrier for drug absorption**.

ii. Tear **volume (5-9 µL),** continuously secreted by a rate of 1.2 µL/min), so the tear **turnover rate is 17% per minute.**

iii. Blinking moves tear fluids and foreign matter to the nasal corner of the lid surface, and is then drained away by the **nasolacrimal ducts** into the inferior nasal passage often called the **"lacrimal pump".**

- **Clearance of Topically Administered Eye Drops:**

➢ Mechanisms of rapid clearance: **Lacrimal drainage and blinking**.

➢ These mechanisms result in **rapid removal of eye drops** from the ocular surface.

➢ Residence Time: Typical ocular residence time **(4–23 min).**

➢ Drainage rate shows a **positive linear correlation** with volume of eye drop instilled **(Larger volumes → faster washout).**

➢ Maximum temporary **holding capacity** of conjunctival sac is **(20–30 µL).**

➢ **Commercial eye-drop volume** is about **(34–63 µL)** → Overflow and rapid drainage → **Reduced ocular bioavailability** → Increased risk of **systemic absorption** → Greater loss when multiple drops are applied at once.

- Optimization of eye drop administration:

i. Eye drops should be **spaced by at least 5 minutes** → Minimizes washout between doses.

ii. **Punctal Occlusion Technique**: Close the eye and gently press the inside corner for 1 minute → Increases local ocular absorption → Reduces systemic exposure by up to 70%. **(↓ systemic absorption via the nasal mucosa).**

❑ **Formulating ophthalmic preparations:**

1. Osmolality:

- Osmolality is determined by the concentration of salts in lacrimal (tear) fluids.
- Major **inorganic ions in tears (Na, K, Ca, Cl and HCO_3)** → **Maintain osmotic pressure** of intra- and extracellular fluids in the corneal and conjunctival epithelium.
- Normal tear osmolality (About **302 mmol/kg during daytime)**.
- **Dry Eye Syndrome** is characterized by tear film **hyperosmolality** which contributes to irritation and discomfort.

Solution type	Effect on cornea	Eye response
Hypotonic	Water flows into cornea, causing oedema	Increased tear production and reflex blinking
Hypertonic	Water drawn out of cornea, causing dehydration	• Increased tear production and reflex blinking. • Used therapeutically in some cases (e.g. 5% NaCl hypertonic drops). • Used to treat corneal oedema.

- This **increased tear turnover rate** **reduces the retention half-life** of a solution that has been applied to the eye.

- **Normal tear osmotic pressure** is equivalent to **0.9% to 1.0%** sodium chloride solution. Solutions of osmotic pressure equivalent to **0.6% to 1.3%** sodium chloride appear to be **well tolerated by the eye.**

2. Hydrogen ion concentration (pH):

- pH of tears is **close to neutral** and is controlled by various substances dissolved in the aqueous layer of tears: CO_2, bicarbonate, proteins, enzymes and fatty acids.

- pH **increases slowly from 6.9 to 7.5** during the waking hours of the day because of **CO_2 evaporation**. The **buffer capacity of tear fluids is low** but significant; it is controlled by the balance of **bicarbonate and CO2**.

- Acidic or basic eye solutions **cannot be neutralized by the tears**, and therefore **reflex tears are generated to dilute the administered drop and eliminate it**.

- Strongly acidic or basic solutions can damage the ocular tissue.

- It is preferable to formulate preparations as **close to physiological tear pH** as possible to reduce damage and discomfort.

- Commonly used buffers in ophthalmic solutions: **Borate and phosphate buffers.**

3. Surface tension:

- Surface tension of **tear fluid** at physiological temperature: **43.6–46.6 mN/m** (healthy eye).

- Solutions with much **lower surface tension** than tears: Destabilize the tear film lipid layer → **Disperse the lipid layer into droplets** → Lipid droplets may be solubilized by drugs or surfactants → **Loss of the lipid layer** → Increased evaporation of the aqueous layer → Formation of **dry spots on the cornea** → Results in pain, irritation.

- Surfactants are a major contributor to lipid layer disruption.

❑ Role of Surfactants in Ophthalmic Preparations:

- Surfactant are used to:

i. Solubilize **poorly soluble drugs**.
ii. **Disperse** drugs uniformly.
iii. Stabilize **micro- and nanoemulsions**.

- **Nonionic Surfactants are least irritating** (e.g. Polysorbates 20, 60, 80 & Polyoxyl 40 stearate and Polyoxypropylene-polyoxyethylene diol).

- **Potential Adverse Effects of Surfactants**

➢ Even non-ionic surfactants may:

i. Remove the **mucous layer**.
ii. Disrupt corneal **tight junctions**.
iii. Increase **drug permeation** (sometimes intentionally).
iv. **Reduce the effectiveness of preservatives**.

4. Viscosity:

- Viscosity-enhancing polymers are used to:

i. Reduce the **drainage rate**.

ii. Prolong drug retention in the precorneal tear film.

iii. Enhance **drug absorption**.

- Water-soluble polymers that have been used: **poly(vinyl alcohol)** (PVA), polyvinylpyrrolidone, and various **cellulose derivatives**, particularly methylcellulose, HPMC and CMC (at conc of 0.2% to 2.5%) and polyethylene glycol (at conc of 0.2% to 1%).

- Tears are non-Newtonian fluids with shear-dependent viscosity **(Shear thinning system)** → **Viscosity decreased during blinking**.

- This is commonly seen with linear, multiple-charged polymers such as **sodium hyaluronate and carbomers.**

- Zero shear viscosity values of approximately **6.4 mPa.s** for normal tears.

- **Acceptable** viscosity of ophthalmic preparations is **up to 15 mPa.s.**

- If viscosity is high:

i. Increased **lacrimation**.
ii. **Accelerated drainage** to restore the tear film to its physiological viscosity.

- If viscosity is excessively high:

i. **Blurring of vision.**
ii. Potential **blocking** of the ducts.
iii. **Pain on blinking.**

❑ **Topical, liquid ophthalmic preparations:**

A. Solutions:

- **Advantages of ophthalmic solutions:**

i. Easy to manufacture and **low cost.**

ii. **Easy for patient** to administer.

iii. Rapid onset of action, **do not need to undergo dissolution**, such as **anesthetic (lidocaine), diagnostics (fluorescein sodium) and preoperative drugs.**

iv. **Homogenous** and display a better **dose uniformity.**

- **Disadvantages:**

i. **Rapid drainage out of the eye.**

B. Suspensions:

- Used for drugs which are **sparingly soluble in water** (e.g. **steroids**) or to **prolong drug release.**

- Particles tend to be **retained in the conjunctival sac** (pouch where the conjunctiva covering the inside of the lower eyelid and the sclera meet) and **slowly go into solution, thus increasing the contact time.**
- Particle **size** and **shape** should be selected to **avoid irritation** of the sensory nerves in the epithelium.
- Particle size influences the rate of **drug dissolution.**
- The particles need to be **readily dispersible** on shaking by the patient to ensure uniform dose administration.
- A problem that can arise with suspensions is a change in the crystal form of the drug (i.e. **polymorphic changes during storage**), which can lead to **altered drug solubility and dissolution behavior.**

- Using a polymer solution as a **viscosity-enhancing agent** (e.g. **Carbomer 934P**) can **prevent caking and allow particle resuspension by shaking.**

C. Sub-micrometer emulsions:

- **Ciclosporin** is an **immunomodulator** with anti-inflammatory effects.
- Ciclosporin is **hydrophobic** (log P =3.0) and has a very poor aqueous solubility of 6.6 mg/mL and cannot therefore be formulated in conventional aqueous ophthalmic vehicles.
- It has been successfully **solubilized in an oil-in-water submicrometer emulsion** formulated at a pH of 6.5-8.0.
- Oil phase is castor oil, nonionic surfactant polysorbate 80 and glycerol, (cosurfactant).
- Ocular emulsions with a **droplet size of approximately 0.1 µm** have also shown potential for **prolonging drug release** and achieving significantly **higher drug concentrations in the cornea and aqueous humour compared with suspensions.**

❑ Topical, semisolid ophthalmic preparations:

A. Ointments:

- Ophthalmic ointments constitute approximately 10% of ophthalmic products and are usually used for the **treatment of inflammation, infections and ocular surface disease.**

- Advantages of ointments:

i. **Reducing drug drainage** by tear flow.
ii. Increasing corneal **residence time.**
iii. Can be entrapped in the **conjunctival sac (reservoir for the drug)**.
iv. Sustained drug release **over 2 - 4 hours** is usually observed.
v. Incorporation of drugs with **poor aqueous solubility**.
vi. Hydrophobic ointments sometimes **increase the stability** of hydrolysable compounds, particularly peptides.
vii. **Total bioavailability** in the aqueous humour can also be significantly **greater than with solutions or suspensions.**

- **Soft paraffin and liquid paraffin** are commonly used as bases for ophthalmic ointments.

- Antibiotics, antifungals and steroids are the classes of drugs most available as ointments.

- Disadvantages:

i. Drug **bioavailability** usually **peaks later** with ointment vehicles than with solutions or suspensions.
ii. **More difficult to administer than solutions.**
iii. May give rise to a **more variable dose.**
iv. **Blurring of vision** arises which reduces patient adherence.

B. Gels:

- Gels, which are semisolid systems comprising **water-soluble bases**, are also available and are **more favorable** than ointments for **water-soluble drugs**.

- They include polymers such as **PVA**, **poloxamer**, **hydroxypropyl methylcellulose** or carbomers dispersed in a liquid.

- **In situ gelling systems**: Certain ophthalmic gels are activated by physiological triggers **(Ions, pH, and Temperature).**

➢ These systems undergo a phase transition: **(Liquid → viscoelastic gel).**

➢ **Gelation occurs in the conjunctival sac.**

➢ Advantages:

i. Provide more **reproducible dosing**.
ii. Are **easier to administer** → Improve patient adherence and comfort.
iii. Easy instillation with **prolonged residence time**.

- Example for temperature-activated gels:

➢ Common **thermosensitive polymers** (e.g. **Poloxamer 407**).

➢ **Liquid at room temperature** and **gel at ocular surface/body temperature**.

- **Smart Hydrogel**: Graft copolymer of **poly(acrylic acid) and Poloxamer**.

➢ Undergoes **gelation at body temperature**.

➢ Requires **only 1-3%** polymer concentration.

➢ Exhibits bioadhesive properties due to **poly(acrylic acid)**.

➢ Advantages:

i. **Lower polymer conc** → Reduce irritation → Improve patient adherence.

ii. **Bioadhesion** properties → Enhance ocular **residence time** → Improves drug bioavailability.

C. Mucoadhesive systems:

- To **increase the contact time** of topical ophthalmic solutions with the ocular surface have been through the use of mucoadhesive polymers.

- Mucoadhesive polymers are commonly **macromolecular hydrocolloids** with numerous hydrophilic functional groups possessing the correct charge density.

- These polymers can **associate with mucin coat** that covers the conjunctiva and cornea.

- **Electrostatic and hydrogen-bond interactions** are the most common interactions between mucoadhesive polymers and mucin.

- Mucoadhesive polymers can be natural, synthetic or semisynthetic.

i. **Synthetic** polymers as **poly(acrylic acid)** and polycarbophil and cellulose derivatives.

ii. **Semi-natural** mucoadhesive polymers as **chitosan** and various gums (guar, xanthan, carrageenan, pectin and alginate).

- Examples for mucoadhesive polymers:

a) **Chitosan**: Cationic polymer, mucoadhesive with good wetting properties.

- Biodegradable and biocompatible **(Has good ocular tolerance).**
- **Positively charged** at neutral pH → **Electrostatic forces** arise between it and the negatively charged sialic acid residues of the mucus glycoproteins.

b) **Polycarbophil:**

- Higher bioavailability than conventional aqueous eye drops.
- Therapeutic effect **lasts for several days** in the eyelids and conjunctiva following the administration.
- Insoluble in water, **swell at pH (6 - 7)** → On exposure to tears, swells and **entangles with mucin at the ocular surfaces.**
- **Hydrogen bonds exist between unionized carboxylic acid of polycarbophil and mucin.**

D. Ion-exchange resins:

- **The drug (acidic or basic)** is **ionically bound** to an **ion-exchange resin**, forming an **insoluble complex**.
- Release of the drug from this complex occurs only through the **exchange of bound drug ions with physiological ions present in body fluids.**

- The ion-exchange resin itself is an insoluble ionic material composed of:

i. Structural portion: Polymer matrix.
ii. Functional portion: The ion-active group (Positive or negative).

- Drug–resin complexes are spherical, porous and hydrate upon exposure to aqueous fluids.

- They are insoluble, non-absorbable, and considered **safe for use in oral and ophthalmic** pharmaceutical preparations in humans.

- Example: (**Betaxolol Hydrochloride**), cardioselective beta-blocker.

✓ Available as an **ion-exchange resin suspension**.

✓ Cation-exchange resin: **Amberlite IRP-69.**

✓ Drug charge: **Positively charged (basic drug).**

➢ Resin Composition

i. Polymer matrix.

ii. Functional group: Sodium polystyrene sulfonate (**Sulfonic acid group ($-SO_3^-$), acts as a strong cation exchanger).**

➢ Drug Release in the Eye

- Upon ocular instillation → **Sodium ions in the tear film displace Betaxolol** from the resin → **Drug release occurs gradually**.

➢ Advantage:

✓ Betaxolol is **polar**, which may cause **ocular discomfort**. However, formulation as an ion-exchange resin → **Slows drug release** → Reduces ocular irritation.

❑ Barriers to topical ocular drug absorption:

- The topical route is the most common way of treating the anterior segment of the eye.

- Advantages of topical route:

i. **Provide selectivity** with an enhanced therapeutic index.
ii. Avoid **first-pass metabolism**.
iii. Administered in a simple, **non-invasive manner**.

- Disadvantage: **Only 1% to 5%** of the instilled dose reaches the aqueous humour.

- The mechanisms responsible for low ocular drug bioavailability:

i. Highly efficient **lacrimal drainage system** taking drug away from the tear film to the nose.
ii. **Drug absorption by conjunctiva blood vessels** into the systemic circulation.

iii. The **corneal barrier** to drug permeation.
iv. Drug **binding to proteins** (protein levels of lacrimal fluids are higher in inflamed or infected eyes).

A. The corneal barrier:

- Drugs can cross the cornea by: **Passive diffusion, facilitated diffusion or active transport.**

- **Facilitated diffusion and active transport** occur via **specific transporter proteins** which are expressed on the corneal epithelium.

- Passive diffusion does not require transporters but depends on the **physicochemical properties** of the drug **(lipophilicity, molecular size and degree of ionization).**

- The cornea consists of **five layers** (outer → inner): Epithelium, Bowman's membrane, Stroma, Descemet's membrane, and Endothelium.

- The principal barriers to drug transport are: **Epithelium, stroma and endothelium**.

- Epithelium & Endothelium are rich in lipids, while the stroma has high water content

➢ This **alternating lipophilic-hydrophilic structure** strongly influences drug permeation.

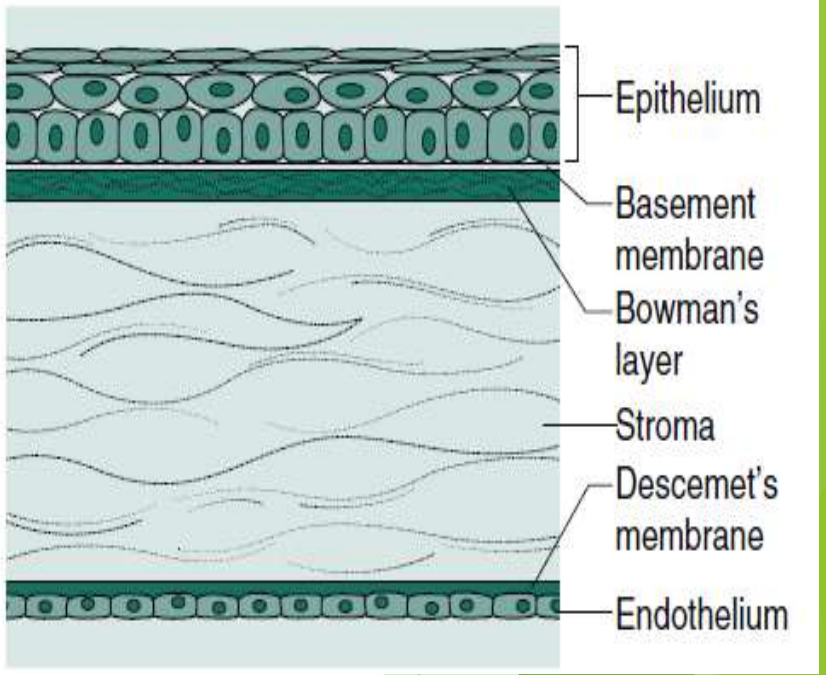
- The **corneal epithelium** (0.1 mm, 6 cells thickness), is the rate-limiting step, contribute **(90% barrier for hydrophilic drug, 10% barrier for hydrophobic).**

- Pathways of drug transport through the epithelium:

i. **Transcellular route**: Drugs pass through epithelial cells, preferred by lipophilic drugs.

ii. **Paracellular route**: Drugs pass between epithelial cells, **limited by tight junctions,** permits only small molecules **(M.Wt ‹ 350 Da)** or ions, **exclude macromolecules with radius › 1 nm).**

- The stroma: Cellular, **aqueous environment**, composed of (glycosaminoglycans and Collagen fibrils (Types I and III)).
- ➢ Collagen fibers arranged in parallel lamellae. Open-knit structure.
- ➢ **Allows hydrophilic molecules** to pass through relatively easily.
- ➢ Acts as a **barrier to highly lipophilic drugs** and high molecular weight compounds.



The human cornea in cross-section

- The **corneal endothelium**: Single – cell layer, contains large intercellular junctions, in direct contact with the aqueous humour.

➢ **Partially resists lipophilic compounds**, and **NOT permit the passage of hydrophilic drugs.**

- **Ophthalmic drugs with modest lipophilicity and low molecular weight are absorbed more efficiently via the corneal route than are hydrophilic, ionized drugs.**

- The **optimal lipophilicity** for the permeation of steroids and beta-blockers corresponds to **log P of 2-3.**

i. Compounds with a **higher lipophilicity** (log P > 3) have **lower permeability** as their permeation is rate limited by the **slow transfer through the hydrophilic stroma.**

ii. Drugs need to have an **appropriate balance of lipid solubility and water solubility** for good corneal permeation.

B. Non-corneal routes of absorption:

- Drug absorption can also occur via the **conjunctival-scleral pathway**.

- Important for **large hydrophilic molecules** (e.g. timolol maleate, carbonic anhydrase inhibitors), Proteins and peptides (may act as drug carriers).

- The conjunctiva has 5-15 layers of squamous epithelial cells with tight junctions at the apical end.

➢ **More permeable or leaky than the cornea** and allows drugs to permeate through both the **paracellular route and the transcellular route**.

➢ **Highly vascularized** → Drug absorption results in **systemic distribution of the drug** away from the eye → Reduced drug availability in eye.

- The cornea covers only about 1/6 of the ocular surface; conjunctival absorption can readily occur.

- Drugs with MW > 1000 Da → Poor corneal permeation.
- Large molecules have good scleral permeation: Dextran (MW ~40,000 Da), Albumin (MW ~69,000 Da).

- Conjunctival-Scleral route is considered nonproductive because:

i. Rapid uptake by **conjunctival blood vessels**.
ii. Drug is diverted into **systemic circulation**.
iii. **Limited drug reaches the aqueous humour**.

- Clinical Implications: (Systemic Drug Interactions)

i. **Ocular** and **oral** drugs **may interact**.
ii. Some topical ocular drugs are **contraindicated in certain patients**.

➢ Examples: **β-blocker** eye drops are contraindicated in **asthma and cardiac failure.**

- Although ocular doses are **much lower than oral doses** → Direct access via **nasal or inhaled mucosal absorption** → Bypasses Intestinal absorption and hepatic first-pass metabolism → can still produce **significant systemic effects**.


Thank you