Ocular Formulation

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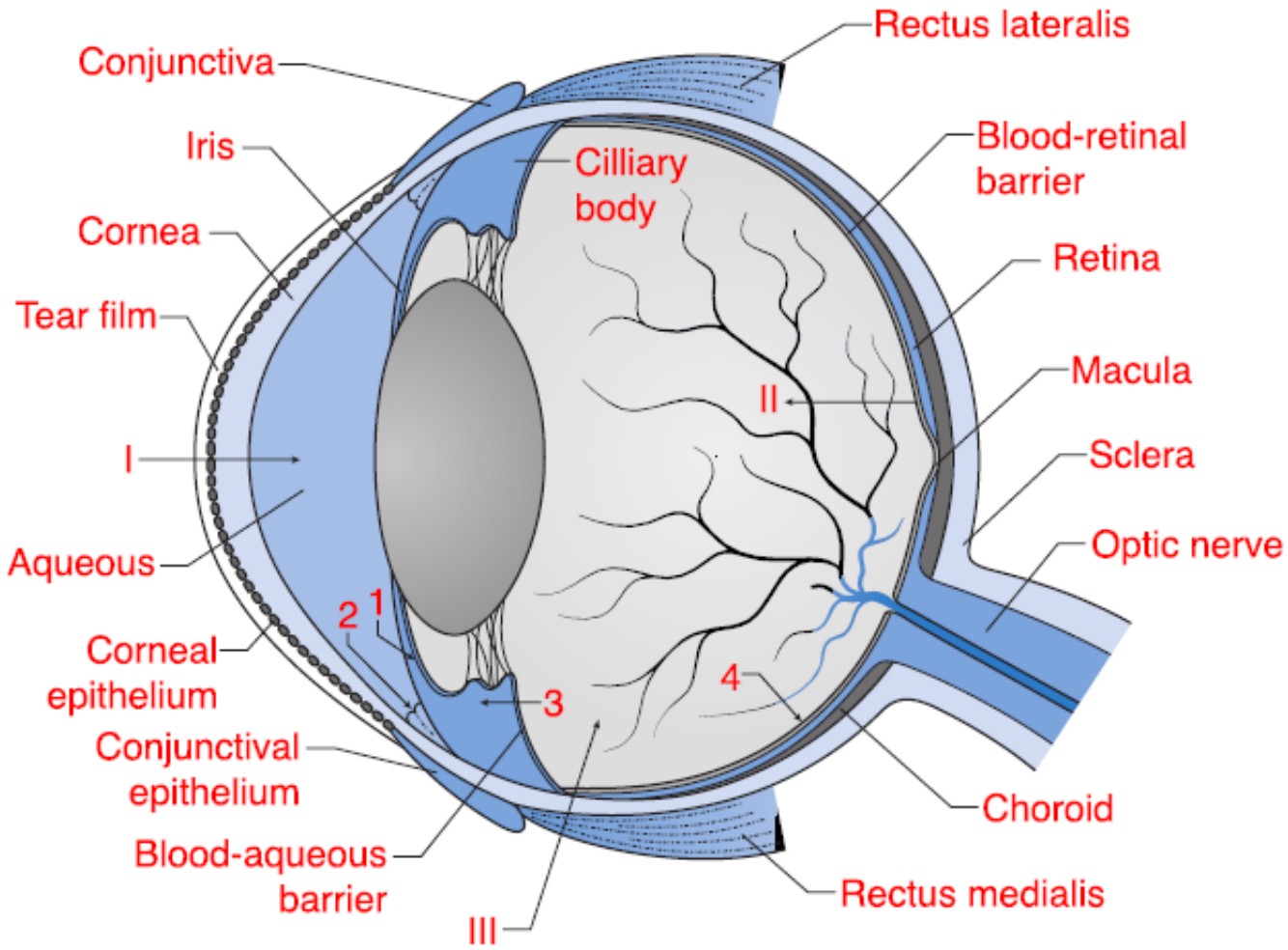
Introduction

- Drug delivery to the eye is one important areas and presents many opportunities and challenges. Eye drops have been used since the times of Cleopatra and comprise over 90% o the ophthalmic preparations in the clinic.
- The front of the eye is accessible and can be treated by simple topical eye drops. The back of the eye is, however, treated as an entirely separate ocular region, and intraocular injections or implants can provide sustained drug release over two years

Anatomy and physiology of the eye



Ocular drug delivery routes and elimination pathways

The routs

I. The cornea is the main route that drugs reach the aqueous humour.

II. The blood retinal barrier that restricts entry of drugs from the systemic circulation into posterior segment of the eye.

III. Intravireal delivery route to directly reach the back of the eye

Drug elimination

I. Drug elimination from the aqueous humour

II. **A**queous humour through the trabecular meshwork and Schlemm's canal

III. Drug elimination from the vitreous humor via diffusion into the anterior chamber.

IV. Drug elimination via posterior route across blood retinal barrier.

Topical ophthalmic preparations

- Topical ophthalmic preparations include: *solutions*, *suspensions*, *ointments/ gels and the newer dispersion systems*.

Protective mechanisms sometimes present a barrier to drug absorption

- lacrimal system → tear volume is 5–9 μL (1.2 μL/minute) / irritants trigger by from 3 to 400 μL/minute
- Blinking moves

The combined mechanisms of lacrimal drainage and blinking rapidly cleared drug with residence time ranging rom 4 to 23 minutes. Moreover, the rate of drainage has a linear correlation with instilled volume.

It is important that the topical preparations do not cause irritation that can be achieved by designing close to the lacrimal fluids

Formulation

- **Osmolality**

The concentration of salts in lacrimal fluids determines its osmolality (sodium, potassium, calcium, chloride and bicarbonate).

Osmolality in healthy eyes has an average value of 302 mmol/kg. Patients with dry eye syndrome have been found to present with tear film hyperosmolality

- Hypotonic ophthalmic solution → corneal epithelium more permeable → water flows into the cornea (oedema).
- Hypertonic solutions → dehydrating of the corneal epithelium

Hypotonic and hypertonic solutions are irritating to the eye and induce an increased production rate of tears.

Osmolality and Osmolarity

- The amount of osmotically active particles in a solution is expressed osmoles (molecules or ions). ***Osmole values depend on the number of particles dissolved in a solution, regardless of charge***.

For substances that maintain their molecular structure when they dissolve (e.g. glucose), osmolarity and the molarity are essentially the same.

For substances that dissociate when they dissolve, the osmolarity is the number of free particles. Thus a 1 molar solution of pure NaCl solution would be 2 osmolar (1 for Na+ and 1 for Cl−).

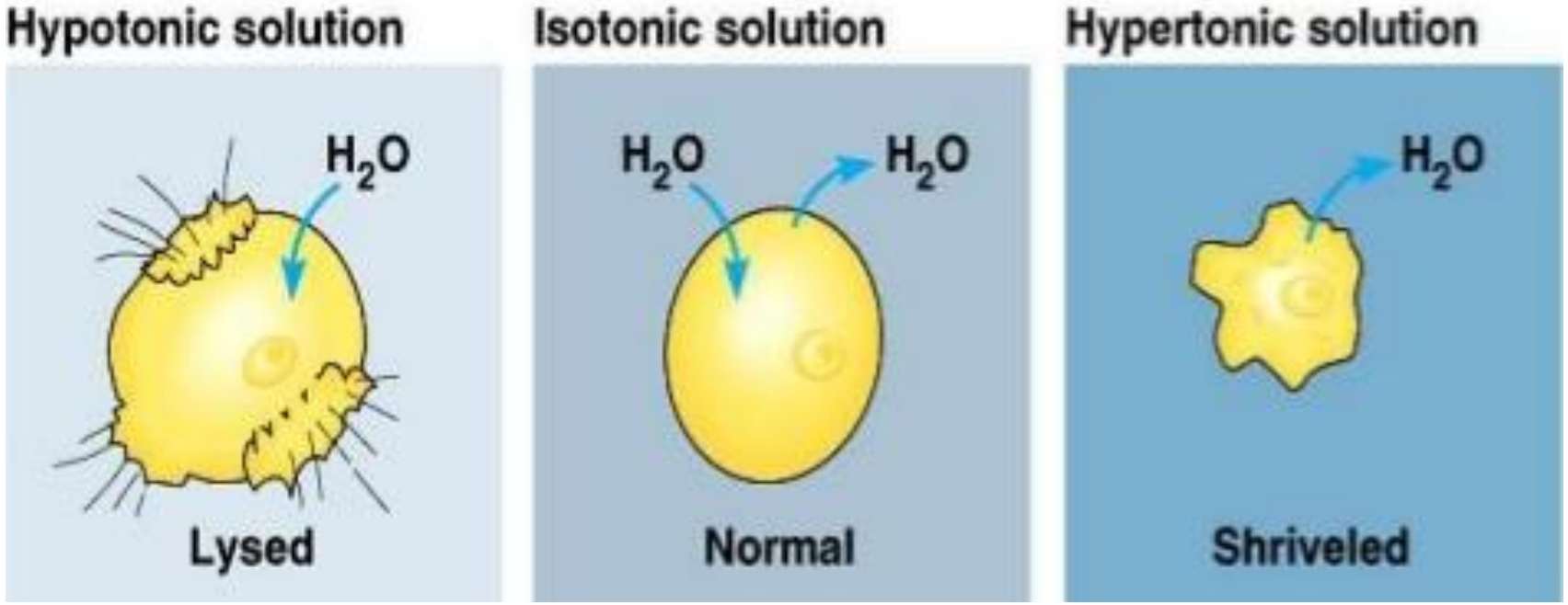
Osmolarity is the number of osmoles per litre of solution and osmolality is the number of osmoles per kilogram of solvent.

- ***Isoosmotic solutions***

If two solutions are separated by a perfect semipermeable membrane, (permeable only to solvent molecules) and no net movement of solvent occurs, then the solutions are said to be ***isoosmotic*** and have equal osmotic pressures.

- ***Isotonic solutions***

Biological membranes do not always function as perfect semi-permeable membranes and some solute molecules in addition to water are able to pass through them. If two isoosmotic solutions remain in osmotic equilibrium when separated by a biological membrane, they may be described as being ***isotonic*** with respect to that particular membrane


Hypotonic solution
H_2O
Lysed
Isotonic solution
H_2O
H_2O
Normal
Hypertonic solution
H_2O
Shriveled

pH of Formulation

- The pH of tears is in the range 6.9 to 7.5. The buffer capacity of tear fluids is low but significant; it is predominantly controlled by the ***balance of bicarbonate and carbon dioxide, as well as proteins.***
- Acidic or basic solutions instilled into the eye cannot be neutralized by the tears that are present and therefore more tear are generated to dilute the administered drop and eliminate it.
- ***The recovery to the original pH of the tear can vary from a few minutes up to 20 minutes. The duration of recovery is influenced by:***

the pH, volume, and buffer capacity of the administered solution, as well as the age of the patient

The eye can generally tolerate topical ophthalmic preparations at a pH within the range 3.5 to 9. However, it is preferable to formulate as close to physiological tear pH.

Preservatives

- Preservatives are included in multi-dose containers to destroy and inhibit the growth of microorganisms that may have been accidentally introduced on opening the container.
- They are not to be used in products for intraocular administration as they can lead to irritation.
- Benzalkonium chloride is the most commonly used preservative, at concentrations ranging from 0.004 to 0.02%. It is a quaternary ammonium salt and causes epithelial toxicity on repeated administrations.