Ocular drug delivery
Introduction

• Drug delivery routes available for treating ocular conditions are topical, systemic (oral or injection), intraocular or periocular (injection or implant).

• Drug delivery to the eye is one of the most important areas of modern ocular therapy and presents many opportunities and challenges.

• The current market for ophthalmic pharmaceuticals is now worth many billions of dollars a year. 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, however, treated as an entirely separate ocular region, and more advanced delivery systems have been designed for its treatment, including intraocular injections and implants that can provide sustained drug release over two years.

• A range of new therapies have and are being developed for treating ocular conditions including cells, genes and proteins, not only the traditional small molecules.
Anatomy and physiology of the eye/Layers of the eye

• The outer layer of the eye can be considered as segments of two spheres: sclera and cornea.
• The sclera is a tough fibrous tissue that protects the eye from internal and external forces and maintains its shape.
• The conjunctiva is a thin, transparent mucous membrane that covers the visible part of the sclera and extends to the inside of the eyelids.
• The optic nerve emerges from the sclera in the posterior part of the eye. The cornea is the most anterior part of the eye, in front of the iris and pupil.
• The cornea refracts and transmits light to the lens and retina. It also protects the eye against infection and structural damage to the deeper parts. The cornea and sclera are connected at the limbus.
Anatomy and physiology of the eye/Layers of the eye

• The surfaces of the cornea and conjunctiva are covered by a film of tears produced by the lacrimal gland. It lubricates the eye surface and protects it from chemicals, microbes and airborne solid particles.

• It comprises three layers: a mucous layer adhering to the epithelium, an aqueous layer and a superficial lipid layer. The aqueous layer constitutes electrolytes, proteins, glycoproteins, biopolymers, glucose and urea, and has a thickness of 8–12 µm. The lipid layer is composed of sterol esters, wax esters and fatty acids. The mucous layer interacts with the epithelial cells of the cornea, and so each eyelid blink allows spread of the tear film over the eye surface. A dynamic equilibrium exists in the pre-corneal tear film as it goes through a continuous cycle of production, evaporation and drainage.

• The middle layer of the eyeball consists of the iris, ciliary body and choroid.

• The inner layer of the eye is the retina, which is a complex network of neurons that process light.
Fig. 41.1 • Structure of the eye and the ocular barriers. (Courtesy of Willoughby et al., 2010.)
Fig. 41.5 • Different routes of ocular drug administration.
Anatomy and physiology of the eye

• The eye contains three main chambers: anterior chamber, posterior chamber and vitreous cavity. Aqueous humour fills the anterior and posterior chambers. It is a clear, colourless, watery fluid that comprises a vast array of electrolytes, organic solutes, growth factors and other proteins that nourish the non-vascularized tissue of the anterior chamber.

• Aqueous humour leaves the anterior chamber through the trabecular meshwork into Schlemm’s canal and aqueous veins (conventional pathway) or through the ciliary muscle and other downstream tissues (unconventional pathway). If the exit of aqueous humour from the eye is blocked, the amount of fluid within the eye increases, leading to an increase in pressure which may lead to glaucoma and cause damage to the optic nerve.
Anatomy and physiology of the eye/Chambers of the eye

• The vitreous cavity comprises 80% of the volume of the eye. This is a hydrogel containing approximately 98% water. The other 2% of vitreous components are predominantly collagen fibrils and hyaluronic acid. Proteins, inorganic salts, glucose and ascorbic acid are also present. Vitreous humour has a pH of approximately 7.5 and a viscosity 2–4 times that of water. The presence of sodium hyaluronate is primarily responsible for the viscosity of the vitreous humour.
Ocular drug delivery routes and elimination pathways

• Routes and barriers to ocular drug delivery can be summarized here with reference to Fig. 41.1 (see I, II and III).

I. The cornea is the main route through which ocular topically administered drugs reach the aqueous humour.

II. The blood retinal barrier (retinal pigment epithelium and retinal capillary endothelium) restricts entry of drugs from the systemic circulation into posterior segment of the eye.

III. Intravitreal delivery route to directly reach the back of the eye.
Ocular drug delivery routes and elimination pathways

• Ocular drug elimination (Fig. 41.1) is via:

1. drug elimination from the aqueous humour into the systemic uveoscleral circulation

2. aqueous humour outflow through the trabecular meshwork and Schlemm’s canal.

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

4. Drug elimination via posterior route across blood retinal barrier.
Some common ocular conditions and pharmacological interventions

• Ocular drug delivery is undertaken for treatment of local disease at different sites in the eye, thus a brief introduction to common eye conditions is appropriate:

- **Dry eye syndrome**: Dry eye is a common disease which occurs when either the tear volume is inadequate or of poor quality (poor functional tear). This often results in unstable tears and consequently ocular surface disease. Dry eye is not curable and management is to control the symptoms and protect the ocular surface from being damaged. The initial treatments include use of tear substitutes and mucolytic eye drops. In advanced cases, the use of anti-inflammatory eye drops, surgical intervention to reduce punctual drainage and contact lenses have been shown to be beneficial.
Some common ocular conditions and pharmacological interventions

➢ **Cataract.** Cataract is the opacity of lens, which often results from denaturation of the lens protein. Cataracts, which are usually age-related, are the most common cause of treatable blindness worldwide. Surgery is the only treatment and is very effective. It involves replacement of the clouded lens with a synthetically produced intraocular lens.

➢ **Glaucoma.** The glaucomas are a group of diseases in which there is a specific type of damage to the optic nerve (optic disc cupping), resulting in a characteristic pattern of visual field loss; first peripheral and then central vision loss. Glaucoma, a life-long condition, is the leading cause of irreversible blindness worldwide and is the second most common cause of blindness, after cataract. The most important and only modifiable risk factor in this group of diseases is raised intraocular pressure (IOP). It has been shown that reduction in intraocular pressure, medically (eye drops) or surgically, can halt or decrease the progression of the visual field loss.
Some common ocular conditions and pharmacological interventions

- **Age-related macular degeneration (AMD).** AMD is a degenerative disorder that affects the macula, the most sensitive part of the retina, and consequently results in the loss of central vision.

- **Endophthalmitis.** Endophthalmitis is the inflammation of the internal layers of the eye. Infectious endophthalmitis most frequently occurs following ocular surgery and penetrating trauma, particularly with retained foreign body.
Topical ophthalmic preparations

- Topical ophthalmic preparations include: solutions, suspensions, ointments/gels and the newer dispersion systems. These have been traditionally used for treating pathological conditions of the anterior segment, such as infection, inflammation, allergy, dry eye, glaucoma, and corneal ulceration, as well as for instilling anaesthetic and diagnostic agents.

- Physiological and biochemical mechanisms exist to protect the eye from harmful stimuli, however, they do sometimes present a barrier to drug absorption. For example:

- Basal tears are continuously secreted by the lacrimal glands at an average rate of 1.2 µL/minute. Reflex tears are triggered by irritants and can vary from 3 to 400 µL/minute, to rapidly eliminate the stimulus.

- The eyelid movements associated with blinking. Blinking moves tear fluids and foreign matter to the nasal corner of the lid surface,

- Tears contain lysozymes and immunoglobulins which impart an anti-infectious activity

- The combined mechanisms of lacrimal drainage and blinking means that administered eye drops are rapidly cleared from the conjunctival sac with residence time ranging from 4 to 23 minutes. Moreover, the rate of drainage from the eye has a positive, linear correlation with instilled volume.
Topical ophthalmic preparations

- To reduce the elimination rate of administered eye drops, it is important that the topical preparations do not cause irritation. This can be achieved by designing their properties to be as close as possible to the lacrimal fluids covering the surface of the eye.

Fig. 41.2 • Illustration of nasolacrimal drainage.
Formulating ophthalmic preparations

➢ Osmolality

Osmolality in healthy, non-dry eyes has an average value of 302 mmol/kg during the daytime. Patients with dry eye syndrome have been found to present with tear film hyperosmolality which contributes to the symptoms of the disease.

When the eye is exposed to a hypotonic ophthalmic solution, the corneal epithelium becomes more permeable and water flows into the cornea causing oedema. Hypertonic solutions have a dehydrating effect on the corneal epithelium. Hypotonic and hypertonic solutions are irritating to the eye and therefore induce an increased production rate of tears.

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. Ophthalmic solutions can be made isotonic by the use of tonicity agents such as sodium chloride, potassium chloride, buffering salts, dextrose, mannitol and glycerol, as long as they are compatible with the other ingredients in the formulation.
Formulating ophthalmic preparations

➢ pH of the formulation.

The pH of tears is close to neutral (6.9 to 7.5) and is controlled by various substances dissolved in the aqueous layer of tears: carbon dioxide, bicarbonate and proteins such as the basic lysozyme and an acidic tear prealbumin.

Acidic or basic solutions instilled into the eye cannot be neutralized by the tears that are present and therefore reflex tears are generated to dilute the administered drop and eliminate it. The recovery to the original pH of the tear film 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.

It is preferable to formulate as close to physiological tear pH as possible to reduce discomfort and the associated increased lacrimation.
Formulating ophthalmic preparations/pH

• Pilocarpine is a natural alkaloid used in the treatment of glaucoma. It undergoes pH-dependent hydrolytic degradation and one of the ways to maintain stability of pilocarpine aqueous solution is to maintain the pH at 4–5 through the use of a weak acidic buffer. Since the pH deviates from the physiological pH of the lacrimal fluids, the constituting buffer must be weak to allow the lacrimal fluids to be restored to their normal pH within a short period time following instillation.

• Drug ionization is also important in determining drug solubility and permeability across the corneal epithelium. The extent of ionization can be manipulated through control of the pH of ophthalmic preparations.

• Commonly used buffers in ophthalmic solutions include borate and phosphate buffers. To prepare solutions of lower pH range acetic acid/ sodium acetate and citric acid/ sodium citrate buffers are used. It is important that strong buffers are not used and to use a low concentrations of weak buffers.
Surface tension

• The surface tension of tear fluid at physiological temperature in a healthy eye is 43.6 to 46.6 mN m⁻¹. Administration of solutions that have a surface tension much lower than that of the lacrimal fluid destabilizes the tear film and disperses the lipid layer into droplets that are solubilized by the drug or surfactants in the formulation. The oily film reduces the rate of evaporation of the underlying aqueous layer and therefore once it is lost, dry spots are formed which are painful and irritant.

• Surfactants are typically included in ophthalmic preparations to solubilize or disperse drugs. Irritation power of surfactants decreases in the following order: cationic > anionic > zwitterionic > non-ionic. Nonionic surfactants are therefore the most commonly used, examples include; polysorbate 20, polyoxyl 40 stearate, polyoxypropylene-polyoxyethylenediol.
Viscosity

- Viscosity enhancing polymers are used in ophthalmic solutions to prolong drug retention in the precorneal tear film and thus enhance drug absorption. Mechanisms proposed are not just reduced drainage rate;
- the thickness of the precorneal tear film is also increased due to the ability of viscosity-enhancing polymers to drag water and stabilize the aqueous layer as they spread over the corneal surface on blinking. This increased volume acts as a reservoir or the drug so that it is re-spread in the tear film over the cornea with each blink.
- Water soluble polymers that have been used to increase solution viscosity include poly (vinyl alcohol), poly (vinylpyrrolidone), various cellulose derivatives, particularly; methylcellulose, hydroxypropyl methylcellulose and carboxymethyl cellulose (at concentrations o 0.2–2.5%) and poly(ethylene glycol)s (at concentrations o 0.2–1%).
Topical, liquid ophthalmic preparations (solutions, suspensions and submicron emulsions)

➢ **Solutions:**

- Ophthalmic solutions are the most common topical ophthalmic preparation. They are typically the easiest to manufacture (have the lowest cost of production) and are relatively easy for a patient or healthcare provider to administer.

- Ophthalmic solutions are also desirable where a rapid onset of action is required as they do not need to undergo dissolution. This would be the case for local anaesthetics (e.g. lignocaine, proxymetacaine hydrochloride); ocular diagnostics (fluorescein sodium) and ocular preoperative drugs. Moreover, solutions are homogeneous and therefore display a better dose uniformity.

- A limitation of solutions, however, is that they are rapidly drained out of the eye. Moreover, the rate of drainage is proportional to the size of the drop administered. The volume of eye drops administered from commercial eye dropper bottles has been reported to be in the range of 25 to 56 µL.
Topical, liquid ophthalmic preparations

➢ **Suspensions**

Ocular suspensions have been used to administer drugs which are sparingly soluble in water, e.g. steroids, or to prolong drug release. Particles tend to be retained in the ocular cul-de-sac (the space between the eyeball and eyelid) and slowly go into solution thus increasing the contact time. Particle size and shape need to be carefully selected as some particles can cause irritation of the sensory nerves in the epithelium.

The particles of a suspension need to be readily dispersible on shaking by the patient to ensure uniform dose administration. Homogeneity and dose uniformity need to be confirmed in multi-dose containers from first to last use.
Topical, liquid ophthalmic preparations

➢ **Submicron emulsions**

• Ciclosporin is an immunomodulator with anti-inflammatory effects. It is available at a concentration of 0.05% as a sub-micron emulsion (Restasis®, Allergan) or topical application to the eye.

• Ciclosporin is hydrophobic (log P=3.0) and has a very poor aqueous solubility of 6.6 µg/ml and cannot therefore be formulated in conventional aqueous ophthalmic vehicles.

• It has been successfully solubilized in an oil-in-water (o/w) submicron emulsion. The oil phase in Restasis is castor oil and the emulsion is stabilized with the non-ionic surfactant polysorbate 80 and glycerin, which behaves here as a co-surfactant.

• Ocular submicron emulsions with a droplet size of ~ 0.1 µm have also shown potential for prolonging drug release and achieving significantly higher drug concentrations in the cornea and aqueous humour compared to suspensions.
Topical, semisolid ophthalmic preparations

➢ Ointments

• Ophthalmic ointments have been used as an option to reduce drug drainage by tear flow and therefore increasing corneal residence time. Sustained drug release effects of 2–4 hours are usually observed.

• Ointments also have the advantage of allowing the incorporation of drugs with poor aqueous solubility. Hydrophobic ointments sometimes improve the stability of hydrolysable compounds, particularly peptides. Soft paraffin and liquid paraffin are commonly used as bases for ophthalmic ointments. Anhydrous, water-soluble bases such as carbomer with poly(ethylene glycol) are also used.

• Antibiotics, antifungals and steroids are the classes of drugs most available as ointments. Drug bioavailability usually peaks later with ointment vehicles than with solutions or suspensions. Total bioavailability in the aqueous humour can also be significantly greater than with solutions or suspensions.

• Ointments are however more difficult to administer compared to solutions and may give rise to a more variable dose. Also blurring of vision arises which tends to reduce patient compliance making ointments more useful or night-time administration.
Topical, semisolid ophthalmic preparations

**Gels**

- Gels, which are semisolid systems comprising water-soluble bases, are also available and are more favourable than ointments or water soluble drugs. These utilize polymers such as polyvinyl alcohol (PVA), poloxamer, hydroxypropyl methylcellulose (HPMC), Carbopol or Carbomer, dispersed in a liquid.

- Pilocarpine is a cholinomimetic agent which reduces intraocular pressure and is licensed for glaucoma. It is available as a gel (Pilogel®, Alcon) containing more than 90% water and employing Carbopol 940 (a synthetic high molecular weight polymer of acrylic acid). An equivalent duration of response has been shown with a single instillation.
Topical, semisolid ophthalmic preparations

Mucoadhesive systems

• Other ways to increase the contact time of topical ophthalmic solutions with the ocular surface have been through the use of mucoadhesive polymers. These attach to the mucin coat that covers the conjunctiva and cornea.

• Mucin has a protein or polypeptide core with carbohydrate chains branching off. The mucin coat serves to protect, hydrate and lubricate the surface of the eye. Mucoadhesive polymers are commonly macromolecular hydrocolloids with numerous hydrophilic functional groups possessing the correct charge density.

• They should also exhibit good wetting of the ocular surface to facilitate maximum interaction with the mucin coat. Electrostatic, covalent and hydrogen interactions are the most common between mucoadhesive polymers and mucin.

• Mucoadhesive polymers can be natural, synthetic or semi-synthetic in nature. The synthetic polymers include polyacrylic acid, polycarbophil as well as cellulose derivatives. The (semi)natural mucoadhesive polymers include chitosan and various gums such as guar, xanthan, carrageenan, pectin and alginate.
Improving drug solubility and absorption in topical ophthalmic preparations

Drug ionization and salt form

- The pKa of the drug (acid dissociation constant) and pH determine its degree of ionization in solution. While the pKa can only be altered through structural changes in the molecule, the pH of the drug vehicle can be controlled.

- A higher proportion of unionized species displays a greater degree of transcorneal permeability, as has been shown with pilocarpine. Pilocarpine is a weak base but to achieve good solubility and stability the eye drops are formulated with an acidic vehicle (pH 3.5–5.5).

- The physical form of the drug can also be an important determinant of its ocular bioavailability. The salt form can affect solubility and lipophilicity of the drug. Dexamethasone acetate ester displays the optimum balance of solubility and corneal permeability compared to the very water-soluble phosphate salt or lipophilic free base.
Improving drug solubility and absorption in topical ophthalmic preparations

➢ Cyclodextrins

Cyclodextrins (CDs) have shown great potential in improving the solubility of poorly water-soluble drugs. CDs are cyclical oligosaccharides with a lipophilic centre and hydrophilic outer surface. They can complex lipophilic drugs in their interior, thus forming water-soluble complexes. This maintains the structure, lipophilicity and hence the permeability of the compounds. The drug is associated with CD by hydrogen bonding, hydrophobic interactions or van der Waals forces. The hydrophilic CDs acts as carriers, delivering water insoluble molecules to the corneal membrane where they can partition from the CD complex.
Improving drug solubility and absorption in topical ophthalmic preparations

**Prodrugs**

- Improved corneal penetration can be gained through the use of prodrugs. A prodrug is a drug with added functionalities that converts into the active parent drug through enzymatic or chemical reactions. Approaches of enhancing corneal penetration through the use of prodrugs include; optimization of lipophilicity, enhancement of aqueous solubility, improved affinity or uptake transporters and evasion of efflux pumps.

- Drugs with carboxylic acid groups, such as the prostaglandin analogues indicated or glaucoma, have low corneal permeation. This is due to the ionization of the carboxylic acid group at the near neutral pH of tears which reduces permeability through the lipophilic epithelium. One strategy to mitigate this has been esterification of the carboxylic acid group. Since the cornea has high esterase activity, these derivatives can easily revert to their parent form.
Sterility of ophthalmic preparations

• It is a regulatory requirement that preparations intended for ophthalmic use, including those or cleansing the eyes, must be sterile at the time of filling and closing in a sealed container.

• Ocular infections are extremely dangerous and can rapidly lead to the loss of vision. Eye-cups, droppers and all other dispensers should also be sterile and regulated I packaged with the drug product.

• For ophthalmic preparations, terminal sterilization o products in their final containers should be adopted wherever possible. If the product cannot withstand terminal sterilization then filtration under aseptic conditions should be considered, usually performed using a filter pore size o 0.22 µm or less.

• The raw materials used for aseptic manufacture should be sterile, wherever possible, or should meet a low specified bioburden control limit. Ophthalmic preparations must furthermore be labelled with duration of use once opened,
Sterility of ophthalmic preparations

• Preservatives are included in multi-dose containers to destroy and inhibit the growth of microorganisms that may have been accidentally introduced on opening of 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.

• Single dose units have been developed to circumvent the use of preservatives while maintaining stability.

• Several multi-dose bottles have been developed that maintain sterility without the use of a preservative; one of these is the ABAK patented filter system which uses a 0.2 µm nylon membrane to prevent bacteria from entering the bottle. It is known as Airless Antibacterial Dispensing System (AADS™, Pfizer) and works by preventing air, and therefore bacteria, from entering the container on dispensing. Furthermore, a silver coil is included in the bottle tip. Silver has antibacterial properties and therefore any bacteria contacting the tip do not contaminate the contents. This system guarantees three months of sterility.
Intraocular implants

- Implantable drug delivery systems can be classified into biodegradable and non-biodegradable. In both, drug release kinetics are determined by the polymer system used, drug physicochemical properties and diffusion of the drug through the polymer. Biocompatibility is an essential property for all systems. The inside of the eye is a viable location for implantation as evidenced by the use of intraocular lenses which are implanted to replace the clouded over natural lens during cataract surgery.

Non-biodegradable intraocular implants

Non-biodegradable systems are commonly ‘reservoir’ devices, whereby the drug core is coated by a semi-permeable polymer through which the drug can leave. Or the polymer coating may have an opening of a fixed area through which the drug can diffuse out. The other type of non-biodegradable system is the ‘monolithic’ type which is a homogeneous mix of drug and polymer. It is easier, however, to achieve zero-order kinetics from a reservoir system.
Intraocular implants/ Non-biodegradable intraocular implants

• **Vitrasert®** (ganciclovir 4.5 mg) is the first implantable intravitreal device to be available in the clinic and was approved by the FDA in 1996.

• Ganciclovir is embedded in a polyvinyl alcohol (PVA) and ethylene vinyl acetate (EVA) polymer based system. Drug is slowly released from this implant over 5–8 months. PVA is a hydrophilic polymer acting as the scaffold of the implant as well as controlling the rate of drug diffusion. EVA is hydrophobic polymer used to coat the implant to also control drug diffusion.

• Fluid goes into the implant and dissolves the drug; a saturated solution is formed within the core and drug molecules diffuse out of the system under a concentration gradient. The advantages of this system are that as long as a saturated drug solution remains in the core, the release rate will be constant. Moreover, no initial burst release of drug is observed.

• Intraocular insertion of the implant requires surgery and Further surgery is required to remove the implant devoid of drug.
Intraocular implants

➢ Biodegradable intraocular implants

• Biodegradable systems are composed of polymers that are metabolized by enzymatic or non-enzymatic (e.g. hydrolysis) reactions in vivo into more soluble forms that can be safely eliminated by the body. Their main advantage over non-biodegradable systems is that they do not have to be removed from the body once the drug has been exhausted.

• Ozurdex® (Allergan) is a dexamethasone (0.7 mg) bioerodible ocular implant with a six month duration of action. It is approved by the FDA for the treatment of macular oedema following retinal vein occlusion (RVO), diabetic macular oedema and uveitis. This implant is based on the copolymer poly(lactic-co-glycolic acid) (PLGA) which has been used or over 30 years in bio-degradable sutures or ophthalmic surgery.
The End