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DRUGS IN OPHTHALMOLOGY



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CHAPTER

2

Routes of Drug Administration and Newer Drug Delivery Systems in Ophthalmology

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LEARNING OBJECTIVES

At the end of the chapter, the student should be able to:

- Classify routes of drug administration and describe the anatomical and physiological barriers that influence them.
- Compare the conventional routes of ocular drug administration with respect to efficacy, safety, and clinical indications.
- Explain the principles, advantages, and limitations of intraocular and periocular drug delivery routes.
- Identify the role of newer and advanced ocular drug delivery systems in improving bioavailability and patient compliance.
- Describe the emerging innovations, such as sustained-release implants, nanotechnology, and gene therapy, in ophthalmology.

INTRODUCTION

Targeted drug delivery to specific ocular tissues remains one of the most challenging areas in pharmaceutical research. The complexity arises from the unique anatomy and physiology of the eye, which is naturally equipped with multiple protective barriers to prevent the entry of foreign substances. These barriers, while essential for maintaining ocular integrity and function, significantly limit drug absorption and bioavailability.

This chapter provides a comprehensive overview of the pharmacological principles underlying ocular drug delivery. It discusses conventional routes of ocular drug administration, their advantages and limitations, and explores emerging technologies in drug delivery systems designed to overcome ocular barriers.

Anatomically, the eye is divided into two major segments: The anterior segment and the posterior segment. Each segment is composed of specialized tissues with distinct structural and functional characteristics, which influence drug permeation and distribution. Consequently, the successful design of ocular drug delivery systems requires a comprehensive understanding of these tissue-specific barriers.

OCULAR BARRIERS TO DRUG DELIVERY

Drug delivery to the eye is hindered by several anatomical, physiological, and biochemical barriers that vary depending on the route of administration.

These barriers are inherently designed to protect the eye from toxicants and pathogens; however, they also pose significant challenges to therapeutic drug delivery.

Barriers Associated with Topical Administration

Topical administration is the most commonly used route for ocular drug delivery. However, precorneal factors such as tear dilution, blinking, nasolacrimal drainage, and limited residence time substantially reduce drug availability. In addition, the corneal epithelium, conjunctiva, and sclera act as selective barriers that restrict drug permeation based on physicochemical properties, such as lipophilicity and molecular size.

Barriers Associated with Systemic Administration

Systemic delivery of drugs to ocular tissues is limited by the presence of blood–ocular barriers, primarily the blood-aqueous barrier and the blood-retinal barrier. These barriers tightly regulate the transport of substances from the systemic circulation into the eye, thereby restricting drug penetration to the posterior segment and necessitating higher systemic doses, which may lead to adverse effects.

Barriers Associated with Injectable and Periocular Routes

Injectable and periocular routes offer improved drug access to posterior ocular tissues but are associated with invasiveness and patient discomfort. Even with these approaches, drug distribution may be limited by dynamic clearance mechanisms and tissue-specific diffusion barriers.

In addition to anatomical and physiological barriers, efflux transporters significantly influence ocular drug delivery. Transporters such as P-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRPs) are widely expressed in various ocular tissues and contribute to reduced intracellular drug concentrations. By actively extruding therapeutic agents from ocular cells, these transport systems limit drug retention and ultimately decrease therapeutic efficacy.

ROUTES OF OCULAR DRUG ADMINISTRATION

Depending on the site of action and the nature of the ocular disease, drugs can be administered via topical, systemic, periocular, or intraocular routes, each offering distinct advantages and limitations. Routes of ocular drug administration can be classified as shown in **Flowchart 2.1**.

Topical administration is most commonly employed for anterior segment disorders due to its noninvasive nature and ease of use, whereas systemic administration is useful when ocular involvement is part of a systemic condition. Periocular routes provide enhanced drug delivery to posterior

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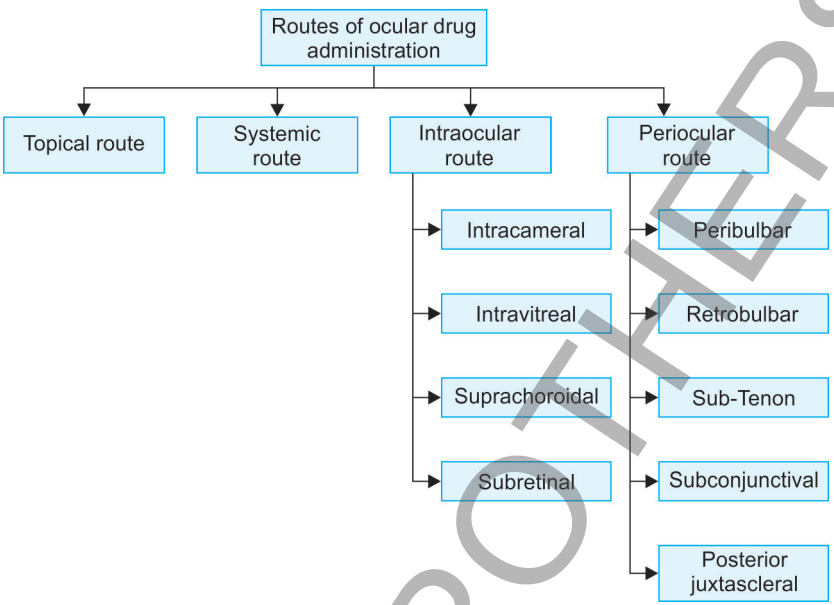
Flowchart 2.1: Routes of ocular drug administration.



segment tissues while reducing systemic exposure, and intraocular routes enable direct delivery to intraocular compartments for conditions requiring high local drug concentrations. In the following section, the various routes of ocular drug administration are discussed in detail.

Topical Route

Topical delivery is the most widely used route in ophthalmology, particularly for the management of anterior segment disorders, such as conjunctivitis, keratitis, and glaucoma. This route is preferred due to its convenience, simplicity, noninvasive nature, and the ability for self-administration, which contributes to good patient acceptance. However, topical delivery is generally ineffective for posterior segment diseases, as drugs administered by this route do not reach therapeutic concentrations in posterior ocular tissues. Additional limitations include short ocular contact time, drug loss through diffusion into the systemic circulation, imprecise and inconsistent dosing, risk of contamination, potential ocular injury from the dropper tip, and the need for frequent dosing, which may reduce patient compliance.

Dosage Forms Used in Topical Ocular Delivery

Eye Drops

Eye drops (solutions, emulsions, and suspensions) are the most commonly used topical dosage forms. They offer a rapid onset of action, are easy to instill, cause minimal interference with vision, and are associated with fewer complications. However, their duration of action is short, and typically

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only 1–5% of the administered dose penetrates the cornea. Suspensions and emulsions require proper shaking before use to ensure uniform drug distribution and accurate dosing. Commonly used eye drops that are formulated in suspension form are prednisolone, nepafenac, brinzolamide, etc., and in emulsion form, cyclosporine (Restasis®), difluprednate, etc. Eye drops in emulsion form are biphasic, either oil in water or water in oil, facilitating the delivery of water insoluble drug and enhancing drug bioavailability to the eye.

Recommended procedure for instilling topical ocular solutions:

- Tilt patient's head backward.
- Instruct the patient to look up.
- Gently grasp the lower outer eyelid below lashes and pull the eyelid away from the globe.
- Without touching lashes or eyelids, instill one drop of solution into the conjunctival sac.
- Continue to hold the eyelid in this position for a few seconds to allow the solution to gravitate into the deepest portion of the lower fornix.
- Instruct the patient to gaze downward while lifting the eyelid upward until it contacts the globe.
- Instruct patients to gently close their eyes.
- The patient should keep their eyes closed for 2–3 minutes.

Ointments

When administered into the inferior conjunctival sac, ophthalmic ointments melt rapidly at ocular surface temperature and may spread onto the lid margins, eyelashes, and surrounding periocular skin. The extent of spreading depends on the quantity applied and the degree of reflex tearing induced by ocular irritation. Drug material retained at the lid margins serves as a reservoir, thereby prolonging contact time with the ocular surface and enhancing drug availability. However, ointments may cause blurred vision, particularly during daytime use, and are, therefore, often preferred for night time administration.

For proper instillation, patients are advised to look upward while the lower eyelid is gently retracted, allowing the ointment to be placed into the inferior conjunctival sac. Smaller quantities are recommended for daytime use to minimize visual disturbance, whereas approximately a 1 cm ribbon of ointment is suitable for bedtime application. As an alternative technique, ointments may be applied using a cotton-tipped applicator and spread along the upper lid margin, eyelashes, and medial and lateral canthi. This method minimizes irritation and blurring of vision while providing sustained drug release for up to 6 hours, making it particularly useful in pediatric and geriatric patients. It is important to note that ophthalmic ointments can interfere with

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the absorption of subsequently administered eye drops; therefore, solutions should always be instilled before ointments.

Gels

Ophthalmic gels represent an intermediate dosage form between solutions and ointments, offering prolonged ocular residence time with reduced visual impairment. Pilocarpine is available as a 4% carbomer gel and is typically administered once daily at bedtime. Although effective, prolonged use may occasionally result in minor and reversible adverse effects, such as superficial corneal haze and superficial punctate keratitis. Artificial tear gels containing polymers such as carboxymethylcellulose, povidone, and carbopol provide enhanced lubrication and longer contact time compared to conventional solutions, with less blurring than ointments. In situ gel-forming systems, including gellan gum and xanthan gum formulations, undergo sol-to-gel transformation upon contact with the ocular surface, thereby increasing drug retention. For instance, timolol 0.5% formulated as a gel-forming solution administered once daily has demonstrated intraocular pressure control comparable to that of twice-daily conventional solutions, with good tolerability and minimal discomfort.

Systemic Route

Systemic administration, particularly via the parenteral route, faces significant challenges in ocular drug delivery due to the presence of specialized blood-ocular barriers. Following systemic dosing, drug access to the anterior segment is primarily limited by the blood-aqueous barrier, while delivery to the posterior segment is restricted by the blood-retinal barrier.

The blood-aqueous barrier is composed of two distinct cellular layers located in the anterior segment: (1) The endothelium of the iris and ciliary body blood vessels, and (2) the nonpigmented ciliary epithelium. These layers are interconnected by tight junctions that effectively prevent the passive diffusion of solutes from the systemic circulation into the aqueous humor, thereby maintaining ocular homeostasis.

The blood-retinal barrier further restricts systemic drug entry into the posterior segment of the eye. It consists of two components: the inner blood-retinal barrier, formed by tight junctions between retinal capillary endothelial cells, and the outer blood-retinal barrier, constituted by the retinal pigment epithelium (RPE). The RPE is a highly specialized monolayer situated between the neural retina and the choroid and plays a critical role in maintaining retinal function through selective molecular transport, metabolic support of photoreceptors, and regulation of retinoid metabolism. Despite its physiological importance, the tight junctions of the RPE severely

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limit paracellular drug permeation. Although systemically administered drugs can readily reach the highly vascularized choroid—owing to the fenestrated nature of the choriocapillaris—the outer blood-retinal barrier restricts further drug diffusion into the retinal tissue. Consequently, achieving therapeutic drug concentrations in the retina via systemic administration remains a major challenge, necessitating the development of targeted delivery strategies capable of crossing these barriers.

Recent advances in nanotechnology have provided promising approaches to overcome the blood-retinal barrier. Experimental studies have demonstrated that intravenously administered nanoparticles of sufficiently small size can penetrate the blood-retinal barrier and distribute across retinal layers without inducing cytotoxicity. For example, gold nanoparticles of approximately 20 nm were shown to traverse the barrier and accumulate in retinal tissues, whereas larger nanoparticles failed to do so. Additionally, systemic delivery of gene therapy vectors, such as polyethylene glycol-conjugated immunoliposomes, has resulted in gene expression within multiple ocular tissues, including the retina, RPE, iris, and conjunctiva. Targeted nanocarrier systems, such as ligand-functionalized poly (lactide-co-glycolide) nanoparticles, have also demonstrated success in delivering therapeutic genes to pathological sites like choroidal neovascularization, particularly in disease states where the blood-retinal barrier becomes compromised.

Pharmacokinetic studies have further confirmed that certain drugs, including antifungal agents, antibiotics, and antiparasitic compounds, can distribute into ocular tissues following intravenous administration. One clinically approved example of systemic ocular therapy is verteporfin (Visudyne®), administered intravenously for photodynamic therapy in patients with neovascular age-related macular degeneration (AMD). Despite such successes, systemic parenteral administration is not commonly preferred for ocular disorders due to concerns related to systemic toxicity, limited ocular specificity, and poor penetration across ocular barriers.

Oral administration has also been explored as a noninvasive and patient-friendly alternative, either alone or in combination with topical therapy, particularly for chronic posterior segment diseases. However, topical delivery alone often fails to achieve therapeutic drug levels in the posterior segment, prompting investigation into oral routes. The major limitation of oral administration lies in its poor ocular targeting efficiency, which often necessitates high systemic doses to achieve therapeutic effects within the eye. Such high doses increase the risk of systemic adverse effects, thereby limiting clinical utility. For instance, oral carbonic anhydrase inhibitors used in glaucoma management have largely been discontinued due to unacceptable systemic toxicity.

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Only a limited number of orally administered drugs have demonstrated potential for ocular therapy, including analgesics, antibiotics, antivirals, antineoplastic agents, and nutritional supplements, such as omega-6 fatty acids. A key requirement for successful oral ocular drug delivery is high oral bioavailability, followed by the ability of the drug to cross the blood-aqueous and blood-retinal barriers after entering systemic circulation. Given these constraints, oral administration plays a limited role in ocular drug delivery and is primarily considered when benefits outweigh the risks associated with systemic exposure.

Intraocular Routes

The intraocular route involves the direct administration of drugs into the internal compartments of the eye to achieve high local drug concentrations, particularly in the posterior segment. Common intraocular routes include intravitreal, intracameral, suprachoroidal and subretinal administration, which effectively bypass most ocular barriers. Although this approach provides precise and efficient drug delivery, it is invasive and associated with risks such as infection, increased intraocular pressure, retinal detachment, and patient discomfort.

Intravitreal Route

Intravitreal injections involve the direct delivery of therapeutic agents into the vitreous cavity of the eye and have become the gold standard for treating many posterior segment diseases. This route is especially effective for drugs that must reach the retina or vitreous in therapeutic concentrations, indicated for neovascular AMD, diabetic macular edema (DME), nonproliferative and proliferative diabetic retinopathy (NPDR/PDR), retinal vein occlusions (RVO), endophthalmitis, uveitis, cystoid macular edema (CME), and choroidal neovascular membranes (CNVMs) secondary to various retinal diseases.

Intravitreal injections provide a highly effective method for delivering drugs directly into the vitreous cavity, allowing rapid and targeted treatment of posterior segment diseases. The primary advantage of this route is its ability to achieve therapeutic drug concentrations in the retina and vitreous that are not attainable with topical or systemic administration, leading to stabilization or improvement of vision and direct treatment of intraocular infections. Additionally, the procedure is relatively quick, outpatient-based, and can be repeated as needed. However, intravitreal injections also have notable disadvantages and risks. Patients may experience pain, foreign body sensation, or tearing, sometimes due to dry eye, corneal abrasion, or irritation. Other complications include bleeding (subconjunctival or vitreous hemorrhage), retinal tears or detachment, cataract formation,

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infection (endophthalmitis), uveitis or retinal vasculitis (particularly with brolucizumab), loss of vision, increased intraocular pressure, optic nerve damage, the need for surgical intervention, and rare systemic effects such as stroke and heart attack with anti-vascular endothelial growth factor (anti-VEGF) therapy. Off-label use of medications and the necessity for repeated injections add to the complexity of management. Alternatives may include laser treatments such as photocoagulation and photodynamic therapy, or surgical procedures such as pars plana vitrectomy, depending on the underlying ocular disease.

The most commonly used intravitreal medications include bevacizumab (Avastin) 1.25 mg/0.05 mL, ranibizumab (Lucentis) 0.5 mg/0.05 mL for neovascular AMD, RVO, and myopic CNVM or 0.3 mg/0.05 mL for diabetic retinopathy/DME, aflibercept (Eylea) 2 mg/0.05 mL or HD Eylea 8 mg/0.07 mL, brolucizumab (Pagenax/Beovu) 6 mg/0.05 mL, faricimab (Vabysmo) 6 mg/0.05 mL, triamcinolone acetonide (Kenalog/Triesence) 2–4 mg, and dexamethasone 0.4 mg/0.1 mL.

Intravitreal Injections: Anesthesia, Technique, and Postprocedure Care

Anesthesia for intravitreal injections can be achieved via topical drops, pledgets, or subconjunctival injections, depending on the physician's preference and the patient's tolerance. Topical tetracaine or proparacaine drops are commonly used, while pledgets soaked with an anesthetic can be placed on the planned injection site. Gel-based anesthetics, such as lidocaine 2–4% or Tetravisc, are alternatives but may trap microbes if not preceded by proper antisepsis. Subconjunctival anesthesia (lidocaine 1–2%) provides more profound analgesia but carries a higher risk of subconjunctival hemorrhage. Retrobulbar blocks are rarely needed but may be considered in inflamed eyes, such as those with endophthalmitis, although acute inflammation is generally a contraindication for anti-VEGF injections.

Patient preparation involves positioning the patient partially supine with a secure headrest, minimizing distractions, and confirming the correct patient, eye, and medication via a surgical "timeout." The injection site is typically superotemporal or inferotemporal, chosen for accessibility and safety. Asepsis is critical—the skin and adnexa are prepared using 10% povidone-iodine solution, and conjunctival sac antisepsis is achieved by instillation of 5% povidone-iodine eye drop. The eyelids are isolated with a sterile speculum. Gloves are compulsory, silence and sterile mask use are recommended to reduce the risk of oral flora-associated endophthalmitis.

The injection technique involves marking the scleral entry site (3–3.5 mm posterior to the limbus in pseudophakic eyes, 3.5–4 mm in phakic eyes), stabilizing the syringe, and inserting a 30-G needle smoothly into the

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midvitreous. The medication is injected slowly without moving the needle to avoid vitreous traction or retinal tears. After withdrawal, the site may be gently pressed with a cotton applicator, and residual povidone-iodine rinsed from the eye. In patients with glaucoma or following steroid injections (e.g., triamcinolone), intraocular pressure should be monitored, and paracentesis is seldom needed.

Post-injection care includes washing off povidone-iodine to prevent corneal irritation, reassuring the patient about possible floaters, and educating them about warning signs of endophthalmitis or retinal detachment. The patient should avoid splashing water in the injected eye for 24 hours, wearing contact lenses, and swimming for 2–3 days postinjection. Follow-up phone calls or office visits within 3–7 days are optional based on the physician's discretion, with routine 1-week follow-up generally not required unless complications are suspected.

Intravitreal anti-VEGF injections are traditionally administered unilaterally, but there has been a growing trend toward simultaneous bilateral injections in patients with disease affecting both eyes. Conditions that commonly require bilateral treatment include DME and neovascular AMD.

Intracameral Route

Intracameral administration involves direct injection of drugs into the anterior chamber of the eye, typically during intraocular surgery. The site of action is the aqueous humor, providing rapid and targeted drug delivery to anterior segment structures. Indications include prevention of endophthalmitis, control of intraocular inflammation, anesthesia, and pupil dilation, especially during procedures such as cataract surgery. Advantages of this route include achieving higher drug concentrations in the anterior chamber, eliminating the need for frequent topical drops, and reducing corneal and systemic side effects associated with topical steroid therapy. Disadvantages include the risk of toxic anterior segment syndrome (TASS), corneal endothelial cell damage, and the requirement for precise, sterile administration. Common intracameral drugs include moxifloxacin and cefuroxime for infection prophylaxis to prevent endophthalmitis, lidocaine for intraoperative anesthesia, epinephrine for pupil dilation, pilocarpine and carbachol for inducing miosis, and dexamethasone or triamcinolone acetonide for inflammation control.

Suprachoroidal Route

Suprachoroidal administration involves the delivery of drugs into the potential space between the sclera and choroid, allowing targeted therapy to the posterior segment of the eye. The site of action includes the choroid and retina, making it particularly useful for diseases affecting the posterior segment while minimizing exposure to the anterior segment of the eye.

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Suprachoroidal microneedles (having a length of 900 μm) are used to deliver the drug in the suprachoroidal space, about 4–4.5 mm from the limbus in the superotemporal quadrant of the eye. In patients where resistance is felt during injection, a 1,100 μm long needle may be required. Indications include treatment of macular edema due to noninfectious uveitis, retinal vein occlusion, diabetic retinopathy and Irivine-Gass syndrome. The advantages of this route include higher drug concentrations in the posterior segment, reduced systemic absorption, lower risk of anterior segment side effects (such as cataract and elevated intraocular pressure), and the potential for sustained drug release. Disadvantages include procedural complexity, risk of suprachoroidal hemorrhage or detachment, and limited availability of suitable delivery devices. Common drugs used via the suprachoroidal route include triamcinolone acetonide, tyrosine kinase inhibitors, and investigational corticosteroid or anti-VEGF formulations.

Subretinal Route

Subretinal injection can be performed via transcorneal approach, transsclerally, suprachoroidal technique, or pars plana route. The most commonly used route is pars plana wherein after vitrectomy the subretinal injection **(Fig. 2.1)** is administered using a 38G subretinal polyTip cannula (MedOne, Sarasota, FL, USA) or a 41G polytetrafluoroethylene (Teflon)-tipped cannula (DORC, Zuidland, The Netherlands). The drugs given by subretinal route include adeno-associated virus (AAV) vectors carrying therapeutic genes, such as for RPE65 mutations (Luxturna), and in some cases anti-VEGF agents like bevacizumab (Avastin), aflibercept (Eylea), ranibizumab (Lucentis), and conbercept, especially for large submacular hemorrhages.

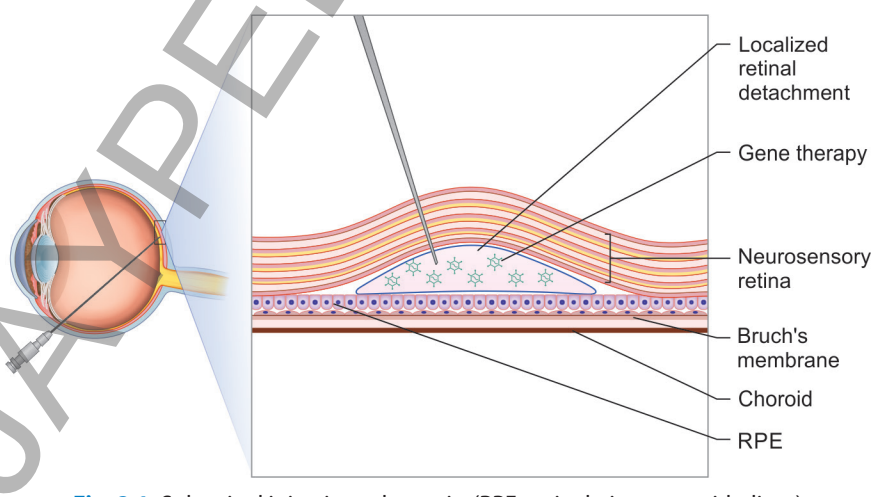

Fig. 2.1: Subretinal injection schematic. (RPE: retinal pigment epithelium)

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Periocular Routes

Periocular routes provide targeted delivery to both the anterior and posterior segments of the eye, offering alternatives to intravitreal injections with potentially fewer complications. Subconjunctival administration involves injection beneath the conjunctiva, allowing drugs to reach ocular tissues via conjunctival and choroidal circulation. It is commonly used for glaucoma, cytomegalovirus (CMV) retinitis, AMD, and posterior uveitis, and can serve as a site for depot formulations. Advantages include relative simplicity, ease of administration, and reduced systemic exposure. However, disadvantages include rapid systemic absorption through conjunctival vessels, limited penetration to deeper ocular tissues, and potential local irritation or hemorrhage.

- *Sub-Tenon injection* delivers the therapeutic agent into the sub-Tenon space **(Fig. 2.2)**, provides relatively high intravitreous drug levels with a minimally invasive approach. Drugs diffuse through the sclera to reach the retina and posterior segment. This route is widely used for DME, AMD, RVOs, and uveitis, offering sustained drug levels while avoiding direct intraocular complications. Advantages include longer drug retention, less invasiveness than intravitreal injections, and lower risk of endophthalmitis. Disadvantages include local discomfort, chemosis, subconjunctival hemorrhage, and variable drug penetration depending on scleral thickness.
- *Retrobulbar injection* delivers drugs into the retrobulbar space **(Fig. 2.3)**, primarily for anesthesia during ocular surgery. It allows administration of high local doses with a rapid onset and minimal influence on intraocular pressure. Advantages include effective anesthesia and rapid onset. Disadvantages are significant and include retrobulbar hemorrhage, globe perforation, optic nerve injury, and, rarely, respiratory arrest, requiring skilled administration.

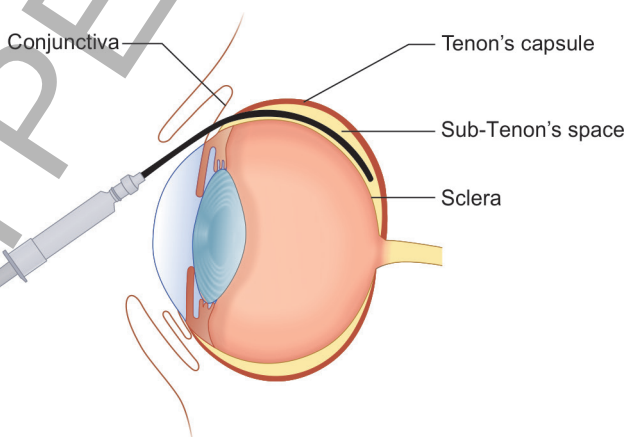

Fig. 2.2: Sub-Tenon injection.

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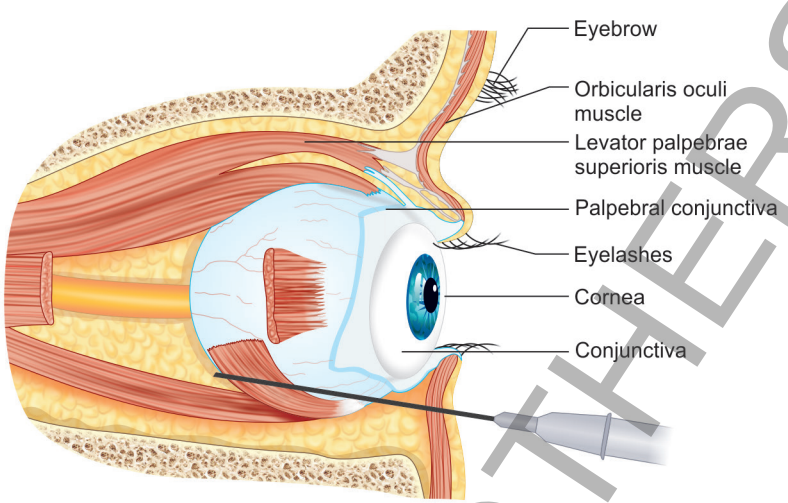

Fig. 2.3: Retrobulbar injection.

- *Posterior juxtascleral route* (also called *submacular or perimacular delivery*) is used for sustained delivery of depot formulations to the macula, achieving therapeutic drug levels for up to 6 months while avoiding intraocular damage and reducing the risk of endophthalmitis. It is primarily indicated for AMD therapy. Advantages include prolonged drug effects, minimal intraocular penetration-related risks, and targeted macular delivery. Disadvantages include the requirement for surgical intervention, limited availability of suitable devices, and the partial barrier effect of the RPE, which can limit drug penetration.
- *Intranasal and intracanalicular routes* are emerging noninvasive periocular routes, including intranasal sprays and drug-eluting punctal plugs. These are designed to enhance patient adherence and reduce systemic exposure, though data are still evolving.

Various routes of drug administration, along with their benefits and challenges in ocular delivery have been summarized in **Table 2.1**.

LIMITATIONS OF CONVENTIONAL OCULAR DRUG DELIVERY

Conventional ocular drug delivery approaches, such as topical, systemic, and periocular administration, are associated with several limitations. Topical drops often exhibit low corneal penetration and poor bioavailability, requiring frequent dosing to achieve therapeutic effects. These methods are generally ineffective for targeting posterior segment diseases due to limited drug diffusion into deeper ocular tissues. Additionally, systemic absorption through the nasolacrimal drainage system can lead to unintended systemic

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TABLE 2.1: Summary of routes of administration.

Route	*Benefits*	*Challenges*	*Application in the treatment of diseases*
Topical	High patient compliance, self-administrable and noninvasive	Higher tear dilution and turnover rate, the cornea acts as a barrier, efflux pumps, BA <5%	Keratitis, uveitis, conjunctivitis, scleritis, episcleritis, and blepharitis
Systemic	Patient compliant and noninvasive route of administration	BAB, BRB, high dosing causes toxicity, BA <2%	Scleritis, episcleritis, CMV retinitis, and PU
Intravitreal	Direct delivery to the vitreous and retina sustains drug levels and evades the BRB	Retinal detachment, hemorrhage, cataract, endophthalmitis, and patient incompliance	AMD, PU, BRVO, CRVO, DME, CME, UME, and CMV retinitis
Intracameral	Provides higher drug levels in the anterior chamber, eliminates the usage of topical drops, and reduces corneal and systemic side effects seen with topical steroid therapy	TASS and TECDS	Anesthesia, prevention of endophthalmitis, inflammation, and pupil dilation
Subconjunctival	Delivery to the anterior and posterior segment, site for depot formulations	Conjunctival and choroidal circulation	Glaucoma, CMV retinitis, AMD, PU
Sub-Tenon	High vitreal drug levels, relatively noninvasive, fewer complications, unlike intravitreal delivery	RPE, chemosis, and subconjunctival hemorrhage	DME, AMD, RVO, and uveitis
Retrobulbar	Administer high local doses of anesthetics, more effective than peribulbar, with minimal influence on IOP	Retrobulbar hemorrhage, globe perforation, and respiratory arrest	Anesthesia

Contd…

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Contd…

Route	*Benefits*	*Challenges*	*Application in the treatment of diseases*
Posterior juxtascleral	Safe for delivery of depot formulations, sustains drug levels up to 6 months to the macula, avoids risk of endophthalmitis and intraocular damage	Requires surgery, and RPE acts as a barrier	AMD

(BA: bioavailability; BAB: blood-aqueous barrier; BRB: blood-retinal barrier; CMV: Cytomegalovirus; PU: posterior uveitis; AMD: age-related macular degeneration; BRVO: branch retinal vein occlusion; CRVO: central retinal vein occlusion; DME: diabetic macular edema; CME: cystoid macular edema; UME: uveitic macular edema; TASS: toxic anterior segment syndrome; TECDS: toxic endothelial cell destruction syndrome; RPE: retinal pigment epithelium; RVO: retinal vein occlusion; IOP: intraocular pressure)

side effects, while complex dosing regimens may result in poor patient compliance.

These challenges have driven the development of novel ocular drug delivery systems, designed to enhance therapeutic efficacy and improve patient adherence. Modern strategies are guided by principles of ocular pharmacokinetics, taking into account multiple factors: the physicochemical properties of drugs, including lipophilicity, ionization, molecular weight, and solubility; formulation factors, such as the use of preservatives or carriers; tissue status, including the integrity of the corneal epithelium, tear film turnover, and conjunctival vascularity; and clearance pathways, such as lacrimal drainage, conjunctival absorption, and uveal and retinal blood flow. By addressing these parameters, newer drug delivery systems aim to achieve more targeted, sustained, and effective ocular therapy.

NOVEL DRUG DELIVERY SYSTEM

Sustained-release Implants

Sustained-release implants are designed to provide long-term intraocular drug release, reducing the frequency of administration and increasing adherence.

- *Biodegradable implants:* Dexycu is an intracameral dexamethasone suspension used after cataract surgery to control postoperative inflammation, providing drug release for up to 21 days with a single injection. It is delivered into the posterior chamber immediately post-surgery through a cannula **(Fig. 2.4)**. The formulation employs Verisome

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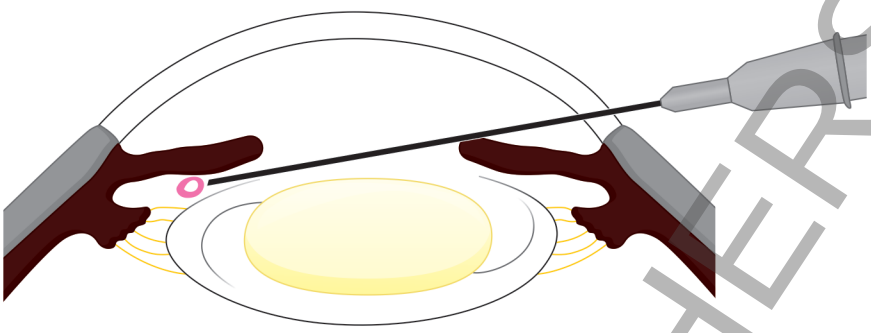

Fig. 2.4: Dexamethasone implant placed in the posterior chamber.

bioerodible technology, enabling sustained and customizable drug release from 1 to 6 months. Advantages are a higher concentration of the drug at the desired site and fewer ocular surface complications. The most common reported adverse reactions within the first 90 days postoperatively are an increase in intraocular pressure (IOP), corneal oedema, and iritis.

Dexamethasone intravitreal implant (Ozurdex®) for macular edema, fluocinolone acetonide implant (Iluvien®) for DME and bimatoprost SR implant placed in the anterior chamber through an injector system for the reduction of intraocular pressure in patients with open-angle glaucoma are other examples of intraocular biodegradable implants used in ophthalmic practice. These implants gradually degrade, releasing drug over months.

- *Nonbiodegradable implants:* These are surgically placed devices that provide prolonged release of a drug, e.g., a ganciclovir implant for CMV retinitis. However, they require removal or replacement when exhausted. *iDose® TR* (travoprost intracameral implant) is an example of a nonbiodegradable implant and is indicated for patients with open-angle glaucoma or ocular hypertension. iDose TR is administered intracamerally through a small, clear corneal incision and is anchored into the sclera at the iridocorneal angle. The intracameral implant consists of a titanium implant reservoir with a membrane controlling the sustained release of travoprost. The sterile implant is preloaded in a sterile single-dose inserter to facilitate insertion directly through the trabecular meshwork of the anterior chamber angle into the sclera **(Figs. 2.5A to C)**. It provides dosing for over 3 years. Dislocation of the iDose TR has been observed in clinical trials. Patients should be monitored routinely to confirm the location of the iDose TR at the site of administration. If the iDose TR implant becomes dislocated, it should be surgically removed.

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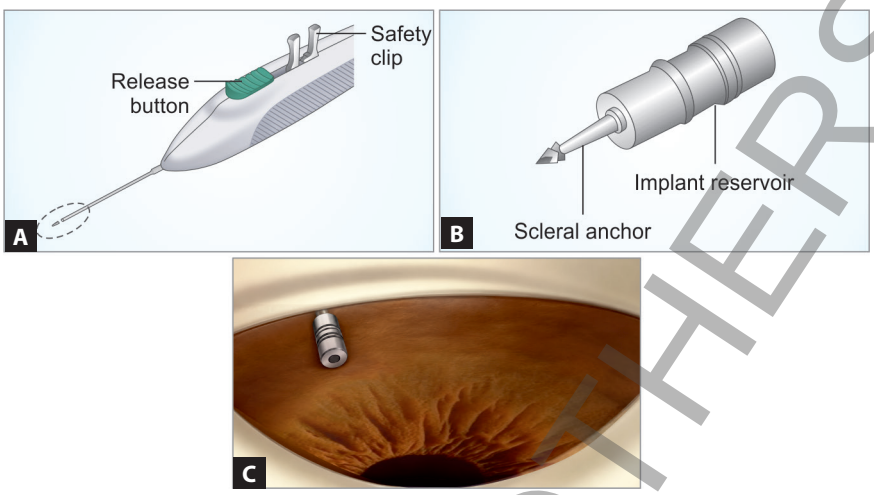

Figs. 2.5A to C: Insertion of iDose implant. (A) Tip of the sterile inserter; (B) Drug-filled titanium implant; and (C) iDose implant insitu in the angle of anterior chamber.

Intracanalicular Inserts

Dextenza® sustained-release preservative-free insert, containing 0.4 mg of dexamethasone, is implanted into the lacrimal canaliculus immediately following cataract surgery. The proprietary hydrogel plug-like device is designed to remain in the vertical canaliculus for 30 days as it delivers the drug. During the month-long period, the dexamethasone insert softens, liquefies, and is cleared through the nasolacrimal duct—eliminating the need for removal. The intracanalicular insert improves compliance and avoids drop-related toxicity. It is contraindicated in active corneal, conjunctival, or canalicular infections.

Drug-eluting Contact Lenses

Contact lenses can be loaded with drugs, allowing sustained delivery to the cornea and anterior chamber. This approach improves bioavailability compared with drops and may be used to deliver antibiotics, anti-inflammatory agents, and antiglaucoma drugs. The examples include dexamethasone-eluting lenses for inflammation and latanoprost-eluting lenses for glaucoma.

Nanoparticles and Microparticles

Nanoparticle-based delivery systems, including liposomes, micelles, and dendrimers, enhance corneal penetration and provide sustained release.

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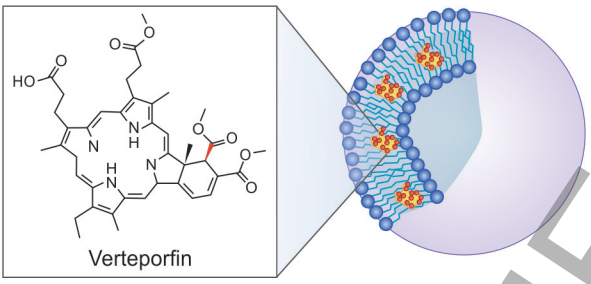

Fig. 2.6: Visudyne liposome.

Liposomes

Biocompatible vesicles that encapsulate hydrophilic or lipophilic drugs. Visudyne® is a liposomal formulation of verteporfin. Egg phosphatidylglycerol and dimyristoyl phosphatidyl choline form the liposomes with hydrophobic verteporfin partitioning into the lipid bilayer **(Fig. 2.6)**.

Nanomicelles

Increase the solubility of poorly soluble drugs, such as cyclosporine and steroids. Examples Cequa® (cyclosporine ophthalmic solution) 0.09% is approved, while rapamycin nanomicelles and terbinafine hydrochloride nanomicelles are in clinical trials.

Polymeric Nanoparticles

Provide controlled release and can be functionalized with ligands for tissue-specific targeting.

Mucoadhesive Systems and In-situ Gels

Mucoadhesion refers to the binding of polymers to the mucus membrane, leading to higher viscosity and retention on the surface. Poliopine HS (carbomer 940 gel of pilocarpine) and Alphagan P (sodium carboxymethyl-cellulose solution of brimonidine tartrate) are two examples of mucoadhesive formulations. Other common mucoadhesive polymers that are commonly used are carbopol, hyaluronan, chitosan, sodium carboxymethylcellulose (CMC), and hydroxypropyl methylcellulose (HPMC).

In-situ gelation can be induced on the corneal surface via a change in pH, temperature, or ionic strength when the drug solution mixes with the tear film. Polymers such as hydroxypropyl guar (HP)-Guar, poloxamer, and gum transition from liquid to gel upon contact with the tear fluid enhance retention time and bioavailability. The over-the-counter (OTC) dry eye treatment Systane uses the principle of gelation between borates and

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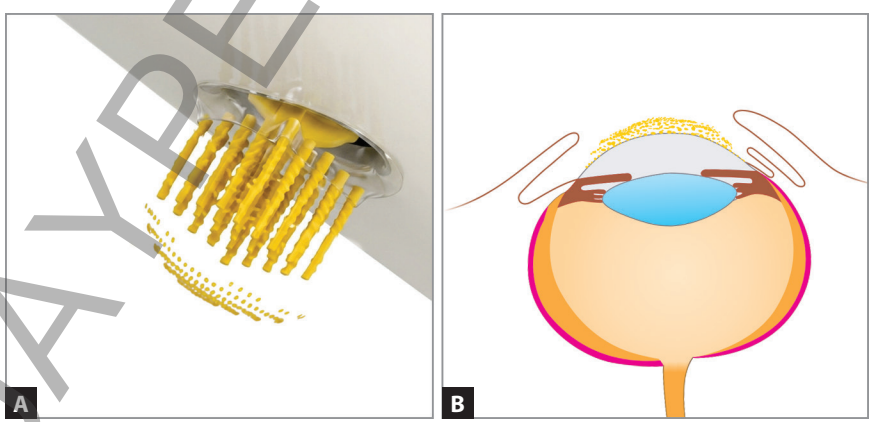
HP-Guar as the pH is increased after administration. Another example is Timoptic-XE (timolol maleate solution in gellan gum).

Iontophoresis and Ultrasound-mediated Delivery

Electrically or ultrasonically driven drug delivery enhances penetration of charged or large molecules across ocular barriers. Ocular iontophoresis has been explored for corticosteroids and antibiotics. EyeGate® II delivery system utilizes a low-level electrical current to deliver drugs; dosing takes approximately three minutes per eye. The system can be an alternative to injection and has been studied in several clinical trials. Companies such as Opharmic Technology and MeticTouch are exploring the use of low-frequency ultrasound to deliver drugs noninvasively through the sclera to the retina. Both iontophoresis and ultrasound-mediated delivery technologies are in the investigational stage.

Piezo-print Microdose Delivery

Piezo-print microdose ophthalmic dispenser releases a precisely calibrated and tightly collimated stream of aqueous ocular medication microdroplets **(Figs. 2.7A and B)**. The medication is dispersed at the micron level using electrostatic droplet charging for high-adhesive ocular surface coating. Microdoses (6–8 µL) of topical latanoprost and combination of phenylephrine-tropicamide are instilled in the eye using high precision piezo-print delivery system. Approximately 30–50 µL drops are delivered by the conventional eyedroppers which exceed the tear film volume (7–10 µL) and the normal storage capacity of conjunctival sac (about 30 µL). Piezo-print delivery system, therefore, markedly decreases the incidence of spillage and wastage of drug, and ocular and systemic side effects (by reducing systemic absorption).



Figs. 2.7A and B: Piezo-print microdose delivery: (A) Drug droplets sprayed from the dispenser; and (B) Dispersion of drug on the ocular surface.

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TABLE 2.2: Summary of advanced ocular drug-delivery systems.

System	*Description/mechanism*	*Examples/applications*
Aqueous gels	Increasing viscosity helps prolong drug contact time on the ocular surface	Artificial tear gels and lubricants
Solid matrices and devices	Provide sustained release via inserts or bioadhesive polymers	Ocuserts (pilocarpine insert), bioadhesive inserts (hydroxypropyl cellulose), gelfoam (drug-impregnated), lacrisert (dry eye therapy)
Cyclodextrins	Encapsulate hydrophobic drugs, enhance solubility and stability; act as molecular carriers	Gentamicin, carbenicillin, and ciprofloxacin
Soft contact lenses	Drug-loaded polymers (e.g., poly-2-hydroxyethyl methacrylate) for prolonged release	Chloramphenicol and gentamicin
Liposomes	Phospholipid vesicles entrapping a drug for controlled topical delivery	Acetazolamide, hydrocortisone, tropicamide
Niosomes	Nonionic surfactant vesicles; entrap hydrophilic drugs in the core and hydrophobic drugs in the bilayer	Dorzolamide, timolol, and gentamicin
Pharmacosomes	Vesicles of amphiphilic drugs linked to lipids that improve stability and sustained release	Indomethacin and diclofenac formulations
Collagen shields	Cross-linked collagen tissue; dissolves slowly, delivering the drug while acting as a corneal bandage	Antibiotics and steroids (postulcer or surgery)

Some of the advanced ocular drug-delivery systems with the objectives of prolonging precorneal residence time, enhancing corneal penetration, providing sustained and controlled drug release, minimizing systemic absorption, and improving patient compliance have been summarized in **Table 2.2**.

Clinical Applications of Newer Systems

- *Glaucoma:* Sustained-release prostaglandin analogs (e.g., bimatoprost 10 µg implant, Durysta®) reduce dependence on daily drops. Durysta® is a polylactide-glycolide copolymer that is biodegradable. The implant is inserted intracameral using a fine needle. The implant is about 1.1 mm

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in length and 0.2 mm (200 μm) in diameter and can provide drug over several months.

- *Dry eye disease:* Cyclosporine nanomicellar formulations and intracanalicular steroid inserts provide improved efficacy and tolerability.
- *Posterior segment diseases:* Anti-VEGF sustained-release devices (port delivery system with ranibizumab) reduce injection frequency for neovascular AMD.
- *Postoperative inflammation*: Intracanalicular and subconjunctival depot steroids simplify perioperative regimens.

RECENT ADVANCES IN OCULAR DRUG DELIVERY

The future of ocular drug delivery is moving toward precision pharmacology, aiming for targeted, sustained, and patient-specific therapy. One major development is smart drug delivery systems, which respond to physiological or environmental stimuli, such as pH, temperature and glucose levels. For example, glucose-sensitive hydrogel-based systems can release drugs in response to elevated glucose, offering potential benefits in managing diabetic retinopathy. Similarly, pH- or temperature-responsive nanoparticles can provide on-demand drug release at specific ocular sites.

Another area of innovation is biodegradable film on the surface of drug-eluting intraocular lenses (IOLs). These implants can provide localized drug delivery for infection prophylaxis, control of inflammation, or prevention of posterior capsular opacification following cataract surgery, eliminating the need for frequent topical drops and reducing systemic exposure.

Ocular gene therapy represents a transformative approach to treating inherited and complex retinal diseases by delivering therapeutic genetic material directly to target cells in the eye. The eye is a particularly favorable organ for gene therapy owing to its immune-privileged status that limits inflammatory responses and reduces the risk of systemic exposure. Further, the presence of terminally differentiated cells in the retina lowers the likelihood of harmful gene integration events. These features, combined with the accessibility of ocular tissues, make the eye an ideal site for viral gene delivery. In gene therapy, viral vectors are engineered to carry therapeutic genes into target cells, replacing, correcting, or augmenting defective genes responsible for disease. The most commonly used vectors in ocular applications are adeno-associated viruses (AAVs), adenoviruses, and lentiviruses, each with distinct characteristics, advantages, and limitations. AAV vectors are the most widely studied and used due to their ability to transduce retinal cells with relatively mild immune responses, though their small gene-carrying capacity (~4.8 kb) limits use for larger genes. Adenoviral vectors can accommodate larger genetic payloads but provoke stronger immune reactions, while lentiviral vectors integrate into host

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deoxyribonucleic acid (DNA) and can carry intermediate-sized genes but carry a higher risk of insertional mutagenesis.

A landmark milestone in ocular gene therapy was achieved in 2017 with the FDA approval of voretigene neparvovec (Luxturna), an AAV2-based therapy for Leber congenital amaurosis caused by mutations in the retinal pigment epithelium-specific 65 kDa protein (*RPE65*) gene. Administered via the subretinal route, Luxturna demonstrated sustained improvement in visual function, marking the first approved gene therapy for an inherited retinal disease.

Numerous other retinal disorders are under investigation in preclinical and clinical trials, including X-linked retinoschisis, Stargardt disease, choroideremia, Usher syndrome, achromatopsia, and even genetically influenced conditions, such as AMD and glaucoma. Delivery of viral vectors can be achieved through various routes—intravitreal, subretinal, and suprachoroidal—each with unique advantages and limitations in terms of tissue targeting, immune response, and procedural invasiveness.

Despite promising outcomes, challenges remain. Ocular inflammation can occur due to immune recognition of viral capsids and transgene products, and subretinal delivery requires surgical intervention. The long-term durability and safety of many viral gene therapies are still under evaluation, and high production costs are significant barriers to widespread adoption. Nonetheless, ongoing research continues to expand the potential of gene therapy as a precision medicine approach for a wide spectrum of ocular diseases.

The integration of artificial intelligence (AI) and personalized medicine is also shaping ocular drug delivery. AI can help predict individual drug responses based on pharmacogenomics, ocular anatomy, and disease progression, enabling the design of customized drug formulations and dosing regimens.

SAFETY CONSIDERATIONS

While newer ocular drug delivery systems offer significant advantages in terms of targeted therapy, sustained drug release, and improved patient compliance, they are not without potential concerns. Local tissue toxicity may occur due to preservatives or degradation of products from polymer-based carriers. Device-related complications, such as implant migration and punctal plug extrusion, can also arise. Additionally, the long-term safety of nanocarriers and gene delivery vectors remains under investigation, and intraocular implants carry an inherent risk of infection. Consequently, careful safety surveillance, thorough risk–benefit assessment, and individualized patient selection are essential to ensure optimal outcomes with these advanced ocular delivery strategies.

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SUMMARY

The chapter provides a comprehensive overview of routes of drug administration and newer drug delivery systems in ophthalmology, emphasizing the challenges posed by the eye's unique anatomy and protective barriers. Ocular drug delivery is limited by precorneal factors, corneal and conjunctival barriers, blood-aqueous and blood-retinal barriers, and active efflux transporters, all of which restrict drug penetration and bioavailability. Conventional routes such as topical, systemic, periocular, and intraocular administration are discussed in detail, highlighting their specific advantages, limitations, and clinical applications. Topical therapy remains the mainstay for anterior segment diseases, while systemic therapy plays a limited role due to poor ocular targeting and systemic toxicity. Intraocular routes, particularly intravitreal injections, provide effective treatment for posterior segment disorders but are invasive and associated with potential complications.

To overcome the shortcomings of conventional methods, newer ocular drug delivery systems have been developed. These include sustained-release implants, intracanalicular inserts, drug-eluting contact lenses, nanoparticles, in situ gels, and microdose delivery technologies, all designed to enhance drug retention, improve targeting, and reduce dosing frequency. Advances such as gene therapy, smart responsive systems, and biodegradable drug-eluting devices represent the future of precision ophthalmic pharmacotherapy. Overall, the chapter underscores the importance of selecting appropriate delivery strategies to maximize therapeutic benefit while minimizing risks.

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