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REVIEW ARTICLE

Novel Anterior Segment Ocular Drug Delivery Systems in Ophthalmology: A Review Study

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ABSTRACT

Objective(s): The anterior segment of the eye represents distinct challenges for drug delivery, characterized by rapid clearance, limited absorption, and anatomical barriers that restrict drug bioavailability. This review seeks to examine the latest developments in anterior segment ocular drug delivery systems designed to enhance therapeutic efficacy and patient adherence.

Methods: A comprehensive review was performed by searching pertinent literature in the PubMed, Google Scholar, and Scopus databases. Selected articles were analyzed regarding emerging ocular drug delivery methods for the anterior segment, focusing on systems based on nanotechnology and sustained-release platforms.

Results: Contemporary drug delivery systems provide enhanced drug retention, prolonged release profiles, and precise delivery mechanisms. Significant advancements encompass nanofiber scaffolds, drug-loaded soft contact lenses, punctal plug-based release systems, and intracameral/intrastromal injections that circumvent traditional barriers. These advancements improve drug bioavailability and minimize systemic side effects.

Discussion: In contrast to conventional eye drops and systemic administration, these innovative methods address significant pharmacokinetic and physiological challenges. Although there is potential, the majority are still in preclinical or early clinical stages, and issues concerning safety, scalability, and patient tolerability continue to exist.

Conclusions: Advanced anterior segment ocular drug delivery systems signify a notable transformation in ophthalmic treatment. Their implementation may lead to improved treatment outcomes, increased patient adherence, and a decrease in dosing frequency. Future research should focus on advancing AI-enabled drug delivery technologies and integrating personalized medicine approaches to improve therapeutic outcomes.

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INTRODUCTION

Topical application is the predominant technique for ocular medication delivery, accounting for over 95% of marketed ocular medicines [1]. This approach has garnered significant attention in ophthalmic research, leading to numerous studies focused on the efficacy, formulation, and application of topical drug delivery systems for the management of diverse ocular conditions [2]. Despite topical administration being the most practical method, the bioavailability of most

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ophthalmic formulations is still below 5% because of blinking, fast tear turnover, and the strong corneal and conjunctival barriers. This means that there are still a lot of unmet therapeutic needs in ocular drug delivery [3]. As a result, advancements in these systems are crucial for improving therapeutic outcomes and enhancing patient care in ophthalmology [1, 2]. Other traditional drug delivery methods, such as systemic administration, have less application in ophthalmology. This review summarizes key findings from recent investigations into ocular drug delivery systems for administration in ophthalmic therapies with a focus on anterior segment types. This review covers a range of traditional types including topical and systemic administration to novel drug delivery systems including nanoinsert systems, collagen shields, and iontophoresis.

To review previous and novel ocular drug delivery routes, as well as to hypothesize for the design of future systems, it is necessary to first become familiar with the specific physiological conditions of the eye and the existing pharmacokinetic and pharmacodynamic limitations. The present article examines these issues with a focus on the anterior segment of the eye.

Primary Obstacles in Ocular Drug Administration

Ocular drug delivery encounters numerous substantial obstacles that impede the successful treatment of diverse visual diseases. The limitations arise from the distinctive anatomical and physiological attributes of the eye, which restrict pharmaceutical penetration and absorption [1, 2].

Anatomical Barriers

The blood-ocular barrier (BOB) significantly impedes the ingress of therapeutic molecules from systemic circulation to intraocular tissues, thereby limiting the efficacy of systemic delivery methods such as oral and intravenous routes. Pharmaceuticals often remain sequestered in the circulation and fail to intraocular penetration, leading to reduced bioavailability (approximately 2%) and necessitating elevated systemic dosages to achieve therapeutic outcomes [4]. This situation may result in systemic adverse effects due to increased doses [5]. Ocular medication transport faces challenges from the protective systems and barriers present within the eye. Topical administration is commonly used; however, it frequently results in subtherapeutic medication concentrations, particularly in posterior ocular disorders [6]. Static barriers: The eye is protected by several layers, including the cornea, sclera, and retina, which together create a formidable barrier to drug penetration. The blood-ocular barrier is particularly stringent, limiting the ingress of therapeutic agents into the posterior portion of the eye. Dynamic barriers: Elements like as tear turnover, lacrimal drainage, and blood circulation facilitate the swift removal of medications from the ocular surface. This dynamic milieu diminishes the effective concentration of drugs that can penetrate deeper into ocular tissues [1, 2].

Low Bioavailability

Systemically given medications frequently exhibit inadequate ocular absorption. Conventional eye drops generally provide less than 5% of the active pharmaceutical ingredient to the intended location because of rapid drainage and absorption into systemic circulation. The limited bioavailability requires elevated dosages or more frequent administrations, potentially resulting in heightened adverse effects [1, 2].

Enzymatic Degradation

Enzymes in the ocular environment can destroy specific drugs prior to their arrival to designated target locations**.** This enzymatic activity poses significant challenges to the development of effective ophthalmic pharmaceuticals. Numerous enzymes, including esterases, peptidases, and CYP-450s, are found in ocular tissues and play critical roles in drug metabolism and excretion [7]. These enzymes, in conjunction with membrane transporters, can influence drug disposition and result in suboptimal ocular bioavailability [8]. Conventional eye drops face hurdles such as rapid removal and enzymatic degradation, which lead to reduced ocular residence time and bioavailability. Researchers have explored nanoformulations as potential solutions to address these challenges.

Immune Privilege of the Eye

The unique immunological characteristics of the eye can limit the effectiveness of systemic medications. The immune response may alter the distribution and efficacy of these medications, complicating the achievement of therapeutic levels without causing adverse effects. Protective barriers, such as the cornea, sclera, and BOB, impede drug penetration and bioavailability [9].

This immunological privilege promotes systemic, antigen-specific tolerance rather than inflammation upon the introduction of antigens. However, the intraocular delivery of biotherapeutics may elicit immunological responses, potentially leading to the formation of anti-drug antibodies with significant clinical implications [10]. Factors influencing immunogenicity include the formulation of the medication, manufacturing processes, and administration techniques. Researchers are exploring innovative strategies, such as sustained-release devices, nanotechnology, and gene therapy, to address these challenges [9].

Need for Sustained Release

Attaining prolonged drug release in ocular tissues continues to be a difficulty. Contemporary formulations frequently need regular administration to sustain therapeutic levels, potentially resulting in patient non-compliance and heightened risk of adverse consequences. These techniques entail the creation of sustained-release implants and devices capable of administering medications over prolonged durations, hence diminishing the necessity for frequent administration [11]. Innovative delivery strategies, such as polymeric controlled release systems and nanofibers, are being investigated for protein and peptide-based therapies to address challenges related to their considerable size and susceptibility to degradation. [12].

Potential Benefits

Systemic distribution via the ocular route has potential, providing benefits such as accurate dose, convenience of administration, and fast absorption [13]. Diverse drug delivery strategies, including nanoparticles, liposomes, and implants, are being developed to improve pharmacokinetics and target specific ocular regions [14, 15]. Certain studies suggest that systemic administration, including intravenous delivery of bevacizumab (an anti-vascular endothelial growth factor (VEGF) agent), may improve visual acuity in patients with age-related macular degeneration (AMD) without significant systemic side effects, particularly in those without pre-existing conditions such as hypertension. Investigations are underway about advancements in drug delivery methods, including nanoparticles and colloidal formulations, to enhance the efficacy of systemic drug administration [16, 17].

Systemic routes are limited by the BOB [18]. Novel methodologies employing nanotechnology and temporary disruption of the BOB have been suggested to enhance systemic distribution [19]. The ocular route has been investigated for the systemic distribution of polypeptide medicines, with benefits including accurate dosage, rapid absorption, and evasion of first-pass metabolism [13]. These innovations in ocular drug delivery systems seek to surmount physiological limitations and improve bioavailability for ocular and systemic therapies [18, 19].

DRUG DELIVERY ROUTES IN OPHTHALMOLOGY

Systemic administration (oral and parenteral)

The systemic delivery of pharmaceuticals for ocular disorders has been explored as a potential alternative to invasive ocular injections, presenting varying levels of efficacy and limitations. Commonly used Oral medications are antibiotics, antivirals and carbonic anhydrase inhibitors [20]. Carcinine, a carnosine derivative, may be taken orally for ocular therapeutic applications [21]. Oral administration may be advantageous when topical therapies are ineffective or unfeasible. The efficacy of oral medications for ocular disorders is constrained by variables including systemic absorption and the necessity for elevated bioavailability to achieve therapeutic concentrations in the eye. This may result in systemic side effects, requiring meticulous evaluation of safety and toxicity [20]. Nevertheless, restricted access to various ocular tissues and the requirement for elevated doses to get therapeutic outcomes in the eye may lead to systemic adverse effects. Oral administration is not a primary route, and only a restricted number of chemicals have been explored for ocular medication delivery using this method [18].

Systemic administration techniques, including intravenous and subcutaneous injections, can be employed to deliver medications to the eye. Nevertheless, the medicine must traverse the blood-aqueous barrier and the BOB to access the intraocular tissues [6, 18].

A prevalent approach in clinical and preclinical research involves comparing the pharmacokinetics and pharmacodynamics of systemic medicines with other delivery techniques.

A compelling study demonstrated that prolonged administration of insulin eye drops, in conjunction with permeation enhancers, effectively

reduced blood glucose levels and facilitated insulin absorption into systemic circulation [22]. Furthermore, a study comparing an oral vitamin A-based antioxidant formulation with topical vitamin A eye drops for the treatment of dry eye syndrome demonstrated that oral vitamin A antioxidants are more effective and yield a prolonged impact compared to topical applications. It is advisable to utilize oral vitamin A antioxidants in conjunction with lubricating eye drops for the treatment of dry eye disease (DED) to mitigate symptoms and rectify the underlying issues impacting the ocular surface and lacrimal gland [23]. Findings from a research indicated that the oral administration of a curcumin-phospholipid delivery system enhanced visual acuity and decreased retinal thickness in individuals with central serous chorioretinopathy (CSC) [24]. Intravitreal dexamethasone demonstrates a depot effect with minimal plasma concentrations, whereas intravenous and subconjunctival administration indicate more rapid clearance [25]. Innovative drug delivery technologies, such as N-acetylcarnosine eye drops, have potential for addressing diverse ocular disorders by local and systemic administration [21]. Moreover, other aspects must be evaluated while providing medicine. One research demonstrated that oral treatment of prednisone in dogs, at dosages ranging from 0.5 to 4 mg/kg/day, yielded detectable quantities of both prednisone and its active metabolite prednisolone in tear fluid, with greater doses corresponding to larger concentrations. Inducing conjunctivitis in one eye demonstrated a tendency for elevated steroid levels in the afflicted eye; however, the changes were not statistically significant. Severe conjunctivitis led to markedly elevated prednisolone levels relative to mild instances at dosages of ≥1.0 mg/kg/day; however, these alterations were not considered clinically important [26].

Consequently, it appears that for each medication, a formulation should be selected by the physician that maximizes absorption and minimizes adverse effects, achievable via the meticulous evaluation of each medicine based on recent studies.

Topical Drug Delivery Systems in Ophthalmology (Eye Drops, Ocuserts & Ointments)

Ocular illnesses are generally managed with topical administration, such as eye drops or ointments. This treatment typically necessitates frequent application throughout the day [27]. The main drawback of administering medications in the form of eye drops is the relatively low efficiency of this method, as the unique physiology and anatomy of the eye surface can result in limited bioavailability [28]. Two primary physiological obstacles impede the efficacy of topical medications: the cornea and the tear film [7]. The tear film, approximately 3 μm thick, covers both the cornea and conjunctiva, providing essential lubrication, nutrition, and antibacterial protection [8]. The three layer construction of the eye makes it more difficult for drugs to be absorbed by processes like drainage, protein binding, or continuous turnover. Additionally, the six-layered structure of the cornea largely prevents the penetration of hydrophilic agents [9, 10]. The uptake of drugs by the cornea is largely dependent on its hydrophilic-lipophilic balance, with worse absorption noticed in drug therapy of corneal erosions or ulcers [11, 12]. This explains the significant role of tear film in ocular pharmacology and, more so, the limitations of topical drug application.

As topical administration does not involve any invasive procedure, it remains the preferred mode of therapy for ocular disorders. However, it faces major obstacles when it comes to the efficient delivery of the drug [17]. The primary challenge in drug delivery via eye drops is the limited volume (~10 μL) that can be applied to the corneal surface due to its restricted surface area. Furthermore, the administered volume is mostly removed during the initial blink reflex, which is triggered by a sudden surge in tear volume [18, 29]. Consequently, eye drops need to contain high concentrations of medication to counteract factors that contribute to low ocular bioavailability. These factors include tears, blinking, lacrimal drainage, blood and lymphatic vessel flow in the conjunctiva, metabolic breakdown, and ocular and corneal blood barriers [18, 29]. Moreover, the high concentration of medications in bolus administration can lead to both local and systemic complications. For instance, the use of pilocarpine can result in accommodative spasm that causes eyebrow ache [30]. There are also variations in drug concentration, depending on the administration technique and patient compliance with the use of eye drops. Therefore, an efficient delivery system that can control drug release and decrease the frequency of dosing is required [31, 32]. Accordingly, different drug administration methods have been developed to maintain a

steady dosage of medication, aiming to achieve consistent therapeutic effects while minimizing the side effects [33]. In addition, several classes of therapeutic agents pass through the aqueous humor to the anterior uvea and have differing affinities for melanin, with some showing minimal affinity while others show maximal affinity. Such binding may also influence how drugs are absorbed and where they are distributed within the body since these agents might be stored in pigment tissues rendered by melanin. Topical treatment regimens are particularly ineffective in treating intraocular diseases, even with multiple doses, due to the persistent physical barrier of the cornea [19].

Viscosity enhancers are essential for enhancing ocular bioavailability by extending the precorneal residence time of pharmaceuticals at the targeted ocular location [12]. For instance, hydrophilic viscosity enhancers such as cellulose, polyacrylic acid, and polyalcohols extend the duration for which the drug remains in contact with ocular tissues [12, 15]. Additionally, other suitable polymers have been investigated, including chitosan, hydroxypropyl methyl cellulose (HPMC), and xyloglucan. Among these, natural urea-containing polymers such as hyaluronic acid, alginates, acacia, xanthan gum, Veegum®, tragacanth, and gelatin are also utilized due to their beneficial effects [20, 34]. Many of these polymers provide essential properties necessary for the development of advanced systems, including biocompatibility, gel formation capabilities, and mucoadhesion [22]. Overall, this highlights the importance of incorporating viscosity enhancers and polymers in the formulation of ocular drug preparations to enhance their efficacy [34].

Ophthalmic emulsions are essential since they extend precorneal residence time for sustained drug release, augment corneal absorption, and promote the dissolution and bioavailability of poorly soluble medications [23]. Among these, oil-in-water (o/w) emulsions are preferred in most of the ophthalmic uses due to their better comfort levels and decreased chances of ocular toxicity when compared to their w/o counterparts [24]. The formulations as ophthalmic emulsions have effectively improved bioavailability within the eye by prolonging drug retention and enhancing permeability across the cornea, thereby significantly advancing pharmacotherapeutic strategies for ocular drug delivery [25, 26].

Ophthalmic ointments are among the most commonly used dosage forms after solutions and suspensions and must be non-irritating and compatible with other components [15]. Usually, these ointments are anti-inflammatory, anti-epidemic, or anti-infective. Water-soluble gel bases have been more popular recently since they have several benefits over conventional Vaseline, such as improved spreading, pH stability, lubricity, and less irritation [27, 28]. Common polymers used in these gels, such as PEG 200, PEG 400, carboxymethyl cellulose, and others, often exhibit mucoadhesive properties that prolong drug contact duration. These components are increasingly being used by pharmaceutical services in compounded formulations, such as hyaluronic acid in artificial tears and carboxymethyl cellulose in eye drops that contain vancomycin and cysteamine [28]. Additionally, in situ gelling formulations transition from liquid to gel state upon application, responding to stimuli such as temperature, ionic composition and pH [27, 28].

In ocular therapy, the method of drug administration is one of the key considerations, with the topical route being the most popular [13, 14]. Ideally, drugs should be in the pH range of 7.4 to 7.7, which corresponds to tears and minimizes pain; however, these extremes may be controlled but are readily counteracted [14]. It is imperative to maintain sterility to prevent any chance of an infection, and the solution has to be clear enough to prevent scratch injuries to the cornea; hence, particles in ophthalmic suspensions have to be sized less than 10 μm [15]. Furthermore, the osmolarity should be close to that of tears (approximately 300.5 mOsm/kg); however, for practical reasons, a little higher than isotonic solutions is encouraged to prevent dilution of the drug [15, 16].

Another novel strategy is the use of prodrugs, like prostaglandin F2α analogues latanoprost, travaprost, and bimatoprost, which effectively lower intraocular pressure in glaucoma. Additionally, the FDA has approved loteprednol etabonate, a topical corticosteroid derived from prednisolone, for treating eye allergies and inflammation, although it is not available in Europe [15].

Autologous serum eye drops (ASEDs) and exosomes have advanced the topical application of drugs in ophthalmology. ASEDs are rich in trophic factors and are made from a patient's own blood to effectively treat disorders like dry eye syndrome [35, 36]. The addition of exosomes, which also aid in increasing the effectiveness of therapeutic agents by their stability and corneal penetration, takes it

a notch higher [37, 38]. Additionally, orthokine therapy involves using self-made patients' conditioned serum to achieve anti-inflammation [39-41]. All these methods come in handy to treat design objective factors in patients in a very efficient and practical way.

Ophthalmic inserts, such as Ocuserts, are sophisticated medication delivery systems positioned within the eye, usually in the cul-de-sac or conjunctival sac [42, 43]. These devices are classified according to their solubility into insoluble, soluble, and bioerodible inserts [42]. Ocusert is characterized as an innovative ocular drug delivery system that provides benefits such as extended drug release, potentially improving therapeutic results [43]. Ocular inserts are drug delivery devices made from polymeric materials with solid or semi-solid consistency, designed to release the embedded medicine to the ocular surface when positioned in the conjunctival sac. Ocular inserts exhibit numerous benefits, including precise dosage delivery, reduction of systemic side effects associated with ocular treatments, extension of ocular residence time, thereby decreasing administration frequency and enhancing patient adherence, and the potential for sustained and consistent drug release, which could enhance shelf life stability from an industrial perspective [44]. Typically, all varieties of ocuserts comprise three layers (fig. 2). A central drug reservoir is a slender disc carrying a medication formulation. The medication is incorporated into a polymer, facilitating its dispersion from the reservoir. A rate-controlling membrane comprises two transparent discs fabricated from ethylene vinyl acetate, a copolymer. This membrane facilitates the controlled release of medication from the drug reservoir. A peripheral annual ring for enhanced manipulation and precise insertion [45].

Depending on the type of ocusert, one of the following mechanisms can release the drug: diffusion, osmosis, or bioerosion (fig. 1) [43].

The overarching principle is to enhance patient adherence and diminish administration frequency relative to conventional approaches such as eye drops [42].

Nanocarriers

Thanks to recent advances in nanocarrier technologies, transporting and delivering a variety of active agents, including macromolecules, to the eyes has become simpler and more efficient [29, 33].

Some of these methods, like calcium phosphate nanoparticles, liposomes, and nanoemulsions, have shown promise in making drugs more bioavailable by reducing protein binding, keeping drugs in the cornea longer, and making drug release easier over time [35]. However, the majority of these technologies remain in the development phase and require further testing to determine their commercial viability. Numerous systems for nanocarrier design are currently under development, including emulsions, liposomes, cyclodextrins, polymer nanoparticles, niosomes, lipid nanocarriers, and dendrimers [30]. The development of these systems offers significant advantages. For instance, the use of cyclodextrins in ocular formulations enhances the solubility of active ingredients while minimizing the toxicity of the solvent [32, 33]. Nanosuspensions not only improve solubility but also enhance absorption, while vesicular systems such as liposomes and niosomes increase drug bioavailability, prolong retention time, and reduce systemic side effects [33]. The design purpose of liposomes is to enable the delivery of specific therapeutic agents through targeted tissues into the eye, based on the principle that their structure closely resembles that of cell membranes, thereby facilitating the transport of therapeutic agents across physical barriers such as the corneal epithelium and lacrimal drainage systems [18, 30, 46]. Moreover, copolymeric micelles have markedly enhanced topical ocular drug delivery by augmenting the solubility and stability of pharmaceuticals designed for intraocular disease treatment, especially via corneal or conjunctival-scleral administration, where traditional methods such as eye drops may prove inadequate [32, 33]. These advancements in nanocarrier technologies enhance the pursuit of more effective and targeted treatment options for ocular conditions.

When someone loses their corneal vision, corneal transplantation is usually the only way to fix it. However, there aren't many cornea donors available, and there's also a chance that the new cornea will get infected or not work right. To help different types of corneal cells grow, like keratocytes, epithelial cells, endothelial cells, and corneal fibroblasts, different electrospun, self-assembled amphiphilic peptide nanofibers and nanotopographies have been studied. These can help corneal epithelium, stroma, and endothelium regeneration or full corneal tissue replacement [36].

Table 1. Summary of experimental studies on nanofiber production and their therapeutic applications.

Nanofiber	Nanofiber loaded drug	Diameter	Fabrication method	Mechanism	Therapeutic application	References
Eudragit	Ketorolac	350 nm	Electrospinning	Increasing the duration of drug action (increasing drug retention time)	Inflammatory ophthalmic diseases	[33]
polycaprolactone	Ketorolac	350 nm	Electrospinning	Increasing the duration of drug action (increasing drug retention time)	Inflammatory ophthalmic diseases	[33]
copolymer PA6/12	LSC	290 to 539 nm.	Electrospinning	Providing a scaffold for stem cell growth	ocular surface injuries	[39]
copolymer PA6/12	MSC	290 to 539 nm.	Electrospinning	Providing a scaffold for stem cell growth	ocular surface injuries	[39]

Electrospinning generates nanometer-scale fibers with a superior specific surface area, in contrast to dry/wet and melt spinning methods. Consequently, electrospun nanofibers can enhance various surface-dependent structures and products. A potential use involves the cultivation of nanofibrous cellular scaffolds and nanofibers for tissue engineering and stem cell purposes [40]. Today, electrospun fibers are used in many stem cell and regenerative medicine applications [37].

Liu et al. (2010) developed an experimental model to evaluate the possibility for alleviating the corneal deficit in keratoplasty for congenital corneal disorders associated with genetic abnormalities. The research sought to enhance the opaque and attenuated corneas in lumican-null mice via the administration of human umbilical mesenchymal stem cells (UMSCs). The implantation of UMSCs resulted in significant enhancements in corneal stromal thickness and clarity. This study indicates that UMSCs may serve as an effective intervention for congenital corneal disorders, including keratocyte failure [38]. Zajicova et al. co-cultured limbal stem cells (LSCs) and mesenchymal stem cells (MSCs) on nanofiber scaffolds and applied them to damaged ocular surfaces, eliciting a local inflammatory response marked by the expression of IL-2, IFN-γ, and iNOS genes subsequent to epithelial debridement and limbal allotransplantation. The expression of inflammatory proteins IL-2, IFN-γ, and iNOS was markedly reduced in tissue obtained from the wounded ocular surface one week after injury, indicating that MSCs attenuate the inflammatory response. Previous research demonstrates that the application of MSCs to the ocular surface can alleviate localized inflammation [39]. For better understanding, the experimental studies discussed have been summarized in Table 1.

Ocular Drug Delivery Systems Based on Soft Contact Lenses (SCLs)

Soaking (Dip-Coating)

The method of soaking soft contact lenses (SCLs) in drug solutions has gained popularity among practitioners as it offers a straightforward approach towards the functionalization of commercial poly-hydroxyethylmethacrylate (pHEMA) contact lenses [47]. This approach's drawback is the quick release of medicines, attributable to the ionic and water absorption of the contact lens material [48, 49]. This technique has been employed in the incorporation of various drugs, especially ophthalmic drugs like antibiotics [50], antihistamines [51], and antiglaucoma drugs [52]. Incorporating vitamin E into the hydrogel matrix as the initial step forms a blocking layer that makes it take longer for the drug to be released [34]. Timolol retention in pHEMA-based contact lenses was extended by Hsu et al. [53], ranging from 1 hour (without Vitamin E) to 25 hours (with 20% Vitamin E). Nonetheless, vitamin E possesses specific disadvantages, including its mechanical properties and reduced permeability to ions and oxygen [54].

Functional Monomer Incorporation

The hydrogels' physical characteristics alter when functional monomers are added. Two distinct approaches can be used to modify contact lenses (CLs) by adding functional monomers. The first is ionic chemicals added during the polymerization process. Strong attachment sites are thereby created between the medication and the CL. Most

frequently, acryl-vinyl compounds are added to the pHEMA to change the ionicity of hydrogels [55]. Methacrylic amino propyl-trimethyl ammonium chloride (MAPTAC), a cationic monomer, enhances the retention of anionic pharmaceuticals and prolongs their release [56]. Other compounds that are utilized to construct cationic medicines include methyl methacrylate (MMA) and 2-methoxy ethyl phosphate (MOEP) [57-59]. Using this technique, daily disposable CLs (DDCLs) filled with different ophthalmic medications were created, and in vitro investigations were carried out. As a result, the medication was retained for two months instead of several hours [60]. The second strategy, which uses functionalized hydrogels containing cyclodextrins, is applied to hydrophobic medicines. A type of cyclic oligosaccharide called cyclodextrin has a hydrophobic pocket that can hold tiny medication molecules [61]. Functionalized cyclodextrin can be covalently bonded to pHEMA through glycidyl methacrylate (GMA) cross-linking or via acrylic/vinyl-assisted copolymerization. Drug release from cyclodextrin can range from a few hours to two weeks, as indicated by specific in vitro studies [47, 62-64]. Li et al. [65] observed that diclofenac sodium was released more often in rabbits than in vitro during the first hour (73% compared to 42%) and for a longer duration (three days versus two days) [60].

Molecular Imprinting

Molecular imprinting employs a pharmacological template produced during polymerization to enhance the interaction between medications and CLs. This technique utilizes functional monomers, chiefly acrylic-vinyl derivatives, to correspond with the molecular architecture of the pharmaceuticals [66]. Through the use of molecular imprint technology, a polymer's affinity for drug molecules can be increased, improving the drug's ability to load and prolonging its delivery duration [67-69]. Hiratani employed MAA as the active monomer for imprinting SCLs and incorporated timolol into hydrogels of N,N-diethyl acrylamide (DEA) and pHEMA. In comparison to pHEMA lenses produced without molecular printing technology, this method facilitated a 300-fold increase in storage capacity. Antibiotics [70], antimicrobials [71], antihistamines [72], non-steroidal anti-inflammatory drugs [73], corticosteroids [74], antiallergics [62, 75], therapeutic agents that can improve eye comfort [76], also used for diabetes patients [55, 74], humectants in the treatment of dry eye [77], and, based on recent research, antiviral drugs [78] have all been loaded using the method that has been presented.

Colloidal Nanoparticles Incorporation

Drug encapsulation within colloidal nanoparticles, including liposomes, micelles, microemulsions, and polymer nanoparticles, has been made possible by the development of nanomaterials. With this method, the duration of continuous medication release can be changed from a few hours to several weeks, depending on the patient's needs. In the process of releasing medications onto the surface of the eye, nanoparticles function as a barrier against metabolic breakdown [79]. Functionalized nanoparticles can be integrated into SCLs by chemical bonding through polymerization reactions, infiltration, or immobilization on the CL surface [47]. Research indicates that nanoparticle-functional CLs have markedly prolonged retention durations compared to ocular drops containing medication nanoparticles [47, 79]. Over the past decade, the following nanoparticle medicines have been applied to SCLs: antibiotics [80], corticosteroids [81], immunosuppressants [82], antihistamines [54], and glaucoma [83]. Animal studies indicate an extension in drug release time for chitosan nanoparticles containing cyconazole, lasting up to seven days [84]. Ten days of observation occurred when ketotifen was administered using silica nanoparticles in rabbits [54], and 14 days when cyclosporine-A was administered using polymer nanoparticles in a murine model [82]. Furthermore, Gulsen and Chauhan [85] conducted a pilot investigation to assess the efficacy of pHEMA enhanced with nanoparticles, creating four microemulsion-based formulations. Jung and Chauhan [86] suggested a contact lens technology utilizing nanoparticles with timolol and pHEMA, fabricated without surfactants. Their product was a transparent hydrogel infused with a medication, exhibiting a temperature-dependent release rate of two to four weeks [86].

Supercritical Fluid

Compounds that surpass their critical point in temperature and pressure are classified as supercritical fluids. Dissolving both hydrophilic and hydrophobic pharmaceuticals in supercritical solvents for application in an SCL matrix is

straightforward. Drug loading is achieved through the molecular imprinting of the lenses [87] or immersing them in a supercritical solvent-drug solution under meticulously regulated conditions [88]. The first approach has the benefit of being able to use commercial SCLs, whereas the molecular imprinting process necessitates a polymerization reaction beforehand. It has been demonstrated that both methods release the medication more effectively than traditional soaking [88, 89]. Subsequent literature reviews, however, have demonstrated that supercritical solvents yield less encouraging outcomes. The drug retention time has only been able to be extended to a few hours thus far [87, 88, 90]. This discovery warrants careful consideration since more research is required.

Drug-Polymer Film Embedded

Another innovation to prolong the drug's retention duration is drug-polymer film-embedded CLs. Polylactic glycolic acid (PLGA) [91] and polyvinyl alcohol (PVA) combined with chitosan [92] or ethyl cellulose (CE) in conjunction with Eudragit S-100® are coating polymers that are used to bind medications to pHEMA. It has been demonstrated that the thickness of the drug film directly correlates with the efficacy of drug release [92-94]. Administration of nonsteroidal anti-inflammatory drugs for 12 hours, antibiotics and antihistamines for 2 days, or corticosteroids for 7 days resulted in sustained drug release in vivo [60, 94, 95]. Additionally, Ciolino et al. [96, 97] discovered that PLGA-film CLs maintained their antifungal qualities for up to three weeks in vitro. For as long as four weeks in vitro, the ciprofloxacin-releasing CL prototype demonstrated regulated release at therapeutically active doses [98]. Methoxypoly (ethylene glycol)-poly (lactide) copolymer (MPEG-PLA) loaded with timolol and latanoprost was used by Xu et al. [83] to investigate SCLs loaded with micelles. When given to rabbits with ocular hypertension, intraocular pressure (IOP) dropped in seven days, which was noticeably better than eye drops [83]. Oil, however, alters the optical characteristics of the lens. Creating a film-free zone within the optical zone is the answer [95, 99].

Drug Dosage Soft Contact Lens (DDSCL) in the Treatment of Eye Conditions

As drug controlled release systems (DCRS), SCLs seem to be a good way to treat a number of eye disorders. They aid in the treatment of infections, encourage local healing, and deliver the prompt and efficient release of medications in corneal epithelial defects [100]. Enhancing the bioavailability and effective local distribution of medications is the aim of such systems. Better safety and ease of use enhanced patient compliance are, in this way, also guaranteed by the option to coat the lenses with wetting agents [60].

Glaucoma

One promising therapy option for chronic eye conditions is the use of CLs as a medication reservoir [60], which is crucial for individuals with glaucoma. Glaucoma predominantly impacts the elderly, a chronic condition that often hinders their ability to administer eye drops manually. Molecular imprinting, drug-loaded colloidal nanoparticles, and simple soaking are prevalent methods for preparing glaucoma DCRS. The soaking-and-release method was employed to administer pilocarpine to SCLs in the initial DCR glaucoma systems [101]. Better SCL-based devices were obtained through modifications [60]. After two hours of wearing CLs containing 1% and 4% pilocarpine, the same therapeutic effects were eventually obtained. Unwanted systemic adverse effects are less likely when SCLs are used [102]. This approach has been utilized in innovative systemic glaucoma treatments, including the incorporation of melatonin and its analogs into SCLs. Putting SCL in the medication solution overnight makes it possible to use custom SCLs for three days in a row with the same release properties. However, no research has demonstrated sustained drug release beyond three hours, highlighting the necessity for improved SCL parameters. Vitamin E extends drug release by forming a biocompatible diffusion barrier in the hydrogel matrix. This modification has shown particular disadvantages. An antioxidant improved the drug release characteristics of silicone hydrogel [53, 103], whereas pHEMA lenses did not exhibit any improvement for timolol or brimonidine when vitamin E was added [104].

Antibiotics

The objective of Malakooti et al. was to develop a drug-eluting SCL capable of releasing antimicrobial peptides on the surface of the eye under controlled conditions [70]. The study involved the use of molecular imprinting techniques and functional monomers to formulate HEMA hydrogels for the

sustained release of vancomycin and polymyxin B. In hen egg test chorioallantoic membrane (HET-CAM) experiments, hydrogels loaded with polymyxin B exhibited good biocompatibility. Although vancomycin was incorporated and released continuously from the functionalized hydrogels, only the imprint effect associated with polymyxin B was observed. To extend the release duration of the ciprofloxacin, Hui et al. conducted investigations (both in vitro and in vivo) on novel silicone hydrogel SCLs developed through molecular imprinting techniques [71].

Antiviral Drugs

Hydrogel CLs have been engineered to demonstrate a preference for the antiviral drug acyclovir (ACV) and its prodrug, valacyclovir (VACV), used in the treatment of herpes simplex (HSV) keratitis. These lenses are engineered to facilitate the sustained release of therapeutic doses throughout regular wear. A variety of functional methacrylic acid (MAA) monomer concentrations was utilized to produce both printed and unprinted hydrogels, which were then assessed for swelling, transmittance, mechanical characteristics, and ocular compatibility via the HET-CAM method. The assessed values for these parameters were within the standard range for SCL. VACV exhibited a markedly superior charging capacity relative to ACV, attributable to its augmented electrostatic interactions with MAAs. The benefits of the printing technique for VACV have been unequivocally demonstrated [78]. The few licensed antifungal drugs and stringent dosage guidelines make treating fungal keratitis, a condition that can cause blindness. Therefore, the therapy of fungal keratitis may be enhanced by the creation of SCLs as a vehicle for the delivery of antifungal medications. SCLs can act as a reservoir for medications, allowing them to be constantly released into the cornea while preventing drug loss due to nonspecific absorption, blinking, and tear drainage [63].

Advantages and disadvantages of DDSCL

Therapeutic SCLs offer several advantages over traditional eye drops, including (1) prolonged drug contact time with the precorneal tear film, (2) improved adherence to complex and frequent dosage regimens, and (3) minimized systemic toxicity resulting from the precise amount of medication incorporated into the SCLs [105]. However, the commercialization of therapeutic CLs is subject to certain limitations. Key properties of SCLs, such as low water content, diminished tensile strength (mechanical characteristics), reduced transparency, and decreased ion and oxygen permeability, may be adversely affected by drug loading [60]. The potential for eye irritation and dryness at the end of the wearing period is another of the CLs' weak therapeutic aspects [106]. Additionally, prolonged CL use has been linked to ocular toxicity [107]. Hygienic CL handling is another issue. Therefore, incorrect handling could be more dangerous than using standard eye drops, increasing the chance of infection or pain while wearing (leaving CLs unworn), which could result in treatment failure [108]. However, in cases where CL insertion is part of the patient's management (e.g., following refractive surgery, in persistent corneal epithelial defect, etc.), the use of this drug can be an ideal option that, in addition to using CLs to heal the corneal surface, eliminates the need for eye drop use [108].

Punctal Plugs Delivery System (PPDS)

Originally designed to manage tear drainage in conditions such as DED, punctal plugs have evolved into multifunctional medical devices that serve as a system for drug delivery [109]. These rod-shaped devices, commonly known as particle plugs, are generally composed of various polymeric materials, including collagen, hydrogels, and silicone, and are implanted into the upper or lower punctum to block tear flow. By prolonging the contact between the ocular surface and tear fluid, punctal plugs create a stable tear film, which can be particularly advantageous in cases where patients are unable to tolerate CLs or during refractive surgeries. However, the application of these devices has expanded beyond their initial purpose of managing tear dynamics [110].

Recent innovations in ocular medication administration include punctal plugs. Once the required medications are incorporated in their core, these devices discharge them unidirectionally and regulated onto the ocular surface [110]. Although punctal plugs are limited to low-dose medications like prostaglandins and corticosteroids, they have been successfully used in clinical settings, particularly with the FDA-approved Dextenza™ system for dexamethasone delivery. This controlled medication release method offers a viable alternative to topical eye drops, which have low bioavailability and quick tear drainage [111, 112].

PPDS for DED and Glaucoma

The continuous ocular drug delivery of these plugs is encouraging, particularly for individuals with DED and glaucoma. Long-term topical therapy for these patients can lead to adherence concerns and unwanted effects. Drug distribution by punctal plugs can solve these difficulties by retaining effective medicine concentrations on the ocular surface while decreasing dosage. This approach decreases systemic absorption and side effects, such as beta-blocker cardiovascular risks, while enhancing treatment outcomes [113].

Those punctal plugs, designed for drug delivery purposes, are made of a variety of components. One of these components is a polymer-based cylindrical body in which the drug compound has been incorporated. In a number of designs, there is a porous cap for controlling the medication release [114]. Given that the body part is nearly impermeable to tear fluid and drugs, it ensures unidirectional delivery of medications to the ocular surface [115]. In advanced designs, such as the thermosensitive SmartPlug, which is composed of hydrophobic acrylic materials, adaptability and retention rates have been improved to enhance drug delivery. These characteristics render the plugs more effective and reliable for extended periods [116].

As a renowned investigational tool, the travoprost ophthalmic insert (OTX-TP) system is designed to deliver travoprost through a resorbable hydrogel rod impregnated with polylactic acid microparticles. This system can sustain drug release for over 90 days, making it preferable to daily eye drops. In clinical trials, the OTX-TP system has demonstrated significant reductions in intraocular pressure (IOP) compared to the commonly used timolol eye drops. Although the trials indicated a greater reduction in IOP within the timolol group, this observation may be attributed to the extended contact time afforded by the presence of a placebo punctal plug. This finding underscores the potential of punctal plugs to enhance drug retention [117].

Although the associated results were encouraging, the OTX-TP system faces challenges regarding retention rates, with only 48% of the plugs remaining in place by the 90th day. Nevertheless, its tolerability improved over time, and overall, this device was well accepted by patients, primarily due to minimal adverse effects, such as mild irritation and foreign body sensation [117].

In addition, to address the needs of patients suffering from DED and glaucoma, various drug-eluting punctal plug systems have been developed. The Latanoprost–PPDS (L-PPDS) has successfully completed phase II clinical trials. Its use for the treatment of ocular hypertension and primary open-angle glaucoma (POAG) through sustained IOP reductions has been approved [118]. Likewise, a number of systems are underway for delivering moxifloxacin and cyclosporine, and although the use of an olopatadine PPDS has not led to significant efficacy in the treatment of allergic conjunctivitis, such attempts indicate the continued innovation in this field [119-121]. With the investigational advancements in these plug-based systems, they may present a transformative solution that leads to decreased limitations in daily medication use and enhanced quality of life for a great number of patients.

PPDS Complications

Despite their advantages, PPDS are associated with several significant drawbacks that may limit their long-term effectiveness. One common complication is extrusion, which leads to the dislodgment of the plug from the punctum. This occurrence is reported in 25-50% of cases, sometimes within a month following their insertion [122, 123]. Such a phenomenon may result in other problems, e.g., punctal enlargement, a higher likelihood of re-extrusion, and granulation tissue formation [123-125]. In general, the retention rates of the plugs are poor, and most of them are lost within the first few weeks, in particular in scenarios in which patients suffer from conditions such as lid laxity and when the punctal size is larger [126]. Another issue that frequently arises is excessive tearing, or epiphora, which affects up to 10% of patients with permanent punctal plugs. This condition may significantly diminish patient satisfaction and comfort [127]. In addition, patients commonly report localized discomforts, e.g., irritation, itching, or a persistent foreign body sensation, which may result from the plug's design or material [124]. In a number of cases, the defects found in the surface of the plugs, e.g., irregularities and sharp edges, may lead to exacerbated irritation that results in additional discomfort or even damage to the surrounding ocular tissues, such as the cornea and conjunctiva [128]. If the plugs migrate into the canalicular system, they may cause infections, such as dacryocystitis and canaliculitis, and even fungal infections resulting from

deep migration of the plug into the canalicular system. Although such infections rarely occur, their treatment can be difficult and require plug removal [129, 130]. Another serious concern is canalicular and punctal stenosis following the plug extrusion/loss that may lead to narrowing and scarring of the ducts. Such a condition may lead to more challenges in future treatments and may necessitate more invasive solutions [125, 131]. As inflammatory lesions, pyogenic granulomas may arise from irritation caused by plugs, particularly in cases where silicone plugs are utilized. This can lead to additional complications, such as plug extrusion or the need for plug removal [132]. The formation of surface biofilms on the plugs, especially silicone plugs, increases the risk of bacterial infection and contamination, with Staphylococcus species commonly isolated in these instances [133, 134]. Such complications indicate the challenges encountered when attempting to achieve long-term success using the PPDS.

Corneal Intrastromal Injection

The cornea is a specialized, transparent, avascular, immune-privileged, and highly innervated tissue that accounts for two-thirds of the eye›s refractive power. Ocular injuries, infections, and hereditary factors can profoundly affect corneal function and result in vision impairment [135]. The cornea is structurally comprised of three distinct layers: an outer stratified epithelium, a dense collagenous stroma, and a cuboidal monolayer of endothelial-like cells. The stroma, the middle portion of the cornea, predominantly consists of an extracellular matrix and constitutes 90% of the corneal thickness. The primary cell type in the stroma is the keratocyte, a specialized fibroblast essential for the repair and maintenance of corneal tissue [136]. Due to the unique physiological characteristics of the cornea, including avascular tissue along with hydrophobic epithelium and endothelium and hydrophilic stroma, drug delivery to corneal and anterior segment tissues presents particular challenges. A novel drug delivery system to address these challenges is intrastromal corneal injections, which can deliver the drug closer to the target site [137, 138].

Corneal Intrastromal Injection in the Treatment of Eye Conditions

Corneal Neovascularization

Corneal neovascularization, a condition that can diminish visual acuity, results from various corneal disorders, including congenital anomalies, hypoxia associated with CLs, inflammatory diseases, chemical injuries, limbal stem cell deficiency (LSCD), allergies, trauma, infectious keratitis, autoimmune disorders, and corneal graft rejection [139]. Steroids are the primary medications utilized to inhibit angiogenesis; however, their indirect effects on this process are limited. Furthermore, the use of steroids is associated with the development of glaucoma and cataracts [140]. Researchers documented a cohort of patients who had intracorneal bevacizumab injections for the treatment of corneal vascularization. In comparison to alternative administration methods, intrastromal injection may facilitate enhanced exposure of the corneal capillaries to the drug, together with the delivery of a precise drug concentration. The topical application of this medicine may be hindered by restricted penetration through intact epithelium, attributable to bevacizumab's elevated molecular weight. Their findings indicate that corneal intrastromal injection of bevacizumab may serve as a beneficial alternative for the treatment of corneal vascularization [141].

Fasciani et al. conducted a study to examine the efficacy of subconjunctival and/or intrastromal bevacizumab injections in preventing graft failure in high-risk keratoplasties. The findings suggest that bevacizumab injections may serve as a preconditioning treatment to enhance the prognosis of high-risk corneal transplantation. The procedure appears to be safe and may contribute to the reduction of the inflammatory response, which is a critical factor in corneal graft rejection [142].

Fungal Keratitis

Infectious keratitis is a major contributor to corneal blindness globally. This condition is most commonly found in tropical and subtropical regions, affecting primarily young agricultural workers from low socioeconomic backgrounds. While it is less common in developed countries, fungal keratitis represents nearly half of all keratitis cases. Timely diagnosis and treatment are crucial for preserving vision [143]. The primary treatment is topical natamycin, but voriconazole is the preferred alternative, particularly for non-Fusarium infections. For cases specifically caused by Aspergillus and Candida, topical amphotericin B is considered the optimal choice [144, 145].

In a study, a combination of intrastromal and intracameral amphotericin B injections effectively treated nine severe cases of fungal keratitis without requiring surgical intervention. Amphotericin B in the anterior chamber can penetrate the endothelium, gradually increasing stromal concentrations for therapeutic effect. The injections were found to be safe, with no systemic toxic effects or corneal decompensation observed. Most corneal ulcers healed, although patients did experience leucoma and extensive scarring. All patients developed cataracts, likely due to inflammation, amphotericin B toxicity, or injection trauma [146]. Additionally, another study demonstrated that intrastromal injection of 5% natamycin, when paired with topical treatment, offers minimal advantage over topical therapy in a rabbit model of Fusarium keratitis. Intrastromal injection should be limited to the most severe or resistant instances [147].

A separate trial assessed the effectiveness and safety of a new tricyclic corneal stroma injection (TCSI) of voriconazole for the treatment of fungal keratitis. Retrospective findings suggest that this approach may improve visual acuity or expedite epithelial repair in instances of fungal keratitis, indicating potential for therapeutic application. Moreover, no notable alterations were detected in endothelial cell density, intraocular pressure measures, or the likelihood of corneal perforation subsequent to the stromal injections. TCSI seems to be a feasible and secure adjuvant therapeutic alternative for fungal keratitis [148].

The pharmacokinetics of voriconazole delivered by injection into the corneal stroma is not well understood. A study demonstrated that voriconazole administered into the ocular stroma lacks sustained retention. Therefore, many injections are required for the management of fungal keratitis [149].

Corneal Opacity

Another study evaluated the safety, feasibility, and therapeutic effects of injecting human corneal stromal keratocytes (CSKs) into a rodent model of early corneal opacity. The results showed that injected CSKs maintained appropriate marker expression and minimal inflammation, preserving corneal clarity and stability. In the opacity model, CSK injections reduced stromal reflectivity and thickness, enhancing corneal clarity compared to non-injected corneas [150].

Soleimani et al. evaluated the effectiveness of intrastromal versus subconjunctival administration of human bone marrow-derived mesenchymal stem cells (hBM-MSCs) in a corneal epithelial damage model. Although both injection strategies enhance wound healing and diminish neovascularization and opacity, the intrastromal method exhibits superior results for corneal repair [151].

A study sought to examine the impact of hyaluronidase (HAse) injection into the corneal stroma on stromal stiffness and ultrastructure. The degradation of glycosaminoglycans, crucial constituents of the corneal stroma, by hyaluronidase reduces corneal thickness and enhances stromal stiffness via enhanced collagen fibril packing in a time-dependent manner [152].

Infectious Crystalline Keratopathy (ICK)

A case report details an 84-year-old Caucasian female with nonprogressive conjunctival scarring who developed infectious crystalline keratopathy (ICK) unresponsive to topical therapy. After determining the antibiotic sensitivities of the causative organism, the patient underwent superficial keratectomy and received an intrastromal corneal injection of cefuroxime. Postoperatively, the ICK fully resolved, resulting in enhanced visual acuity and diminished ocular irritation [153].

A case report details a 62-year-old man with a history of ocular graft-versus-host disease (GVHD) who developed ICK in his corneal graft. Given his complex ocular history, ongoing immunosuppression, and newly emerging cardiac issues, the focus shifted to minimally invasive therapies. Two intrastromal injections of cefuroxime and moxifloxacin were administered, effectively treating his ICK. This case underscores the potential benefits of repeated intrastromal antibiotic injections for ICK that is resistant to topical treatment, which may eliminate the need for therapeutic keratoplasty and assist in preserving the patient's vision [154].

Intracameral Injection (ICI)

An intracameral injection (ICI) entails the direct administration of a medication into the anterior chamber of the eye. This targeted drug delivery approach circumvents ocular obstacles, facilitating a high concentration of medication at the required site, resulting in enhanced clinical outcomes [155].

Intracameral Antibiotics

Cataract surgery is the most prevalent ophthalmologic procedure conducted in numerous affluent nations, and its incidence is steadily rising. The increase in cataract procedures is primarily ascribed to advancements in technology [156].

Gungor et al. evaluated the prophylactic use of intracameral antibiotics for the prevention of postoperative endophthalmitis (POE) following cataract surgery. The study compared the effectiveness of various antibiotics, specifically vancomycin, cefazolin, cefuroxime, and moxifloxacin. All tested antibiotics demonstrated efficacy in preventing POE [157]. Also, intracameral cefuroxime injections significantly reduced the incidence of postoperative endophthalmitis in cataract surgery compared to no antibiotic use [158]. In support of this, another study indicated that researchers advocated for the administration of intracameral or intravitreal antibiotics to mitigate the risk of endophthalmitis following open globe injuries [159]. These findings highlight the growing emphasis on improving surgical outcomes alongside the rising frequency of cataract procedures [158].

Regular intracameral antibiotic use may raise healthcare costs [160]. Approximately 4 million cataract operations are conducted annually in the United States [161]. Three often utilized antibiotics include cefuroxime ($5.08 and $80.16), vancomycin ($82.08 and $234.16), and moxifloxacin ($41.18 and $152.36). Operating rooms should refrain from utilizing several antibiotic dosages from a single vial, as this contravenes chapter 797 of the USP (United States Pharmacopeial Convention, Rockville, MD, USA). Pharmacokinetic studies indicate that 50% of the administered cefuroxime is eliminated from the anterior chamber 4–5 hours post-surgery; however, pathogens can infiltrate a non-sutured anterior chamber from the eyelids and surrounding environment at any time during the initial postoperative days. This prompts inquiries on the effectiveness and expense of intracameral antibiotics [160].

Intracameral Anesthesia

Intracameral mydriatic injection is found to be effective for anesthesia and mydriasis in cataract surgery with phacoemulsification and manual small-incision cataract surgery (MSICS) [162]. In a study researchers found that the combination of intracameral lidocaine injection and anesthetic eye drops likely reduced pain levels during cataract surgery more effectively than using anesthetic eye drops alone and resulted in fewer patients reporting pain during the procedure. However, pain ratings were generally low with or without the lidocaine injection, suggesting that the difference may not be clinically significant. Additionally, the lidocaine injection combined with eye drops did not lower the level of postoperative pain reported by patients. However, pain ratings were generally low with or without the lidocaine injection, suggesting that the difference may not be clinically significant [163]. It is important to note that the use of intracameral mydriatic and anesthetic injections at the start of cataract surgery is safe and provides clear benefits compared to the traditional topical mydriatic approach. This method eliminates the need for repeated application of topical solutions, thus improving patient flow in ophthalmology clinics and reducing the risk of corneal toxicity associated with topical administration. Moreover, the availability of a specifically approved intracameral preparation mitigates the risks linked to "homemade" mixtures and minimizes the likelihood of dosing errors [164]. Further research focusing on the potential adverse effects of intracameral anesthesia could provide a clearer understanding of its safety profile. Additionally, economic evaluations would be valuable in assessing the cost implications associated with its use.

Intracameral Bevacizumab

Glaucoma refers to a group of diseases characterized by optic nerve head cupping and degeneration, often accompanied by visual field loss, which can occur with elevated or normal IOP. It is the second most common cause of blindness globally [165]. Neovascular glaucoma (NVG) is a severe kind of secondary glaucoma that endangers vision, characterized by the proliferation of aberrant blood vessels on the iris and the formation of fibrovascular tissue in the anterior chamber angle. Retinal ischemia is the principal underlying cause, with branch and central retinal vein occlusion (BRVO/CRVO), proliferative diabetic retinopathy (PDR), and ocular ischemic syndrome (OIS) as prevalent contributions [166].

Bevacizumab (Avastin) is a humanized monoclonal antibody that targets and binds to all forms of VEGF [167]. Bevacizumab attaches to the receptor-binding region of all VEGF-A isoforms, thereby obstructing the interaction between VEGF-A and its receptors (FLT-1 and KDR) on

endothelial cells. This inhibition prevents the activation of intracellular signaling pathways that initiate endothelial cell growth and the formation of new blood vessels. Research has demonstrated that injection of intravitreal bevacizumab (IVB) can contribute to the regression of iris neovascularization [168, 169].

In managing NVG, intracameral bevacizumab shows greater effectiveness in lowering IOP compared to intravitreal injection. Significant IOP reduction was seen in the intracameral group at 4, 8, and 12 weeks for patients with IOP between 11 and 30 mm Hg, while no reduction was observed in higher IOP ranges or during the first week. In contrast, the intravitreal and combined intracameral-intravitreal groups showed no significant IOP reduction at any time [170]. Another study also supports intracameral bevacizumab, with 8 out of 9 patients achieving IOP control without needing surgery [171].

Intracameral Dexamethasone

Intracameral dexamethasone provides a distinct advantage over topical steroids by potentially reducing postoperative inflammatory symptoms and lowering anterior chamber cell and flare scores [172]. This method delivers dexamethasone directly to the target site, allowing for higher concentrations of the drug within the anterior chamber and potentially minimizing local side effects, such as elevated IOP [173]. Studies have shown that intracameral injection of dexamethasone demonstrates significantly higher efficacy compared to other administration methods, such as subconjunctival or sub-Tenon's routes [174, 175]. Furthermore, intracameral delivery reduces the risk of complications associated with other administration methods, including skin hypopigmentation, extraocular muscle atrophy, and subdermal fat [173, 175]. However, intracameral drug delivery does come with certain disadvantages. One potential issue is the risk of toxic anterior segment syndrome (TASS), a sterile postoperative inflammatory response triggered by the introduction of a noninfectious substance into the anterior segment [176]. Plasma levels following intracameral dexamethasone injection were significantly lower than any known toxic concentrations of steroids [172].

Collagen Shields (CSs)

Collagen inserts and shields represent one of the most extensively investigated corneal drug delivery systems utilizing collagen [177]. Collagen, which constitutes over 25% of an animal's body and is the primary component of gelatin, mainly consists of types I and IV. It plays a crucial role in maintaining the structure and clarity of the eye [178]. Due to its unique properties compared to synthetic polymers, collagen has been utilized in various medical applications since 1986 [4, 5]. Research studies by McPherson et al. indicate that collagen is less antigenic, more biocompatible, and more biodegradable than natural polymers such as albumin and gelatin [178]. Crosslinking through chemical methods enhances collagen membranes, allowing them to better mimic the native properties of the cornea. This unresolved issue necessitates the implementation of a collagen shield drug delivery system (CS-DDS) to facilitate corneal healing, which was initially developed for burn injury repair [179, 180].

The introduction of CS-DDS began in 1980, initiated by Fyodorov as a corneal bandage for use following the radial keratotomy procedure [181, 182]. These shields serve as a pre-corneal reservoir, allowing for the concentration and prolonged retention of drugs within the eye, thereby enhancing their bioavailability without increasing the frequency of dosing or toxicity to the corneal epithelium. This ultimately improves patient compliance and reduces the duration of hospitalization [180]. CSs are capable of releasing therapeutic doses of corticosteroids, immunosuppressants, and antibiotics for up to 72 hours [179, 183]. They are particularly useful following ocular surgical procedures for the delivery of drugs such as antibiotics and antivirals, as demonstrated in studies involving rabbits and mice [177, 184]. Additionally, CSs can facilitate the implantation of human corneal epithelial cells for wound restoration. Numerous studies have shown that gentamicin sulfate and dexamethasone can be effectively delivered using CSs in a manner comparable to subconjunctival injections following surgery [181].

Corneal CSs are derived from the collagen found in the corneas of cows or pigs; porcine sclera is utilized due to its closer resemblance to human corneal collagen [185]. These shields are maintained in a dry state and require rehydration prior to application on the eye. Upon insertion, the shields absorb ocular fluids and conform to the shape of the cornea [181, 186]. The dissolution time of the shields that lasts from 12 to 72 hours is determined by how much crosslinking of the collagen used in the preparation of the shields was achieved [187].

As tears bathe the outer surface of the device, they also carry with them and load onto the cornea and aqueous humor any hydrophilic active compounds that are embedded in the shield. There is also the possibility of intramatrix implantation of hydrophobic drugs. Available treatment drugs include ofloxacin, fluorescein, cyclosporine, and prednisolone [185, 186]. In addition, CSs are currently utilized in greater numbers in glaucoma operations for the purposes of delivery of plasmid DNA to modulate healing of a wound. However, it requires precise medical personnel to place it on the patient because it can be uncomfortable for the patient, as it may obstruct thick instruments in their vision [188, 189].

Although CS fulfill their intended purpose, they exhibit several shortcomings, one of which is low patient comfort due to insufficient transparency, leading to impaired vision. Additionally, their commercial adoption has been affected by safety concerns associated with cross-linkers, as the increased bioavailability is limited to a narrow time frame [180]. On the one hand, some CSs may be used by patients themselves, but traditional ones have to be implanted surgically and are opaque, which increases the chances of discomfort and the possibility of the shield being lost to the eye [177, 190]. On the other hand, modern dosage forms known as 'collasomes,' which consist of small collagen particles suspended in a 1% methylcellulose solution, offer the benefits of collagen while minimizing its drawbacks. These advancements aim to enhance the bioavailability and transcytosis of the system while also addressing comfort and visual concerns [185, 191].

Iontophoresis

Iontophoresis is a non-invasive method that enables the transdermal administration of drugs through anatomical barriers using a low electric current. This method has been utilized in several pharmacological investigations and clinical contexts [192]. Generally speaking, iontophoresis employs either direct current or alternating current as its voltage source. Direct current iontophoresis is the methodology of choice [193]. Iontophoresis in ocular therapy has been utilized to administer antibiotics, resulting in increased concentrations of pharmacological drugs in the vitreous humor, with its safety and efficacy validated by several animal studies and clinical trials [194]. Iontophoresis is often classified into transcorneal and transscleral kinds according to the site of application. Transcorneal iontophoresis has been developed to treat anterior segment problems through the delivery of antibiotics such as gentamicin, tobramycin, ciprofloxacin, and vancomycin [194].

research by Cohen et al. Iontophoresis was administered in one qualified eye to 40 of 42 randomized patients, who completed the research. Patients were randomly assigned to one of four iontophoresis dose groups (1.6, 4.8, 10.0, or 14.0 mA-min), treated with EGP-437 (dexamethasone phosphate solution) via the EyeGate II Delivery System (EGDS), and observed until day 28. After one iontophoresis therapy, two-thirds of patients had a zero anterior chamber cell (ACC) score within 28 days. Lower doses worked best and were well-tolerated [195].

Iontophoretic delivery of EGP-437 is a safe way for administering sufficient quantities of steroid to ocular tissue, effectively managing post-cataract inflammation and pain. This approach could eradicate the daily requirement for corticosteroid eye drops, hence enhancing outcomes for this substantial patient demographic [196].

Iontophoresis, like other medication delivery techniques, may induce adverse consequences. Documented effects encompass localized electrical burns, corneal epithelial or conjunctival edema, mucous discharge, and diminished corneal endothelial cell counts, likely attributable to elevated current densities applied to small ocular surfaces. Histopathological alterations, including hemorrhagic necrosis, edema, and infiltration of polymorphonuclear leukocytes, may also manifest [197].

Before moving on to the conclusion section, let us review a summary table of the key points discussed in this article (Table. 2).

CONCLUSION

The development of new anterior segment ocular drug delivery systems represents a significant advancement in ophthalmology. Low bioavailability, rapid elimination, and patient compliance concerns continue to limit conventional techniques such as topical drops and systemic delivery. Recent advancements in nanocarriers, drug-releasing CLs, punctal plugs, and intracameral injections have led to better drug retention, more precise delivery, and longer-lasting effects. Though some of these technologies have recently entered clinical application, they show significant potential for overcoming present limitations and improving

Table 2 . Overview of the main findings and topics addressed throughout the article

Drug delivery system	Advantages	Limitations	References
Topical Administration (General / Eye Drops)	Predominant technique, accounting for over 95% of marketed ocular medicines. The most practical method. Non-invasive, thus remaining the preferred mode of therapy for ocular disorders.	Low efficiency and limited bioavailability (generally below 5%). Rapid clearance due to blinking, fast tear turnover, and anatomical barriers (cornea and tear film). Limited corneal surface area restricts volume (~10 μL). High concentrations required in bolus administration can lead to local and systemic complications (e.g., accommodative spasm). Ineffective in treating intraocular diseases due to the physical barrier of the cornea.	[7, 8, 27, 28]
Systemic (Oral/Parenteral)	Potential benefits include accurate dose, convenience, and fast absorption (via the ocular route). Oral administration may be advantageous when topical therapies are ineffective or unfeasible. Oral vitamin A antioxidants yield a prolonged impact compared to topical applications for DED.	Efficacy is severely constrained by the blood-ocular barrier (BOB). Often results in reduced bioavailability (approx. 2%). Necessitates elevated systemic dosages, leading to systemic adverse effects. Limited access to various ocular tissues	[18, 20]
Ocular Inserts (Ocuserts)	Precise dosage delivery. Reduction of systemic side effects. Extension of ocular residence time, which decreases administration frequency and enhances patient adherence. Potential for sustained and consistent drug release.	Requires precise medical personnel to place (in the case of thick instruments).	[43-45]
Nanocarriers (Nanoparticles, Liposomes, Cyclodextrins, Micelles)	Provide enhanced drug retention, prolonged release profiles, and precise delivery mechanisms. Improve drug bioavailability and minimize systemic side effects. Cyclodextrins enhance solubility while minimizing solvent toxicity. Vesicular systems (liposomes, niosomes) prolong retention time. Copolymeric micelles augment solubility and stability.	The majority are still in preclinical or early clinical stages. Issues concerning safety, scalability, and patient tolerability continue to exist. Most technologies remain in the development phase and require further testing for commercial viability.	[33, 39]
Soft Contact Lenses (SCLs) / DDSCLs	Provide prolonged drug contact time with the precorneal tear film. Improved adherence to complex regimens. Minimized systemic toxicity. Can deliver antibiotics, antiviral drugs, and glaucoma treatments. Delivery duration can be changed from a few hours to several weeks (with nanoparticle incorporation). Can achieve sustained drug release in vivo for up to seven days (corticosteroids).	Drug loading can negatively affect key SCL properties: low water content, diminished tensile strength, reduced transparency, and decreased ion and oxygen permeability. Potential for eye irritation and dryness. Incorrect handling increases the chance of infection or pain. Simple soaking leads to quick release. Supercritical solvent methods yield less encouraging outcomes, extending retention only to a few hours.	[105, 107, 108]
Punctal Plug Drug Delivery Systems (PPDS)	Enables direct, unidirectional, and controlled release onto the ocular surface. Provides a consistent release for long-term therapies (DED, glaucoma). Minimizes systemic absorption and associated side effects (e.g., cardiovascular risks from beta-blockers)	Small capacity limits application to low-dose drugs. High complication rate: extrusion (25–50% of cases). Poor retention rates overall. Risk of excessive tearing (epiphora). Patients commonly report localized discomfort, irritation, or foreign body sensation. Risk of infection (dacryocystitis, canaliculitis) if plugs migrate.	[122-128]
Collagen Shields (CSs)	Serves as a pre-corneal reservoir for concentration and prolonged retention of drugs. Enhances bioavailability without increasing dosing frequency or toxicity to the corneal epithelium. Can release therapeutic doses for up to 72 hours. Useful following ocular surgical procedures.	Low patient comfort due to insufficient transparency (impaired vision). Increased bioavailability is limited to a narrow time frame. Traditional shields must be implanted surgically. Commercial adoption is affected by safety concerns associated with cross-linkers.	[177-182, 185, 186]

Table 2 . Overview of the main findings and topics addressed throughout the article

Drug delivery system	Advantages	Limitations	References
Intracameral Injection (ICI)	Circumvents ocular obstacles. Facilitates a high concentration of medication at the required site. Significantly reduces the incidence of postoperative endophthalmitis (POE). Eliminates the need for repeated topical solutions, reducing the risk of corneal toxicity associated with topical administration. Greater effectiveness in lowering IOP for NVG than intravitreal injection. Reduces local side effects (e.g., elevated IOP).	Regular use may raise healthcare costs. Risk of Toxic Anterior Segment Syndrome (TASS). Pathogens can infiltrate the anterior chamber post-surgery.	[155-160]
Corneal Intrastromal Injection	Can deliver the drug closer to the target site. Facilitates enhanced exposure of corneal capillaries and delivery of a precise drug concentration. May enhance wound healing and diminish neovascularization and opacity.	Pharmacokinetics are not well understood. May lack sustained retention, requiring many injections (e.g., voriconazole). Should be limited to the most severe or resistant instances (e.g., Natamycin). Risk of scarring/leukoma.	[139-141, 144-146, 148-150, 153, 154]
Iontophoresis	A non-invasive method utilizing a low electric current. Increases concentrations of pharmacological drugs in the vitreous humor. Can eradicate the daily requirement for corticosteroid eye drops. Lower doses were well-tolerated.	May induce adverse consequences: localized electrical burns, corneal epithelial/conjunctival edema, mucous discharge, and diminished corneal endothelial cell counts. Risk of histopathological alterations.	[192-197]

patient outcomes. Artificial intelligence has the potential to significantly enhance ocular drug delivery systems in the future. Artificial intelligence may help with formulation design optimization, medication distribution and response prediction, and the creation of more intelligent delivery systems with adaptive release profiles. Additionally, the use of personalized therapy in ophthalmology may allow for treatment plans that are customized to meet the unique requirements of each patient, resulting in safer and more efficient ocular drug delivery.

Future research should focus on applying artificial intelligence and personalized therapeutic approaches to enhance ocular drug delivery systems.

ABBREVIATIONS

BOB: blood-ocular barrier
VEGF: vascular endothelial growth factor
AMD: age-related macular degeneration
DED: dry eye disease
CSC: central serous chorioretinopathy
HPMC: hydroxypropyl methyl cellulose
O/W: oil-in-water
ASEDs: Autologous serum eye drops
UMSCs: umbilical mesenchymal stem cells
MSCs: mesenchymal stem cells
LSCs: Limbal stem cells
SCLs: soft contact lenses
Phema: poly-hydroxyethylmethacrylate
CLs: contact lenses
MAPTAC: Methacrylic amino propyl-trimethyl ammonium chloride
MMA: methyl methacrylate
MOEP: methoxy ethyl phosphate
DDCLs: daily disposable contact lenses
GMA: glycidyl methacrylate
DEA: diethyl acrylamide
PLGA: Polylactic glycolic acid
PVA: polyvinyl alcohol
MPEG-PLA: Methoxypoly (ethylene glycol)-poly (lactide) copolymer
DCRS: drug controlled release system
HET-CAM: hen egg test chorioallantoic membrane
ACV: antiviral drug acyclovir
VACV: valacyclovir
HSV: herpes simplex
MAA: methacrylic acid
PPDS: Punctal Plugs Delivery System
OTX-TP: travoprost ophthalmic insert
IOP: intraocular pressure
L-PPDS: Latanoprost–PPDS
POAG: primary open-angle glaucoma
LSCD: limbal stem cell deficiency
TCSI: tricyclic corneal stroma injection
CSKs: corneal stromal keratocytes
hBM-MSCs: human bone marrow-derived mesenchymal stem cells
HAse: hyaluronidase
ICK: infectious crystalline keratopathy
GVHD: graft-versus-host disease
ICI: intracameral injection
POE: postoperative endophthalmitis

SICS: small-incision cataract surgery
NVG: Neovascular glaucoma
BRVO/CRVO: branch and central retinal vein occlusion
PDR: proliferative diabetic retinopathy
OIS: ocular ischemic syndrome
IVB: intravitreal Bevacizumab
TASS: toxic anterior segment syndrome
CS-DDS: collagen shield drug delivery system
EGDS: EyeGate II Delivery System
ACC: anterior chamber cell

CONSENT FOR PUBLICATION

All authors have read and approved the final version of the manuscript and consent to its publication.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Akhter MH, et al. Drug delivery challenges and current progress in nanocarrier-based ocular therapeutic system. Gels. 2022;8(2):82. https://doi.org/10.3390/gels8020082
2. Patel P, et al. Ophthalmic drug delivery system: challenges and approaches. Syst Rev Pharm. 2010;1(2):113. https://doi.org/10.4103/0975-8453.75042
3. Yang Y, Lockwood A. Topical ocular drug delivery systems: Innovations for an unmet need. Exp Eye Res. 2022;218:109006. https://doi.org/10.1016/j.exer.2022.109006
4. Tawfik M, et al. Nanomedicine and drug delivery to the retina: Current status and implications for gene therapy. Naunyn Schmiedebergs Arch Pharmacol. 2022;395(12):1477-507. https://doi.org/10.1007/s00210-022-02287-3
5. Kim HM, Woo SJ. Ocular drug delivery to the retina: current innovations and future perspectives. Pharmaceutics. 2021;13(1):108. https://doi.org/10.3390/pharmaceutics13010108
6. Bucolo C, Drago F, Salomone S. Ocular drug delivery: a clue from nanotechnology. Front Pharmacol. 2012;3:188. https://doi.org/10.3389/fphar.2012.00188
7. Duvvuri S, Majumdar S, Mitra AK. Role of metabolism in ocular drug delivery. Curr Drug Metab. 2004;5(6):507-15. https://doi.org/10.2174/1389200043335342
8. Vadlapatla RK, et al. Role of membrane transporters and metabolizing enzymes in ocular drug delivery. Curr Drug Metab. 2014;15(7):680-93. https://doi.org/10.2174/1389200215666140926152459
9. Awwad S, et al. Principles of pharmacology in the eye. Br J Pharmacol. 2017;174(23):4205-23. https://doi.org/10.1111/bph.14024
10. Wakshull E, et al. Advancements in understanding immunogenicity of biotherapeutics in the intraocular space. AAPS J. 2017;19(6):1656-68. https://doi.org/10.1208/s12248-017-0128-y
11. Cao Y, et al. Recent advances in intraocular sustained-release drug delivery devices. Drug Discov Today. 2019;24(8):1694-700. https://doi.org/10.1016/j.drudis.2019.05.031
12. Mandal A, et al. Ocular delivery of proteins and peptides: Challenges and novel formulation approaches. Adv Drug Deliv Rev. 2018;126:67-95. https://doi.org/10.1016/j.addr.2018.01.008
13. Chiou GC. Systemic delivery of polypeptide drugs through ocular route. Annu Rev Pharmacol Toxicol. 1991;31:457-67. https://doi.org/10.1146/annurev.pa.31.040191.002325
14. Kearns VR, Williams RL. Drug delivery systems for the eye. Expert Rev Med Devices. 2009;6(3):277-90. https://doi.org/10.1586/erd.09.4
15. Gaudana R, et al. Recent perspectives in ocular drug delivery. Pharm Res. 2009;26(5):1197-213. https://doi.org/10.1007/s11095-008-9694-0
16. Sharma P, Mittal S. Nanotechnology: Revolutionizing the delivery of drugs to treat age-related macular degeneration. Expert Opin Drug Deliv. 2021;18(8):1131-49. https://doi.org/10.1080/17425247.2021.1888925
17. Yang B, et al. Nanotechnology for age-related macular degeneration. Pharmaceutics. 2021;13(12):2035. https://doi.org/10.3390/pharmaceutics13122035
18. Gaudana R, et al. Ocular drug delivery. AAPS J. 2010;12(3):348-60. https://doi.org/10.1208/s12248-010-9183-3
19. Occhiutto ML, et al. Breakdown of the blood-ocular barrier as a strategy for the systemic use of nanosystems. Pharmaceutics. 2012;4(2):252-75. https://doi.org/10.3390/pharmaceutics4020252
20. Autry J. Oral meds in eye care: habitual prescribing patterns and patient needs. Rev Optom. 2009;146(11):61-5.
21. Babizhayev MA, Khoroshilova-Maslova IP, Kasus-Jacobi A. Novel intraocular and systemic absorption drug delivery and efficacy of N-acetylcarnosine lubricant eye drops or carcinine biologics. Fundam Clin Pharmacol. 2012;26(5):644-78. https://doi.org/10.1111/j.1472-8206.2011.00963.x
22. Chiou GC, Li BH. Chronic systemic delivery of insulin through the ocular route. J Ocul Pharmacol Ther. 1993;9(1):85-90. https://doi.org/10.1089/jop.1993.9.85
23. Ziada HEA. Oral versus topical vitamin A antioxidant in treatment of dry eye syndrome. Int J Ophthalmic Res. 2017;3(4):252-8.
24. Mazzolani F, Togni S. Oral administration of a curcumin-phospholipid delivery system for central serous chorioretinopathy: 12-month follow-up. Clin Ophthalmol. 2013;7:939-45. https://doi.org/10.2147/OPTH.S45820
25. Hosseini K, et al. Pharmacokinetic study of dexamethasone

disodium phosphate using intravitreal, subconjunctival, and intravenous delivery routes in rabbits. J Ocul Pharmacol Ther. 2008;24(3):301-8. https://doi.org/10.1089/jop.2007.0117
26. Sebbag L, et al. Tear fluid pharmacokinetics following oral prednisone administration in dogs with and without conjunctivitis. J Ocul Pharmacol Ther. 2019;35(6):341-9. https://doi.org/10.1089/jop.2019.0020
27. Ting DSJ, et al. 12-year analysis of incidence, microbiological profiles and in vitro antimicrobial susceptibility of infectious keratitis: the Nottingham Infectious Keratitis Study. Br J Ophthalmol. 2021;105(3):328-33. https://doi.org/10.1136/bjophthalmol-2020-316128
28. Gause S, et al. Mechanistic modeling of ophthalmic drug delivery to the anterior chamber by eye drops and contact lenses. Adv Colloid Interface Sci. 2016;233:139-54. https://doi.org/10.1016/j.cis.2015.08.002
29. Ghate D, Edelhauser HF. Ocular drug delivery. Expert Opin Drug Deliv. 2006;3(2):275-87. https://doi.org/10.1517/17425247.3.2.275
30. Gote V, et al. Ocular drug delivery: present innovations and future challenges. J Pharmacol Exp Ther. 2019;370(3):602-14. https://doi.org/10.1124/jpet.119.256933
31. Parveen N, Joshi H. Ocuserts: A novel formulation approach in drug delivery system. Saudi J Med Pharm Sci. 2020;6(4):420-5. https://doi.org/10.36348/sjmps.2020.v06i05.005
32. Vikram S, et al. Fundamentals and principles of ophthalmology. Elsevier, American Academy of Ophthalmology. 2022.
33. Taghe S, Mirzaeei S, Bagheri M. Preparation of polycaprolactone and polymethacrylate nanofibers for controlled ocular delivery of ketorolac tromethamine: Pharmacokinetic study in Rabbit's Eye. Eur J Pharm Sci. 2024;192:106631. https://doi.org/10.1016/j.ejps.2023.106631
34. Babizhayev MA, Khoroshilova-Maslova IP, Kasus-Jacobi A. Novel intraocular and systemic absorption drug delivery and efficacy of N-acetylcarnosine lubricant eye drops or carcinine biologics. Fundam Clin Pharmacol. 2012;26(5):644-78. https://doi.org/10.1111/j.1472-8206.2011.00963.x
35. Ako-Adounvo AM, et al. Recent patents on ophthalmic nanoformulations and therapeutic implications. Recent Pat Drug Deliv Formul. 2014;8(3):193-201. https://doi.org/10.2174/1872211308666140926112000
36. Sahle FF, et al. Nanotechnology in regenerative ophthalmology. Adv Drug Deliv Rev. 2019;148:290-307. https://doi.org/10.1016/j.addr.2019.10.006
37. Gholizadeh-Ghaleh Aziz S, Gholizadeh-Ghaleh Aziz S, Akbarzadeh A. The potential of nanofibers in tissue engineering and stem cell therapy. Artif Cells Nanomed Biotechnol. 2016;44(5):1195-200. https://doi.org/10.3109/21691401.2015.1029627
38. Liu H, et al. Cell therapy of congenital corneal diseases with umbilical mesenchymal stem cells: lumican null mice. PLoS One. 2010;5(5):e10707. https://doi.org/10.1371/journal.pone.0010707
39. Zajicova A, et al. Treatment of ocular surface injuries by limbal and mesenchymal stem cells growing on nanofiber scaffolds. Cell Transplant. 2010;19(10):1281-90. https://doi.org/10.3727/096368910X509040
40. Mousavi Z, et al. Tissue engineering strategies for ocular regeneration; from bench to bedside. Heliyon. 2024;10:eXXXXX. https://doi.org/10.1016/j.heliyon.2024.e39398
41. Mansouri K, et al. The use of orthokine therapy for the treatment of post refractive surgery corneal ulcer: a case report. Int Immunopharmacol. 2023;120:110273. https://doi.org/10.1016/j.intimp.2023.110273
42. Kumari A, et al. Ocular inserts - Advancement in therapy of eye diseases. J Adv Pharm Technol Res. 2010;1(3):291-6. https://doi.org/10.4103/0110-5558.72419
43. Nagpal N, et al. Ocuserts: a novel ocular-drug delivery method: an update. World J Biol Pharm Health Sci. 2023;13(1):470-7. https://doi.org/10.30574/wjbphs.2023.13.1.0025
44. Dawaba AM, et al. Fabrication of bioadhesive ocusert with different polymers: once a day dose. Int J Appl Pharm. 2018;10(3):309-17. https://doi.org/10.22159/ijap.2018v10i6.28495
45. Bagmar NA, et al. A review on ocuserts (an ophthalmic insert). Asian J Pharm Res Dev. 2024;12(6):131-9. https://doi.org/10.22270/ajprd.v12i6.1460
46. Abramson DH, et al. Presenting signs of retinoblastoma. J Pediatr. 1998;132(3 Pt 1):505-8. https://doi.org/10.1016/S0022-3476(98)70028-9
47. Xu J, et al. A comprehensive review on contact lens for ophthalmic drug delivery. J Control Release. 2018;281:97-118. https://doi.org/10.1016/j.jconrel.2018.05.020
48. Dominguez-Godinez C, Carracedo G, Pintor J. Diquafosol delivery from silicone hydrogel contact lenses: improved effect on tear secretion. J Ocul Pharmacol Ther. 2018;34(1-2):170-6. https://doi.org/10.1089/jop.2016.0193
49. White CJ, DiPasquale SA, Byrne ME. Controlled release of multiple therapeutics from silicone hydrogel contact lenses. Optom Vis Sci. 2016;93(4):377-86. https://doi.org/10.1097/OPX.0000000000000849
50. Hewitt MG, et al. In vitro topical delivery of chlorhexidine to the cornea: enhancement using drug-loaded contact lenses and β-cyclodextrin complexation, and the importance of simulating tear irrigation. Mol Pharm. 2020;17(4):1428-41. https://doi.org/10.1021/acs.molpharmaceut.0c00140
51. Minami T, et al. In vitro and in vivo performance of epinastine hydrochloride-releasing contact lenses. PLoS One. 2019;14(1):e0210362. https://doi.org/10.1371/journal.pone.0210362
52. Sekar P, Chauhan A. Effect of vitamin-E integration on delivery of prostaglandin analogs from therapeutic lenses. J Colloid Interface Sci. 2019;539:457-67. https://doi.org/10.1016/j.jcis.2018.12.036
53. Hsu KH, et al. Dual drug delivery from vitamin E loaded contact lenses for glaucoma therapy. Eur J Pharm Biopharm. 2015;94:312-21. https://doi.org/10.1016/j.ejpb.2015.06.001
54. Maulvi FA, et al. Extended release of ketotifen from silica shell nanoparticle-laden hydrogel contact lenses: in vitro and in vivo evaluation. J Mater Sci Mater Med. 2016;27(1):1-13. https://doi.org/10.1007/s10856-016-5724-3
55. Andrade-Vivero P, et al. Improving the loading and release of NSAIDs from pHEMA hydrogels by copolymerization with functionalized monomers. J Pharm Sci. 2007;96(4):802-13. https://doi.org/10.1002/jps.20761
56. Uchida R, et al. Azulene incorporation and release by hydrogel containing methacrylamide propyltrimenthylammonium chloride, and its application to soft contact lens. J Control Release. 2003;92(3):259-64. https://doi.org/10.1016/S0168-3659(03)00368-7
57. Sato T, et al. Application of polymer gels containing side-chain phosphate groups to drug-delivery contact lenses. J Appl Polym Sci. 2005;98(2):731-7. https://doi.org/10.1002/app.22080
58. Kakisu K, et al. Development and efficacy of a drug-

releasing soft contact lens. Invest Ophthalmol Vis Sci. 2013;54(4):2551-61. https://doi.org/10.1167/iovs.12-10614
59. Brahim S, Narinesingh D, Guiseppi-Elie A. Release characteristics of novel pH-sensitive p(HEMA-DMAEMA) hydrogels containing 3-(trimethoxy-silyl) propyl methacrylate. Biomacromolecules. 2003;4(5):1224-31. https://doi.org/10.1021/bm034048r
60. Rykowska I, Nowak I, Nowak R. Soft contact lenses as drug delivery systems: a review. Molecules. 2021;26(18):5542. https://doi.org/10.3390/molecules26185577
61. Xu J, Li X, Sun F. Cyclodextrin-containing hydrogels for contact lenses as a platform for drug incorporation and release. Acta Biomater. 2010;6(2):486-93. https://doi.org/10.1016/j.actbio.2009.07.021
62. Hu X, Gong X. A new route to fabricate biocompatible hydrogels with controlled drug delivery behavior. J Colloid Interface Sci. 2016;470:62-70. https://doi.org/10.1016/j.jcis.2016.02.037
63. Phan CM, Subbaraman LN, Jones L. In vitro drug release of natamycin from β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin-functionalized contact lens materials. J Biomater Sci Polym Ed. 2014;25(17):1907-19. https://doi.org/10.1080/09205063.2014.958016
64. Glisoni RJ, et al. β-Cyclodextrin hydrogels for the ocular release of antibacterial thiosemicarbazones. Carbohydr Polym. 2013;93(2):449-57. https://doi.org/10.1016/j.carbpol.2012.12.033
65. Li R, et al. Poly(2-hydroxyethyl methacrylate)/β-cyclodextrin-hyaluronan contact lens with tear protein adsorption resistance and sustained drug delivery for ophthalmic diseases. Acta Biomater. 2020;110:105-18. https://doi.org/10.1016/j.actbio.2020.04.002
66. White CJ, Byrne ME. Molecularly imprinted therapeutic contact lenses. Expert Opin Drug Deliv. 2010;7(6):765-80. https://doi.org/10.1517/17425241003770098
67. White C, Tieppo A, Byrne M. Controlled drug release from contact lenses: a comprehensive review from 1965-present. J Drug Deliv Sci Technol. 2011;21(5):369-84. https://doi.org/10.1016/S1773-2247(11)50062-0
68. Salian VD, Vaughan AD, Byrne ME. The role of living/controlled radical polymerization in the formation of improved imprinted polymers. J Mol Recognit. 2012;25(6):361-9. https://doi.org/10.1002/jmr.2168
69. Byrne ME, Park K, Peppas NA. Molecular imprinting within hydrogels. Adv Drug Deliv Rev. 2002;54(1):149-69. https://doi.org/10.1016/S0169-409X(01)00246-0
70. Malakooti N, Alexander C, Alvarez-Lorenzo C. Imprinted contact lenses for sustained release of polymyxin B and related antimicrobial peptides. J Pharm Sci. 2015;104(10):3386-94. https://doi.org/10.1002/jps.24537
71. Hui A, Willcox M, Jones L. In vitro and in vivo evaluation of novel ciprofloxacin-releasing silicone hydrogel contact lenses. Invest Ophthalmol Vis Sci. 2014;55(8):4896-904. https://doi.org/10.1167/iovs.14-14855
72. Tieppo A, et al. Sustained in vivo release from imprinted therapeutic contact lenses. J Control Release. 2012;157(3):391-7. https://doi.org/10.1016/j.jconrel.2011.09.087
73. Tieppo A, Pate KM, Byrne ME. In vitro controlled release of an anti-inflammatory from daily disposable therapeutic contact lenses under physiological ocular tear flow. Eur J Pharm Biopharm. 2012;81(1):170-7. https://doi.org/10.1016/j.ejpb.2012.01.015
74. Alvarez-Rivera F, et al. Hydrogels for diabetic eyes: Naltrexone loading, release profiles and cornea penetration. Mater Sci Eng C Mater Biol Appl. 2019;105:110092. https://doi.org/10.1016/j.msec.2019.110092
75. Gonzalez-Chomon C, et al. Biomimetic contact lenses eluting olopatadine for allergic conjunctivitis. Acta Biomater. 2016;41:302-11. https://doi.org/10.1016/j.actbio.2016.05.032
76. White CJ, DiPasquale SA, Byrne ME. Controlled release of multiple therapeutics from silicone hydrogel contact lenses. Optom Vis Sci. 2016;93(4):377-86. https://doi.org/10.1097/OPX.0000000000000849
77. Skalicky SE, Goldberg I, McCluskey P. Ocular surface disease and quality of life in patients with glaucoma. Am J Ophthalmol. 2012;153(1):1-9.e2. https://doi.org/10.1016/j.ajo.2011.05.033
78. Varela-Garcia A, et al. Imprinted contact lenses for ocular administration of antiviral drugs. Polymers (Basel). 2020;12(9):2026. https://doi.org/10.3390/polym12092026
79. Gulsen D, Li CC, Chauhan A. Dispersion of DMPC liposomes in contact lenses for ophthalmic drug delivery. Curr Eye Res. 2005;30(12):1071-80. https://doi.org/10.1080/02713680500346633
80. Maulvi FA, et al. Tailored gatifloxacin Pluronic® F-68-loaded contact lens: addressing the issue of transmittance and swelling. Int J Pharm. 2020;581:119279. https://doi.org/10.1016/j.ijpharm.2020.119279
81. ElShaer A, et al. Nanoparticle-laden contact lens for controlled ocular delivery of prednisolone: formulation optimization using statistical experimental design. Pharmaceutics. 2016;8(2):14. https://doi.org/10.3390/pharmaceutics8020014
82. Maulvi FA, et al. pH triggered controlled drug delivery from contact lenses: addressing the challenges of drug leaching during sterilization and storage. Colloids Surf B Biointerfaces. 2017;157:72-82. https://doi.org/10.1016/j.colsurfb.2017.05.064
83. Xu J, et al. Co-delivery of latanoprost and timolol from micelles-laden contact lenses for the treatment of glaucoma. J Control Release. 2019;305:18-28. https://doi.org/10.1016/j.jconrel.2019.05.025
84. Huang JF, et al. A hydrogel-based hybrid theranostic contact lens for fungal keratitis. ACS Nano. 2016;10(7):6464-73. https://doi.org/10.1021/acsnano.6b00601
85. Gulsen D, Chauhan A. Ophthalmic drug delivery through contact lenses. Invest Ophthalmol Vis Sci. 2004;45(7):2342-7. https://doi.org/10.1167/iovs.03-0959
86. Jung HJ, Chauhan A. Temperature sensitive contact lenses for triggered ophthalmic drug delivery. Biomaterials. 2012;33(7):2289-300. https://doi.org/10.1016/j.biomaterials.2011.10.076
87. Maulvi FA, Soni TG, Shah DO. A review on therapeutic contact lenses for ocular drug delivery. Drug Deliv. 2016;23(8):3017-26. https://doi.org/10.3109/10717544.2016.1138342
88. Costa VCP, et al. Development of therapeutic contact lenses using a supercritical solvent impregnation method. J Supercrit Fluids. 2010;52(3):306-16. https://doi.org/10.1016/j.supflu.2010.02.001
89. Braga ME, et al. Effects of operational conditions on the supercritical solvent impregnation of acetazolamide in Balafilcon A commercial contact lenses. Int J Pharm. 2011;420(2):231-43. https://doi.org/10.1016/j.ijpharm.2011.08.040
90. Choi JH, et al. The efficiency of cyclosporine A-eluting contact lenses for the treatment of dry eye. Curr Eye Res. 2019;44(5):486-96. https://doi.org/10.1080/02713683.2018.1563702
91. Dominguez-Godinez CO, et al. In vitro and in vivo delivery

of the secretagogue diadenosine tetraphosphate from conventional and silicone hydrogel soft contact lenses. J Optom. 2013;6(4):205-11. https://doi.org/10.1016/j.optom.2013.07.004
92. Carreira A, et al. New drug-eluting lenses to be applied as bandages after keratoprosthesis implantation. Int J Pharm. 2014;477(1-2):218-26. https://doi.org/10.1016/j.ijpharm.2014.10.037
93. Zhu Q, et al. Inner layer-embedded contact lenses for pH-triggered controlled ocular drug delivery. Eur J Pharm Biopharm. 2018;128:220-9. https://doi.org/10.1016/j.ejpb.2018.04.017
94. Ciolino JB, et al. In vivo performance of a drug-eluting contact lens to treat glaucoma for a month. Biomaterials. 2014;35(1):432-9. https://doi.org/10.1016/j.biomaterials.2013.09.032
95. Peral A, et al. Contact lenses as drug delivery system for glaucoma: a review. Appl Sci. 2020;10(15):5151. https://doi.org/10.3390/app10155151
96. Ciolino JB, et al. A drug-eluting contact lens. Invest Ophthalmol Vis Sci. 2009;50(7):3346-52. https://doi.org/10.1167/iovs.08-2826
97. Ciolino JB, et al. A prototype antifungal contact lens. Invest Ophthalmol Vis Sci. 2011;52(9):6286-97. https://doi.org/10.1167/iovs.10-6935
98. Morrison PW, Khutoryanskiy VV. Advances in ophthalmic drug delivery. Ther Deliv. 2014;5(12):1297-311. https://doi.org/10.4155/tde.14.75
99. Ciolino JB, et al. Latanoprost-eluting contact lenses in glaucomatous monkeys. Ophthalmology. 2016;123(10):2085-92. https://doi.org/10.1016/j.ophtha.2016.06.038
100. Filipe HP, et al. Contact lenses as drug controlled release systems: a narrative review. Rev Bras Oftalmol. 2016;75(3):241-7. https://doi.org/10.5935/0034-7280.20160051
101. North D. Treatment of acute glaucoma. Can Med Assoc J. 1971;105(6):561-4.
102. Peng CC, et al. Drug delivery by contact lens in spontaneously glaucomatous dogs. Curr Eye Res. 2012;37(3):204-11. https://doi.org/10.3109/02713683.2011.630154
103. Peng CC, et al. Extended drug delivery by contact lenses for glaucoma therapy. J Control Release. 2012;162(1):152-8. https://doi.org/10.1016/j.jconrel.2012.06.017
104. Lee D, et al. Ocular drug delivery through pHEMA-hydrogel contact lenses co-loaded with lipophilic vitamins. Sci Rep. 2016;6:34194. https://doi.org/10.1038/srep34194
105. Jha G, Kumar A. Drug delivery through soft contact lenses: an introduction. Chron Young Sci. 2011;2(1):3. https://doi.org/10.4103/2229-5186.79342
106. Dumbleton K, et al. The TFOS International Workshop on Contact Lens Discomfort: report of the subcommittee on epidemiology. Invest Ophthalmol Vis Sci. 2013;54(11):TFOS20-36. https://doi.org/10.1167/iovs.13-13125
107. Dumbleton K. Adverse events with silicone hydrogel continuous wear. Cont Lens Anterior Eye. 2002;25(3):137-47. https://doi.org/10.1016/S1367-0484(02)00009-7
108. Alipour F, et al. Contact lens-related complications: a review. J Ophthalmic Vis Res. 2017;12(2):193-204.
109. Kumar KS, et al. Sustained release drug delivery system potential. Pharma Innov J. 2012;1(2):1-5.
110. Hadjiargyrou M, et al. Differential bacterial colonization and biofilm formation on punctal occluders. Materials (Basel). 2019;12(2):274. https://doi.org/10.3390/ma12020274
111. Tyson SL, et al. Multicenter randomized phase 3 study of a sustained-release intracanalicular dexamethasone insert for treatment of ocular inflammation and pain after cataract surgery. J Cataract Refract Surg. 2019;45(2):204-12. https://doi.org/10.1016/j.jcrs.2018.09.023
112. Gira JP, et al. Evaluating the patient experience after implantation of a 0.4 mg sustained release dexamethasone intracanalicular insert (Dextenza™): results of a qualitative survey. Patient Prefer Adherence. 2017;11:487-94. https://doi.org/10.2147/PPA.S126283
113. Chen M, Choi SY. Preliminary outcomes of temporary collagen punctal plugs for patients with dry eye and glaucoma. Med Hypothesis Discov Innov Ophthalmol. 2020;9(1):56-61.
114. Kompella UB, Kadam RS, Lee VH. Recent advances in ophthalmic drug delivery. Ther Deliv. 2010;1(3):435-56. https://doi.org/10.4155/tde.10.40
115. Kompella UB, Hartman RR, Patil MA. Extraocular, periocular, and intraocular routes for sustained drug delivery for glaucoma. Prog Retin Eye Res. 2021;82:100901. https://doi.org/10.1016/j.preteyeres.2020.100901
116. Gooch N, et al. Ocular drug delivery for glaucoma management. Pharmaceutics. 2012;4(1):197-211. https://doi.org/10.3390/pharmaceutics4010197
117. Perera SA, et al. Feasibility study of sustained-release travoprost punctum plug for intraocular pressure reduction in an Asian population. Clin Ophthalmol. 2016;10:757-64. https://doi.org/10.2147/OPTH.S102181
118. Goldberg DF, Williams R. A phase 2 study evaluating safety and efficacy of the latanoprost punctal plug delivery system (L-PPDS) in subjects with ocular hypertension or open-angle glaucoma. Invest Ophthalmol Vis Sci. 2012;53(14):5095.
119. Gupta C, Chauhan A. Ophthalmic delivery of cyclosporine A by punctal plugs. J Control Release. 2011;150(1):70-6. https://doi.org/10.1016/j.jconrel.2010.11.009
120. Pescosolido N. J Ocul Pharmacol Ther. 2012;28(5)
121. Sakamoto A, Kitagawa K, Tatami A. Efficacy and retention rate of two types of silicone punctal plugs in patients with and without Sjögren syndrome. Cornea. 2004;23(3):249-54. https://doi.org/10.1097/00003226-200404000-00006
122. Balaram M, Schaumberg DA, Dana MR. Efficacy and tolerability outcomes after punctal occlusion with silicone plugs in dry eye syndrome. Am J Ophthalmol. 2001;131(1):30-6. https://doi.org/10.1016/S0002-9394(00)00620-6
123. Sonomura Y, et al. Clinical investigation of the extrusion rate and other complications of the SuperEagle plug. Nippon Ganka Gakkai Zasshi. 2013;117(2):126-31.
124. Horwath-Winter J, et al. Long-term retention rates and complications of silicone punctal plugs in dry eye. Am J Ophthalmol. 2007;144(3):441-4.e1. https://doi.org/10.1016/j.ajo.2007.05.019
125. Nasu N, et al. Clinical investigation of the extrusion rate and other complications of the new Super Flex Plug punctal plug and other plugs. Nippon Ganka Gakkai Zasshi. 2008;112(7):601-6.
126. Kaido M, et al. Comparison of retention rates and complications of two different types of silicon lacrimal punctal plugs in the treatment of dry eye disease. Am J Ophthalmol. 2013;155(4):648-53.e1. https://doi.org/10.1016/j.ajo.2012.10.024
127. Marcet MM, et al. Safety and efficacy of lacrimal drainage system plugs for dry eye syndrome: a report by the American Academy of Ophthalmology. Ophthalmology. 2015;122(8):1681-7. https://doi.org/10.1016/j.ophtha.2015.04.034
128. Paparizos SC, Edward DP, Osmanovic S. Plug surface

defects as a late complication of silicone punctal plugs. Cornea. 2013;32(9):1224-6. https://doi.org/10.1097/ICO.0b013e31829a6881
129. Takemura M, et al. Canaliculitis caused by Actinomyces in a case of dry eye with punctal plug occlusion. Nippon Ganka Gakkai Zasshi. 2002;106(7):416-9.
130. Tabbara KF. Aspergillus fumigatus colonization of punctal plugs. Am J Ophthalmol. 2007;143(1):180-1. https://doi.org/10.1016/j.ajo.2006.08.026
131. Boldin I, et al. Long-term follow-up of punctal and proximal canalicular stenoses after silicone punctal plug treatment in dry eye patients. Am J Ophthalmol. 2008;146(6):968-72.e1. https://doi.org/10.1016/j.ajo.2008.06.028
132. Kim BM, Osmanovic SS, Edward DP. Pyogenic granulomas after silicone punctal plugs: a clinical and histopathologic study. Am J Ophthalmol. 2005;139(4):678-84. https://doi.org/10.1016/j.ajo.2004.11.059
133. Sugita J, et al. The detection of bacteria and bacterial biofilms in punctal plug holes. Cornea. 2001;20(4):362-5. https://doi.org/10.1097/00003226-200105000-00005
134. Tost FHW, Geerling G. Plugs for occlusion of the lacrimal drainage system. Dev Ophthalmol. 2008;41:193-212. https://doi.org/10.1159/000131090
135. Mohan RR, et al. Corneal stromal repair and regeneration. Prog Retin Eye Res. 2022;91:101090. https://doi.org/10.1016/j.preteyeres.2022.101090
136. Hippert C, et al. Corneal transduction by intra-stromal injection of AAV vectors in vivo in the mouse and ex vivo in human explants. PLoS One. 2012;7(4):e35318. https://doi.org/10.1371/journal.pone.0035318
137. Han H, et al. Polymer- and lipid-based nanocarriers for ocular drug delivery: current status and future perspectives. Adv Drug Deliv Rev. 2023;196:114770. https://doi.org/10.1016/j.addr.2023.114770
138. Holly FJ, Lemp MA. Wettability and wetting of corneal epithelium. Exp Eye Res. 1971;11(2):239-50. https://doi.org/10.1016/S0014-4835(71)80028-3
139. Feizi S, Azari AA, Safapour S. Therapeutic approaches for corneal neovascularization. Eye Vis (Lond). 2017;4:28. https://doi.org/10.1186/s40662-017-0094-6
140. Riazi-Esfahani M, et al. Prevention of corneal neovascularization: evaluation of various commercially available compounds in an experimental rat model. Cornea. 2006;25(7):801-5. https://doi.org/10.1097/01.ico.0000220768.11778.60
141. Vieira ACC, et al. Intrastromal injection of bevacizumab in patients with corneal neovascularization. Arq Bras Oftalmol. 2012;75(4):277-81. https://doi.org/10.1590/S0004-27492012000400012
142. Fasciani R, et al. Subconjunctival and/or intrastromal bevacizumab injections as preconditioning therapy to promote corneal graft survival. Int Ophthalmol. 2015;35(2):221-7. https://doi.org/10.1007/s10792-014-9938-4
143. Brown L, et al. The global incidence and diagnosis of fungal keratitis. Lancet Infect Dis. 2021;21(3):e49-57. https://doi.org/10.1016/S1473-3099(20)30448-5
144. Sharma N, et al. Fungal keratitis: a review of clinical presentations, treatment strategies and outcomes. Ocul Surf. 2022;24:22-30. https://doi.org/10.1016/j.jtos.2021.12.001
145. Mahmoudi S, et al. Fungal keratitis: an overview of clinical and laboratory aspects. Mycoses. 2018;61(12):916-30. https://doi.org/10.1111/myc.12822
146. Hu J, et al. A combination of intrastromal and intracameral injections of amphotericin B in the treatment of severe fungal keratitis. J Ophthalmol. 2016;2016:3436415. https://doi.org/10.1155/2016/3436415
147. Mimouni M, et al. Safety and efficacy of intrastromal injection of 5% natamycin in experimental fusarium keratitis. J Ocul Pharmacol Ther. 2014;30(7):543-7. https://doi.org/10.1089/jop.2014.0004
148. Li C, et al. Efficacy of voriconazole corneal intrastromal injection for the treatment of fungal keratitis. J Ophthalmol. 2021;2021:5597003. https://doi.org/10.1155/2021/5597003
149. Niki M, et al. Ineffectiveness of intrastromal voriconazole for filamentous fungal keratitis. Clin Ophthalmol. 2014;8:1075-9. https://doi.org/10.2147/OPTH.S63516
150. Yam GHF, et al. Safety and feasibility of intrastromal injection of cultivated human corneal stromal keratocytes as cell-based therapy for corneal opacities. Invest Ophthalmol Vis Sci. 2018;59(8):3340-50. https://doi.org/10.1167/iovs.17-23575
151. Soleimani M, et al. Intrastromal versus subconjunctival injection of mesenchymal stem/stromal cells for promoting corneal repair. Ocul Surf. 2023;30:187-95. https://doi.org/10.1016/j.jtos.2023.09.008
152. Kim S, et al. Intrastromal injection of hyaluronidase alters the structural and biomechanical properties of the corneal stroma. Transl Vis Sci Technol. 2020;9(6):21. https://doi.org/10.1167/tvst.9.6.21
153. Khan IJ, Hamada S, Rauz S. Infectious crystalline keratopathy treated with intrastromal antibiotics. Cornea. 2010;29(10):1186-8. https://doi.org/10.1097/ICO.0b013e3181d403d4
154. Martinez-Velazquez L, et al. Successful management of infectious crystalline keratopathy with intrastromal antibiotic injections. Case Rep Ophthalmol Med. 2022;2022:5830617. https://doi.org/10.1155/2022/5830617
155. Gautam M, et al. Intracameral drug delivery: a review of agents, indications, and outcomes. J Ocul Pharmacol Ther. 2023;39(2):102-16. https://doi.org/10.1089/jop.2022.0144
156. Haddad NM, et al. Cataract surgery and its complications in diabetic patients. Semin Ophthalmol. 2014;29(5-6):329-37. https://doi.org/10.3109/08820538.2014.959197
157. Gungor SG, et al. Comparison of intracameral dexamethasone and intracameral triamcinolone acetonide injection at the end of phacoemulsification surgery. Indian J Ophthalmol. 2014;62(8):861-4. https://doi.org/10.4103/0301-4738.141045
158. Wang M, Liu Y, Dong H. Effect of cefuroxime intracameral injection antibiotic prophylactic on postoperative endophthalmitis wound post-cataract: a meta-analysis. Int Wound J. 2023;20(5):1376-83. https://doi.org/10.1111/iwj.13984
159. Thevi T, Abas AL. Role of intravitreal/intracameral antibiotics to prevent traumatic endophthalmitis: meta-analysis. Indian J Ophthalmol. 2017;65(10):920-5. https://doi.org/10.4103/ijo.IJO_512_17
160. George NK, Stewart MW. The routine use of intracameral antibiotics to prevent endophthalmitis after cataract surgery: how good is the evidence? Ophthalmol Ther. 2018;7(2):233-45. https://doi.org/10.1007/s40123-018-0138-6
161. Tommaso R, et al. Cataract surgery practice patterns worldwide: a survey. BMJ Open Ophthalmol. 2021;6(1):e000464. https://doi.org/10.1136/bmjophth-2020-000464
162. Bhat KT, et al. Evaluation of efficacy of intracameral lidocaine and tropicamide injection in manual small-incision cataract surgery: a prospective clinical study. Indian J Ophthalmol. 2022;70(11):3849-52. https://doi.org/10.4103/ijo.IJO_2050_22
163. Minakaran N, Ezra DG, Allan BD. Topical anaesthesia

plus intracameral lidocaine versus topical anaesthesia alone for phacoemulsification cataract surgery in adults. Cochrane Database Syst Rev. 2020;7:CD005276. https://doi.org/10.1002/14651858.CD005276.pub4
164. Nuijts R, et al. Safety of an intracameral fixed combination for mydriasis and intraocular anaesthesia during cataract surgery. Clin Ophthalmol. 2024;18:1103-15. https://doi.org/10.2147/OPTH.S453257
165. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006;90(3):262-7. https://doi.org/10.1136/bjo.2005.081224
166. Senthil S, et al. Neovascular glaucoma: a review. Indian J Ophthalmol. 2021;69(3):525-34. https://doi.org/10.4103/ijo.IJO_1591_20
167. Michels S, et al. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twelve-week results of an uncontrolled open-label clinical study. Ophthalmology. 2005;112(6):1035-47. https://doi.org/10.1016/j.ophtha.2005.02.007
168. Avery RL. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. Retina. 2006;26(3):352-4. https://doi.org/10.1097/00006982-200603000-00016
169. Ghanem AA, et al. Intravitreal bevacizumab (Avastin) as an adjuvant treatment in cases of neovascular glaucoma. Middle East Afr J Ophthalmol. 2009;16(2):75-9. https://doi.org/10.4103/0974-9233.53865
170. Bhagat PR, Agrawal KU, Tandel D. Study of the effect of injection bevacizumab through various routes in neovascular glaucoma. J Curr Glaucoma Pract. 2016;10(2):39-48. https://doi.org/10.5005/jp-journals-10008-1200
171. Chalam KV, et al. Intracameral Avastin dramatically resolves iris neovascularization and reverses neovascular glaucoma. Eur J Ophthalmol. 2008;18(2):255-62. https://doi.org/10.1177/112067210801800214
172. Shah TJ, Conway MD, Peyman GA. Intracameral dexamethasone injection in the treatment of cataract surgery induced inflammation: design, development, and place in therapy. Clin Ophthalmol. 2018;12:2223-33. https://doi.org/10.2147/OPTH.S165722
173. Salmon JF. Kanski's Clinical Ophthalmology: A Systematic Approach. 9th ed. Elsevier Health Sciences; 2024.
174. Mittal V. Spherical and fibrous filler composites. Hoboken: John Wiley & Sons; 2016. https://doi.org/10.1002/9783527670222
175. Jamil AZ, Ahmed A, Mirza KA. Effect of intracameral use of dexamethasone on corneal endothelial cells. J Coll Physicians Surg Pak. 2025;35(11):245-8.
176. Mamalis N, et al. Toxic anterior segment syndrome. J Cataract Refract Surg. 2006;32(2):324-33. https://doi.org/10.1016/j.jcrs.2006.01.065
177. Ana ID. Collagen hydrogel in drug delivery and tissue engineering. In: Jana S, editor. Biomaterial-based Hydrogels: Therapeutics Carrier and Tissue Regeneration. Singapore: Springer Nature Singapore; 2024. p.199-243. https://doi.org/10.1007/978-981-99-8826-6_8
178. Biswas A, et al. Polymers and their engineered analogues for ocular drug delivery: enhancing therapeutic precision. Biopolymers. 2024;e23578. https://doi.org/10.1002/bip.23578
179. Di Girolamo N. Biologicals and biomaterials for corneal regeneration and vision restoration in limbal stem cell deficiency. Adv Mater. 2024;2401763. https://doi.org/10.1002/adma.202401763
180. Abouelatta SM, Sheta AI, Ibrahim RR. Optimized molecular imprints in gamma-irradiated collagen shields of an antifungal drug: in vitro characterization, in-vivo bioavailability enhancement. Eur J Pharm Biopharm. 2021;166:135-43. https://doi.org/10.1016/j.ejpb.2021.06.008
181. Chacko IA, Sudheesh M. Collagen for drug delivery applications. In: Nayak AK, Sen KK, editors. Natural Biopolymers in Drug Delivery and Tissue Engineering. Amsterdam: Elsevier; 2023. p.157-77. https://doi.org/10.1016/B978-0-323-98827-8.00024-2
182. Mofidfar M, et al. Drug delivery to the anterior segment of the eye: a review of current and future treatment strategies. Int J Pharm. 2021;607:120924. https://doi.org/10.1016/j.ijpharm.2021.120924
183. Leonardi F, et al. Synthetic and natural biomaterials in veterinary medicine and ophthalmology: a review of clinical cases and experimental studies. Vet Sci. 2024;11(8):368. https://doi.org/10.3390/vetsci11080368
184. Nair RV, Nair SC, Anoop K. Current trends in ocular drug delivery systems and its applications. Res J Pharm Technol. 2015;8(5):629-36. https://doi.org/10.5958/0974-360X.2015.00101.8
185. Sahoo NR, Biswal S. Advancements in ocular drug delivery systems. In: Nayak AK, Sen KK, editors. Novel Formulations and Future Trends. Cambridge: Academic Press; 2024. p.197-222. https://doi.org/10.1016/B978-0-323-91816-9.00018-7
186. Zhou S, et al. Release of moxifloxacin from corneal collagen shields. Eye Contact Lens. 2018;44:S143-7. https://doi.org/10.1097/ICL.0000000000000421
187. Verma AK. Collagen-based biomaterial as drug delivery module. In: Collagen Biomaterials. London: IntechOpen; 2022.
188. Rana D, et al. Collagen-based hydrogels for the eye: a comprehensive review. Gels. 2023;9(8):643. https://doi.org/10.3390/gels9080643
189. Muthukumar T, et al. Collagen as a potential biomaterial in biomedical applications. Rev Adv Mater Sci. 2018;53(1):29-39. https://doi.org/10.1515/rams-2018-0002
190. Allyn MM, et al. Considerations for polymers used in ocular drug delivery. Front Med. 2022;8:787644. https://doi.org/10.3389/fmed.2021.787644
191. Agban Y, et al. Nanoparticle cross-linked collagen shields for sustained delivery of pilocarpine hydrochloride. Int J Pharm. 2016;501(1-2):96-101. https://doi.org/10.1016/j.ijpharm.2016.01.069
192. Pandey PC, et al. Current advancements in transdermal biosensing and targeted drug delivery. Sensors (Basel). 2019;19(5):1130. https://doi.org/10.3390/s19051028
193. Karpiński TM. Selected medicines used in iontophoresis. Pharmaceutics. 2018;10(4):204. https://doi.org/10.3390/pharmaceutics10040204
194. Wei D, et al. Application of iontophoresis in ophthalmic practice: an innovative strategy to deliver drugs into the eye. Drug Deliv. 2023;30(1):2165736. https://doi.org/10.1080/10717544.2023.2165736
195. Cohen AE, et al. Evaluation of dexamethasone phosphate delivered by ocular iontophoresis for treating noninfectious anterior uveitis. Ophthalmology. 2012;119(1):66-73. https://doi.org/10.1016/j.ophtha.2011.07.006
196. Wirostko BM, et al. Efficacy and safety of an iontophoresis platform to control post cataract inflammation and pain. Invest Ophthalmol Vis Sci. 2017;58(8):1081.
197. Shoeibi N, Mahdizadeh M, Shafiee M. Iontophoresis in ophthalmology: a review of the literature. Rev Clin Med. 2014;1(4):183-8.