International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1857-1869 www.ijprajournal.com ISSN:2456-4494

Ocular Inserts for Multi-Drug Delivery: Design Strategies, Materials, and Clinical Translation for Chronic Eye Diseases

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Date of Submission: 08-01-2026 Date of Acceptance: 18-06-2026

ABSTRACT:
Chronic eye diseases like glaucoma are a major cause of irreversible blindness. This is mainly due to poor eye absorption and low patient compliance with standard eye-drop therapy. Ocular inserts provide a hopeful alternative by allowing sustained, targeted drug delivery with less frequent doses and reduced systemic exposure. While several single-drug ocular inserts and implants are now used in clinics, the growing recognition of the complex nature of chronic eye diseases has sparked interest in multi-drug insert platforms. This review highlights recent progress in designing and developing ocular inserts for multi-drug delivery. It discusses key anatomical and physiological barriers to eye drug absorption and provides an overview of insert types, including soluble, biodegradable, and non-erodible systems, as well as matrix, reservoir, and multilayer designs. New fabrication technologies, such as hot-melt extrusion, electrospinning, microneedle systems, and three-dimensional printing, are noted for their ability to precisely control the shape, drug load, and release rates. Preclinical studies show that multi-compartment and nanocarrier-integrated inserts can provide programmable and sustained release of various drugs, leading to better therapeutic results. Finally, the review outlines clinical and regulatory challenges that hinder implementation, stressing the need for scalable manufacturing and thorough safety assessments. Multi-drug ocular inserts hold great potential as a next-generation solution for long-lasting, patient-centered treatment in chronic eye diseases.

KEYWORDS: ocular inserts; multi-drug delivery; glaucoma; sustained release; 3D printing; stimuli-responsive; ocular pharmacokinetics

I. INTRODUCTION

A clinically distinctive optic neuropathy unites a collection of eye disorders known as glaucoma [1]. Glaucoma continues to be the leading cause of irreversible blindness globally, despite the fact that most cases can be stopped or their progression slowed by treatment that lowers intraocular pressure (IOP) [2]. Until the disease progresses to the point where a person presents with advanced visual field loss and eventually loses all vision, the more prevalent chronic forms of glaucoma are typically asymptomatic. Age, elevated intraocular pressure, sub-Saharan African ethnicity, positive family history, and high myopia are risk factors for primary open-angle glaucoma (POAG), the most prevalent subtype. The visually devastating condition known as primary angle-closure glaucoma (PACG) is characterized by an ocular anatomical predisposition that is especially common in East Asians.

The most common dosage form in ophthalmology is still topical eye drops, but their clinical efficacy is restricted by the physiological and anatomical barriers of the eye, such as nasolacrimal drainage, corneal and conjunctival permeability limits, and rapid tear turnover, as well as by poor patient adherence. These factors combined result in very low ocular bioavailability and the requirement for frequent dosing. When treating chronic conditions that require consistent intraocular drug levels, these factors can lead to therapeutic failure.[4]

By extending residence time, permitting controlled/sustained release, and lowering systemic exposure, ocular inserts—sterile, solid or semi-solid devices inserted in the conjunctival sac or cul-de-sac—were created to get around these restrictions. The insert platform consists of multilayer systems designed for particular release kinetics, matrix and reservoir designs, and biodegradable and non-erodible forms[5].

Why look at multi-drug ocular inserts? Three converging developments make focusing on this appropriate. First, engineered fabrication techniques, in particular 3D printing, now allow the design of patient-centric geometries and tunable porosity that can dramatically alter retention and release profiles. Recent studies have demonstrated that bioerodible

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Volume 11, Issue 3, May-June2026, pp:1857-1869 www.ijprajournal.com ISSN:2456-4494

3D-printed conjunctival inserts have superior corneal retention and customizable release[6,7]. Second, the combination of nanocarriers with stimuli-responsive hydrogels allows for the co-loading of chemically different actives and the release of these actives in order or on demand. These methods can be directly applied to combination therapies (e.g., lowering IOP and protecting nerve cells)[8].

Finally, multi-drug ocular inserts offer a promising approach to improve patient outcomes, driven by the translational imperative (the clinical need for less dosing and better adherence) and recent advances in manufacturing and regulation.

This review systematically compiles the literature on design considerations, materials, manufacturing techniques (with the emphasis on 3D printing), drug-loading approaches for co-delivery, preclinical and clinical data, and translational challenges to define actionable research priorities for the transition of multi-drug ocular inserts from bench to bedside.

1. Eye Anatomy & Barriers to Ocular Drug Delivery

The human eye is a complicated and segmented organ with several static and dynamic barriers to protect its sensitive visual structure. This physiology that maintains the integrity and homeostasis of the eye, however, presents a significant challenge for successful and long-term drug delivery, especially in chronic conditions such as glaucoma, uveitis, or postoperative inflammation.

A. Dynamics of the Ocular Surface and Tear Film

The tear film is the first physiologic barrier to topical drug delivery. The three layers of lipid, aqueous and mucin together preserve the hydration and transparency of the cornea. However, the tear layer also rapidly dilutes and clears administered formulations. With the average tear turnover rate of 16% per min [10], about 95% of the instilled drug volume is lost in 2 min.

The tear reflex and nasolacrimal drainage cause the corneal permeation of the topical drugs to be less than 5%, which further limits the residence time and bioavailability of the drug. The clinical rationale for the ocular inserts is this limitation, as they can be retained in contact with the ocular surface for extended periods of time, thus allowing for controlled release and decreasing drainage losses [11].

B. Conjunctival and Corneal Barriers

It is a structural barrier but the cornea is the major route of entry of drugs into the anterior chamber." This represents a biphasic problem since the hydrophilic stroma prevents the penetration of lipophilic drugs while the lipophilic epithelial layer prevents the diffusion of hydrophilic drugs [12]. On the other hand, the conjunctiva is highly vascularized and more permeable, which leads to the loss of drugs to the systemic circulation rather than targeted delivery to the intraocular area.

All these barriers reduce the permeability of the cornea for most therapeutic agents to 10-3-10-6 cm/s, which is well below the threshold for long-term pharmacological action [13].By creating close, sustained contact with the corneal and conjunctival surfaces, ocular inserts get around these restrictions and guarantee that drug diffusion follows a zero-order kinetic model as opposed to the burst-type release observed in drops. This results in better patient adherence and a more consistent pharmacokinetic profile.

C. Barriers between the blood and the eyes

The BAB and BRB represent two critical physiological barriers that provide additional protection for the posterior segment.The BAB includes the iris vasculature and the non-pigmented ciliary epithelial cells that limit the systemic entry of large and hydrophilic molecules into the aqueous humor. Similarly, the BRB, comprised of tight junctions between retinal pigment epithelial cells and the endothelium of the retinal capillaries, prevents the majority of medicated substances from diffusing passively into the retina and vitreous from the systemic circulation .In addition to allowing for multi-drug delivery for anterior and possibly posterior segment diseases through diffusion enhancers or nanoparticle embedding, ocular inserts provide a non-invasive substitute that can avoid systemic and tear drainage losses.

D. Why Anatomical Barriers Are Addressed by Inserts

Inserts successfully overcome the constraints imposed by tear turnover, corneal permeability, and vascular clearance by offering sustained, localized release and extended residence time on the ocular surface. Advanced inserts, such as films containing nanocarriers, mucoadhesive polymers, or 3D-printed multilayered matrices, can even customize the diffusion profile for several medications that target different chronic disease pathways (e.g., prostaglandin analogs + beta-blockers in glaucoma). According to recent in vivo research and computational fluid dynamics, these systems can

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1857-1869 www.ijprajournal.com ISSN:2456-4494

improve ocular drug bioavailability by 10–20× when compared to traditional drops[14].

2. Ocular insert types and designs

In order to extend residence time and provide controlled drug release, ocular inserts—solid or semi-solid sterile devices—are placed in the conjunctival sac, lacrimal canaliculus, or on the surface of the eye. Solubility/erosion properties (soluble, bioerodible/biodegradable, non-erodible/insoluble), delivery architecture (matrix vs. reservoir), and structural complexity (single-layer, multi-layer, or multi-compartment systems) are the traditional classifications. Drug loading, release kinetics, patient acceptability, and clinical translation are all affected differently by each classification.

2.A.Inserts that are soluble, bioerodible (biodegradable), and non-erodible

a. Soluble inserts

Water-soluble polymers that dissolve in the tear film over a predetermined amount of time make up soluble inserts. Because dissolution and drug diffusion happen simultaneously, they frequently exhibit a decaying (first-order) release profile but avoid a removal step (convenience advantage). One of the original types of ocular inserts, soluble inserts are still helpful when a short-to-medium duration release is required[14].

b. Bioerodible inserts

The polymers used to make bioerodible (biodegradable) inserts—such as PLGA, PCL blends, and specific polysaccharides—degrade hydrolytically or enzymatically. If erosion and diffusion are balanced, bioerodible designs allow for sustained zero-order or near-zero-order release. They also remove the need for device removal, which is a significant safety and compliance benefit. Recent research has shown that biodegradable conjunctival inserts can be 3D printed using stereolithography and extrusion to adjust porosity and erosion for regulated release[7].The polymers used to make bioerodible (biodegradable) inserts like PLGA, PCL blends and specific polysaccharides are degraded hydrolytically or enzymatically. If erosion and diffusion are balanced, bioerodible devices can be designed to provide sustained zero-order or near-zero-order release. They also do away with the need to remove the device, which is a major advantage for safety and compliance. Recent studies have demonstrated that biodegradable conjunctival inserts can be 3D printed by stereolithography and extrusion to customize porosity and erosion for controlled release[7].

c. Non erodible inserts

Non-erodible (insoluble) inserts are made of inert polymers that don't dissolve, like silicone elastomers and ethylene-vinyl acetate. After the dose is finished, these devices, which are usually reservoirs with a rate-controlling membrane, must be taken out or replaced. This class has historically been best represented by early commercial systems like Ocusert (pilocarpine reservoir insert), which offered nearly constant release but had problems with patient comfort and retention that hindered long-term success[17].

d. Design trade off

Design trade-offs: non-erodible reservoir systems can achieve very precise, long-term zero-order release, but they require removal and have a higher risk of mechanical irritation. In contrast, soluble and bioerodible inserts are more convenient for patients (no removal) and generally have better safety profiles for extended use. The intended indication (short postoperative steroid vs. chronic glaucoma therapy), drug physicochemistry, and patient characteristics all influence the class choice[15].

2.B. Reservoir versus matrix designs

a. Matrix Inserts

Drugs are evenly distributed throughout a polymeric matrix (homogeneous or gradient) by matrix inserts. Diffusion through the matrix and, if biodegradable materials are used, concurrent erosion are the main ways that drugs are released. Matrix systems are ideal for burst-limited sustained release and loading of large drug masses, and they are reasonably easy to fabricate using casting, electrospinning, melt extrusion, and 3D printing. Both molecular mixing and embedding various drug-bearing nanoparticles within the matrix allow for multi-drug loading[18,19].

b. Reserviour inserts:

A rate-controlling membrane encloses the liquid, gel, or solid drug core in reservoir inserts. Release is mostly controlled by permeability across the membrane; if membrane characteristics are optimized, this permits near-constant (zero-order) kinetics over long periods of time. When accurate, long-term dosing is needed (for example, chronic IOP control), reservoir designs perform exceptionally well. They must be removed or replaced if they are not erodible, though, and are frequently more complicated mechanically. For about a week, Ocusert, a traditional reservoir example, supplied pilocarpine at a constant[17].

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Volume 11, Issue 3, May-June2026, pp:1857-1869 www.ijprajournal.com ISSN:2456-4494

c. Hybrid strategies

In hybrid approaches, initial dose (loading/prime) and sustainment phase are independently tuned by combining matrix and reservoir elements (e.g., matrix coatings around reservoir cores or matrix bodies with embedded micro-reservoirs). When it comes to multi-drug delivery, these architectures are especially helpful when one compound needs to be released immediately and another needs to be exposed over time. Complex hybrids are becoming more and more possible at the bench scale thanks to recent manufacturing advancements like electrospinning, layer-by-layer deposition, and 3D printing [19].

2.C. Multi-compartment and multi-layer systems: facilitating multi-drug kinetics

Rationale:

Combination therapy (e.g., a pressure-lowering agent + anti-inflammatory/neuroprotective agent) is often beneficial for chronic ocular diseases. Divergent physicochemical and pharmacokinetic requirements of multiple actives (hydrophilic vs. lipophilic; immediate vs. sustained effect) cannot be met by single-formulation eye drops at the same time. By distributing medications among different layers or compartments with unique release mechanisms, multi-layer/multi-compartment inserts decouple these requirements [18].

Mechanisms and architectures:

Layered films: One drug and a polymer selected to provide a specific release profile (fast-releasing hydrophilic layer over a slowly eroding hydrophobic layer) are deposited in successive layers of discrete polymeric material. Layers can be arranged in the desired order of exposure to achieve sequential release (for example, antibiotic release after anti-inflammatory release). Solvent casting, layer-by-layer assembly, and 3D printing are examples of fabrication techniques [19].

Multi-compartment reservoirs (segmented cores or micro-reservoirs): A single device has several mini-reservoirs, each with its own membrane. This lets the release rates happen at the same time but be controlled separately. Recent engineering studies have used microfluidic templating and 3D printing to make these kinds of shapes [20].

Nanocarrier-in-matrix techniques: Drugs that are chemically incompatible can be loaded into various nanocarriers, such as liposomes, polymeric nanoparticles, or neosomes, and then embedded in distinct compartments or layers of a matrix. Co-delivery of small molecules and biologics (e.g., small drug + siRNA) is made possible by the matrix controlling residence time and the carrier controlling local release and penetration. Combining nanocarriers with layered inserts results in enhanced stability and customized diffusion, according to reviews and experimental data [21].

Achievable kinetic profiles:

Simultaneous sustained release: This is accomplished by carefully choosing the polymer diffusivity and membrane permeability so that both medications release continuously at different but overlapping rates.

Sequential release is the rapid (burst or short-term) release of one drug followed by the delayed or sustained release of another (achieved by using an inner reservoir for the second drug or by placing the fast-release drug in an outer soluble layer).

On-demand or disease-state-responsive delivery is made possible by layers that contain pH-sensitive or enzyme-sensitive polymers that can release medications in response to changes in the ocular microenvironment (such as inflammation-associated enzymes). There has been mounting evidence for ocular hydrogels and nanocarriers that respond to stimuli [21].

Clinical relevance and examples:

An example of a translational pathway that multi-drug systems could follow if safety, retention, and manufacturability are addressed is the single-drug sustained-release biodegradable insert Dexamethasone intracanalicular insert (Dextenza), which has reached clinical approval stages and shows that insert platforms can be safe and effective in postoperative inflammation [22].

The feasibility of multi-drug inserts for both anterior and adjunct posterior indications is indicated by recent preclinical and engineering studies that report dual-phase ocular inserts (e.g., PLGA-based systems releasing an NSAID followed by prolonged steroid delivery) and 3D-printed multilayer inserts embedding liposomal antibiotics. These studies also show promising in vitro release profiles and improved corneal retention in animal models [19].

2.D. Design factors for the creation of multi-drug inserts

Polymer selection (hydrophilicity, erosion rate), layer thickness and geometry (surface area to volume controls diffusion path), reservoir system membrane properties (permeability, thickness), drug-carrier compatibility, sterilization method effects, and patient comfort/retention are important

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1857-1869 www.ijprajournal.com ISSN:2456-4494

factors to optimize. For clinical translation, stability (storage and sterilization), manufacturing scalability (GMP-compatible extrusion or printing), and regulatory classification as combination products are equally important. Though careful in-vitro–in-vivo correlation and safety profiling are still necessary steps toward multi-drug commercialization, recent 3D-printing proof-of-concepts and clinical advancements with single-drug inserts indicate the engineering challenges are manageable [7].

3. Components of Multi-Drug Ocular Inserts [23]

Because of their adaptability and capacity to regulate drug release, polymers are essential to the creation of ocular drug delivery systems. Different polymers are used according to how they interact with drugs that are hydrophilic and lipophilic.

3.A. Hydroxypropyl Methylcellulose (HPMC):

Ocular inserts frequently contain hydroxypropyl methylcellulose (HPMC), a cellulose derivative. When hydrated, it takes on the consistency of gel, allowing for prolonged drug release. Ocular retention time is improved by HPMC's mucoadhesive and biocompatible qualities.

3.B. Polyvinyl Alcohol (PVA):

The synthetic polymer PVA is well-known for its capacity to form films and its solubility in water. For regulated drug release, it is frequently utilized in ocular inserts. Because PVA is hydrophilic, it can be used to deliver hydrophilic medications.

3.C. Polyethylene Oxide (PEO):

PEO is a polymer that dissolves in water and can create hydrogels. It enhances drug solubility and offers sustained release in ocular drug delivery systems. PEO's large molecular weight enables the encapsulation of medications that are both lipophilic and hydrophilic.

3.D. Poly(lactic-co-glycolic acid) (PLGA):

A common biodegradable and biocompatible polymer in regulated drug delivery systems is PLGA. It can break down into non-toxic byproducts and encapsulate a variety of medications, including hydrophobic ones.

3.E. Chitosan:

A biopolymer made from chitin is called chitosan. Its mucoadhesive qualities lengthen the duration of ocular retention. Chitosan is adaptable for ocular drug delivery because it can encapsulate both hydrophilic and lipophilic medications.

3.F. Hyaluronic Acid:

A naturally occurring polysaccharide, hyaluronic acid is well-known for its capacity to retain moisture and for being biocompatible. It improves drug bioavailability and offers sustained release in ocular inserts.

4. Fabrication and customization:

Modern inserts and implants use polymeric matrices (PCL-PEG-PCL, EVA, PVA, bioerodible polymers) enabling zero-order or tailored release profiles over weeks–months.3D printing and hot-melt extrusion allow layer-by-layer fabrication with precise control of geometry, dose, and drug combinations, supporting patient-specific designs and complex multi-drug architectures.Emerging approaches include electrospun nanofibers, hydrogels, and nanostructured coatings to tune loading, permeability, and residence time.

4.A.Polymer design for programmable release

Zero-order PCL-PEG-PCL inserts (InEye®) :

ε-Caprolactone was polymerized onto PEG600 to synthesize PCL-PEG-PCL triblock copolymers. The copolymer was melted and deposited onto a micro-tablet core (e.g., moxifloxacin) to fabricate a core–shell insert. Modulation of PEG content (24% vs 33%) enabled precise control over hydrophilicity, swelling behavior, and diffusion-governed drug release, while insert dimensions and drug loading further tuned the release profile. The system demonstrated near zero-order release of approximately 95% of the drug over 20–200 days without an initial burst effect, highlighting its suitability for customized long-term therapy in chronic diseases such as glaucoma[24].

Hot-melt-extruded gelatin/GelMA/PAA inserts:

Metoprolol was incorporated into a molten polymeric matrix com0prising gelatin, methacrylated gelatin (GelMA), and polyacrylic acid (PAA), followed by extrusion into rod- or film-shaped inserts. Matrix composition served as a key modulation parameter: increasing GelMA content significantly reduced the initial burst release (from 38.6% to 19% within 1 h) and promoted a quasi zero-order release profile, while higher PAA concentrations (5–20%) markedly retarded drug release (30% vs 2% at 1 h; 81% vs 50% at 4 h). Through compositional optimization, the system achieved sustained drug release over 12 h, enabling reduced dosing frequency and suitability for twice-daily administration[25].

Mucoadhesive films (PVP K-30 / Eudragit RS100):

Dexamethasone ocular films were fabricated by solvent-evaporation casting and optimized using a

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Volume 11, Issue 3, May-June2026, pp:1857-1869 www.ijprajournal.com ISSN:2456-4494

response-surface experimental design. Polymer ratio was systematically varied to tailor critical film attributes, including thickness, tensile strength, swelling behavior, and mucoadhesive strength, thereby achieving an optimal balance between patient comfort, ocular retention, and controlled drug release. In vivo evaluation demonstrated superior anti-inflammatory efficacy of the inserts, evidenced by a significant reduction in inflammatory cell infiltration compared with conventional eye-drop administration[26].

4.B.3D printing and digital design

HME + FDM 3D printing of ciprofloxacin inserts:

Drug-loaded filaments were prepared by hot-melt extrusion using Klucel™ polymer and subsequently processed into ocular inserts via fused deposition modeling (FDM). A design-of-experiments approach identified thickness and infill density as critical determinants of release kinetics, with increased thickness and higher infill producing slower drug release sustained up to 24 h. Modulation of internal architectures (e.g., grid versus solid infill) further regulated surface area and diffusion path length. The printed inserts formed amorphous solid dispersions, exhibited strong mucoadhesion, and demonstrated prolonged antibacterial activity with superior corneal permeation compared with conventional eye-drop formulations[27].

3D-printed punctal plugs:

Dexamethasone-loaded ocular plugs were fabricated using digital light processing (DLP) 3D printing of PEGDA/PEG400 semi-interpenetrating polymer networks (semi-IPNs). Modulation of resin composition (PEGDA-to-PEG400 ratio) enabled precise control over crosslink density, resulting in tunable drug release profiles ranging from approximately 7 days to over 21 days. Computer-aided design (CAD) further facilitated patient-specific customization of insert dimensions and drug loading, supporting personalized ocular therapy[28].

4.C. Microneedle and multilayer reservoir architectures

Detachable microneedle eye patch:

An array of detachable double-layer microneedles was engineered to penetrate the cornea and remain embedded as localized micro-reservoirs for sustained drug delivery. The layered architecture enabled staged, multi-drug release, comprising a fast-dissolving outer layer delivering diclofenac for immediate anti-inflammatory action and a slow-release inner core encapsulating an anti-VEGFR2 antibody (DC101) for prolonged anti-angiogenic therapy. This combination strategy achieved approximately 90% reduction in corneal neovascularization area and demonstrated superior therapeutic efficacy compared with single-drug delivery[29].

Advanced microneedle fabrication:

Metallic and silicon microneedles were fabricated using advanced micro- and nanofabrication techniques, including laser cutting, photolithography, deep reactive ion etching, and metal-assisted chemical etching, enabling the formation of sub-micron tip geometries with precisely controlled porosity. Drug incorporation was achieved via spray deposition or surface coating to obtain dose-programmable microneedles, while matrix loading with biodegradable polymers facilitated sustained drug release within ocular tissues[30].

4.D. Multi-drug and multi-phase possibilities

Most current ocular inserts are single-drug, but the fabrication methods are inherently multi-drug-capable:

Core–shell or multilayer films (PCL-PEG shells, PVP/Eudragit bilayers) can physically separate drugs with different solubilities or stability profiles for parallel or sequential release [24,26].

3D printing allows distinct compartments, each with its own polymer blend and drug, to achieve:

- Rapid-release antibiotic + slow-release anti-inflammatory in one insert (concept demonstrated with variable infill and geometry control)[27,31].

Microneedle double layers are a concrete proof-of-concept for multi-drug ocular delivery with distinct kinetics from a single device [29].

4.E. Disease-specific customization

- Glaucoma – long-acting inserts, punctal plugs, and intracameral implants providing weeks–months of IOP-lowering therapy, reducing adherence problems [32,33,34].
- Infectious keratitis – high-dose, 24-h ciprofloxacin inserts for intensive topical therapy [27,35].
- Inflammation/dry eye – dexamethasone films and punctal plugs with 7–21-day release [26,27].
- Neovascular and posterior segment diseases – microneedles and intraocular implants for biologics and small molecules over months–years [29,31,34,36].

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Method/Platform	Customization levers	Typical timescale	References
Ring-open polymerization + core–shell casting	PEG fraction, insert size, core mass	20–200 days	24
Hot-melt extrusion films	Gel/GelMA/PAA ratios; diameter	12 h	25
HME + FDM 3D printing	Thickness, infill, shape	24 h	27
DLP 3D-printed punctal plugs	PEGDA/PEG400 ratio, plug size	7–21+ days	28
Solvent-cast mucoadhesive films	PVP/Eudragit ratio, thickness	~hours–day scale	26
Double-layer microneedles	Layer composition, thickness, drug type	Hours–days	29,30

Table 1. Methods with customization and timescale

5. Drug Combinations, Release Kinetics & Mechanisms in Ocular Inserts

Ocular inserts and related surface or intraocular depots are increasingly engineered for multi-drug delivery with tailored release kinetics to manage chronic and postoperative eye diseases. Classical reservoir inserts, such as pilocarpine systems and newer PCL-PEG-PCL devices (InEye®), rely on diffusion through a non-erodible or slowly eroding membrane to achieve near zero-order release over weeks to months, with release rate governed by polymer hydrophilicity, thickness, and drug loading [27,34,37]. Composite systems introduce additional control layers: bromfenac-loaded PLGA microparticles dispersed in a mucoadhesive PVA matrix generate a dual-phase profile, with a small burst from free drug followed by several days of degradation-controlled release from the microparticles, suited to short-term postoperative inflammation control [19].

For combination therapy, multi-implant–laden silicone contact lenses deliver timolol, bimatoprost, and hyaluronic acid from peripheral implants embedded in the lens matrix, markedly reducing burst and providing sustained release for ~72 h in vitro and prolonged intraocular pressure reduction for ≥120 h in vivo compared with multiple eye-drop dosing [38]. More complex architectures, such as detachable double-layer microneedle patches, implement spatiotemporal separation of agents, with a rapidly dissolving outer layer releasing diclofenac and a slowly eroding inner reservoir sustaining delivery of an anti-VEGFR2 antibody (DC101); this biphasic regimen achieves ~90% reduction in corneal neovascular area and superior efficacy over single-drug treatment [39].Thermoresponsive injectable depots composed of polyester–PEG–polyester hydrogels loaded with PLGA microparticles exemplify fully programmable platforms, co-releasing an antibiotic, corticosteroid, and ocular hypotensive on distinct timescales (days vs ≥1 month) by independently tuning polymer hydrophobicity, microparticle composition, and initial load, while maintaining near-constant flux within each phase [39]. Collectively, these innovations show how polymer chemistry, compartmentalization (free drug vs particles vs layered structures), and device geometry are used to decouple and optimize the release of multiple ophthalmic agents for chronic indications such as glaucoma and neovascular disease [37].

Platform / disease focus	Drug(s)	Kinetic behavior	Reference
PCL-PEG-PCL InEye® insert (chronic glaucoma)	Moxifloxacin (model)	Zero-order, 20–200 days	24
IM-R contact lens (glaucoma)	Timolol, bimatoprost, HA	Low burst, 72 h in vitro, 120 h IOP control	38
Double-layer microneedles (corneal NV)	Diclofenac, DC101	Fast + sustained biphasic release	29
PLGA-MP/PVA insert (post-op inflammation)	Bromfenac	Burst + 4–6-day sustained phase	19
Thermoresponsive hydrogel depot (post-op multi-drug)	Antibiotic, steroid, hypotensive	Drug-specific, programmable profiles (days–month)	39

Table 2. Key multi-drug ocular depots and release behaviors.

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1857-1869 www.ijprajournal.com ISSN:2456-4494

6. Preclinical Evidence and In Vivo Models for Ocular Multi-Drug Delivery Systems:

Innovative ocular inserts and related depots are largely supported by preclinical animal and ex vivo data, focusing on safety, residence time, and pharmacodynamic benefit in chronic eye diseases. Most studies use single- or dual-drug systems, but they establish the key models and endpoints a multi-drug insert platform would need to satisfy.

Key In Vivo Disease Models and Readouts:

Glaucoma / IOP control (rabbits, monkeys): Brinzolamide NPs-in-nanofiber ocular inserts in rabbits prolong aqueous humor residence (t½ ~6 h vs 1 h for drops) and reduce IOP for ≥96 h, showing superior pressure control and tolerability [40].A sustained-release brimonidine intravitreal implant in monkeys maintains retinal levels above neuroprotective thresholds for 3–4 months, with PK modeling to define human dosing intervals. A sustained-release brimonidine intravitreal implant in monkeys maintains retinal levels above neuroprotective thresholds for 3–4 months, with PK modeling to define human dosing intervals[41].

Diabetic retinopathy and cataract (rats): Topical PCL–Pluronic nanoparticles delivering PDTC + triamcinolone achieve simultaneous protection of lens and retina in diabetic rats, reducing oxidative stress markers, HIF-1α, neovascular tufts and acellular capillaries[42].Retinal vascular disease / CNV (rats): 3D-printed dual-drug rods (bevacizumab + dexamethasone) implanted intravitreally suppress neovascularization and inflammation longer than bolus bevacizumab injections in rat CNV models [43].

Ex Vivo and Alternative Models:

Ex vivo porcine eyes are used to evaluate intravitreal liposomal biodistribution and half-life, and to screen formulations before live-animal studies[44].Small corneal/scleral disc models in porcine and human tissue allow rapid screening of topical penetration (e.g., siRNA) while reducing animal use [45].

Emerging Systems Relevant to Future Multi-Drug Inserts:

Dissolving microneedles with lactoferrin nanosuspension in a rabbit dry-eye model show marked cytokine reduction and restored tear function [46].Suprachoroidal injectors in non-human primates distribute dye uniformly over the posterior segment with good short-term safety, supporting alternative routes for multi-drug posterior segment deliver [47].Across glaucoma, DR, retinal vascular disease, and dry eye, robust rabbit, rat, and monkey models demonstrate that advanced ocular depots can safely extend drug exposure, improve disease biomarkers, and outperform standard drops or injections. Ex vivo porcine and human tissues are increasingly used to optimize designs before in vivo testing, providing a translational framework for future multi-drug ocular inserts.

7. Clinical Studies & Regulatory Landscape of Ocular Inserts and Multi-Drug Delivery:

Clinical translation of ocular inserts and implants for chronic eye disease is advancing, but most marketed systems are still single-drug products; true multi-drug inserts remain at preclinical or early-development stages.

Product / type	Drug(s)	Indication & status	Citations
Ocusert (historical ocular insert)	Pilocarpine	Approved in 1970s for glaucoma, weekly zero-order release; discontinued due to handling issues and acceptance	32,33
Lacrisert, Mydriasert	Single drug	FDA-approved topical inserts for dry eye and mydriasis; show feasibility of insert route	48
Durysta (intracameral implant)	Bimatoprost	FDA-approved biodegradable implant for IOP lowering; proof of long-acting polymer depot in glaucoma	23,33,49
Ozurdex, Retisert, Iluvien, Vitrasert	Corticosteroid/antiviral	Widely used intravitreal implants for chronic posterior disease (uveitis, DME, CMV)	39,40
OTX-TP (intracanalicular)	Travoprost	Phase III data: up to 3-month IOP control via hydrogel + microspheres	23,52

Table 3. Representative sustained-release ocular devices in the clinic

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Evidence from Clinical Experience:
Reviews highlight that sustained-release systems in glaucoma and retinal disease can improve adherence, reduce visit burden, and stabilize vision, but require head-to-head trials versus eye drops to prove superiority and cost-effectiveness [23,32,33,53,56]. Safety issues include steroid-related IOP rise, endophthalmitis, device migration, and explant procedures for some non-biodegradable implants [23,49,50,53].

Regulatory and Translational Considerations:
Most approved devices use well-known polymers (e.g., PLGA, silicone) and single actives, easing CMC and safety review [23,49,54]. Regulatory agencies expect robust long-term safety, device reliability, and clear benefit over topical therapy, especially for invasive implants[23,32,50,51,55].
Multi-drug depots raise added complexity: drug–drug interactions in release, combination-product classification, and more demanding clinical programs; these are highlighted as key hurdles delaying clinical entry [23,49,54,55].Clinically, sustained ocular inserts and implants are established for several chronic eye diseases, but nearly all deliver a single drug. Reviews agree that multi-drug ocular inserts are scientifically attractive yet still face regulatory, manufacturing, and clinical-trial challenges before they can reach routine use.

8. Safety, toxicity, and stability
Ocular inserts are solid or semi-solid polymer devices placed in the conjunctival sac to give sustained, localized drug release, reducing dosing frequency and systemic exposure compared with eye drops. For chronic eye diseases, combining several drugs in one long-acting insert is attractive but raises questions of polymer biocompatibility, cumulative toxicity, and formulation stability [35].

Safety & Toxicity:
Modern inserts use FDA-accepted biodegradable or inert polymers (e.g., PCL, PVA, PLGA, cellulose derivatives) selected for ocular biocompatibility and minimal inflammatory response [35].Electrospun nanofibrous inserts loaded with antibiotics or azithromycin showed no ocular irritation, high cell viability, and good tolerance in rabbit eyes while maintaining therapeutic levels for days [57].
Nanoparticle-impregnated inserts for acetazolamide reduced intraocular pressure without causing inflammation or discomfort, supporting local safety of polymer–drug systems [58].Reviews of biodegradable ocular polymers emphasize the need for in vivo toxicity testing (histology, intraocular pressure, inflammation) before clinical translation, especially for chronic use and drug combinations [49].

Stability & Multi-Drug Challenges:
Solid inserts are more physically and chemically stable than aqueous drops and can avoid preservatives, extending shelf life [76].
Stability depends on polymer–drug compatibility, moisture uptake, and storage temperature; studies report months-long stability with preserved mechanical properties and drug content [59].
Reviews highlight added complexity for multi-drug systems: risk of drug–drug interactions, differential diffusion rates, and maintaining uniform content; careful polymer selection and layered or reservoir designs are used to control release [45].For chronic eye disease, polymer-based ocular inserts (including nanofiber and nanoparticle-loaded designs) appear non-irritant, preservative-free, and physically stable, with sustained release that can lower systemic and local toxicity. Multi-drug inserts are technically feasible, but require rigorous biocompatibility and stability testing to manage interactions among drugs and degradation products over long treatment periods.

9. Opportunities & future directions for multi-drug ocular inserts
Multi-drug ocular inserts sit at the intersection of implants, nanocarriers, and smart materials. Reviews on long-acting ocular systems highlight several concrete innovation paths that are directly applicable to future multi-drug inserts for chronic eye disease.
Biodegradable and stimuli-responsive matrices (pH, temperature, light, enzyme) allow on-demand release, dose “boosts,” or shut-off in response to inflammation or IOP changes [55].

Translation, regulation, and real-world use:
Future work must develop better in vitro/in silico eye models to predict multi-drug kinetics and toxicity, reducing reliance on animal studies [50].
Regulatory and industrial reviews emphasize scalable manufacturing (HME, 3D printing, injection molding) and clear bioequivalence criteria as critical bottlenecks and innovation targets [55].
For glaucoma and retinal disease, long-acting systems aligned with reimbursement and adherence benefits are highlighted as high-value opportunities [33].
Novel multi-drug ocular inserts will likely combine smart, biodegradable architectures with embedded

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1857-1869 www.ijprajournal.com ISSN:2456-4494

nano-carriers, digital or sensing functions, and personalized manufacturing. The main opportunities lie in truly programmable multi-drug release and minimally invasive, long-acting therapy, while future work must solve stability, safety, and scalable production to bring these concepts into routine care.

II. CONCLUSION:

Ocular inserts have matured from early proof-of-concept devices into clinically validated platforms capable of delivering sustained ophthalmic therapy and addressing long-standing challenges of poor adherence and low ocular bioavailability. Clinical experience with single-drug inserts and implants in glaucoma, postoperative inflammation, and retinal disease clearly demonstrates that localized, long-acting drug delivery can improve therapeutic consistency and reduce treatment burden. These successes provide a strong foundation for extending insert technology toward multi-drug delivery.

This review highlights that the scientific tools required to realize multi-drug ocular inserts—advanced polymers, nanocarriers, multilayer and multi-compartment architectures, and digitally driven fabrication methods such as 3D printing—are already available and increasingly well-characterized. Preclinical studies consistently show that such systems can decouple release kinetics, accommodate chemically incompatible drugs, and outperform conventional eye drops in terms of residence time and pharmacodynamic efficacy. Nevertheless, translation to the clinic remains limited by regulatory complexity, manufacturing scalability, long-term safety requirements, and the need to demonstrate clear clinical benefit over existing monotherapies.

Importantly, the gap between bench and bedside is no longer primarily a question of feasibility, but one of integration. Future progress will depend on rational design frameworks that align polymer chemistry, device architecture, and disease-specific pharmacology, supported by predictive in vitro and in silico models and well-designed translational studies. As regulatory pathways for combination products become clearer and manufacturing technologies continue to mature, multi-drug ocular inserts are well positioned to evolve from experimental systems into practical, patient-centered therapies.

In the context of chronic eye diseases such as glaucoma, diabetic retinopathy, and inflammatory disorders—where long-term, multi-target treatment is often required—programmable multi-drug ocular inserts represent a logical and potentially transformative next step in ophthalmic drug delivery.

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