International Journal of Pharmaceutical Research and Development

ISSN Print: 2664-6862
ISSN Online: 2664-6870
Impact Factor: RJIF 8.55
IJPRD 2025; 7(2): 897-902
www.pharmaceuticaljournal.net
Received: 19-10-2025
Accepted: 22-11-2025

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Recent Advances in Biodegradable Formulations for Ocular Drug Delivery

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DOI: https://doi.org/10.33545/26646862.2025.v7.i2j.256

Abstract
Effective medication administration is severely hampered by the ocular drug delivery barrier's complexity, which results in less than ideal therapeutic effects. Research is concentrating on new medications and delivery strategies to get around this problem, including the utilization of biodegradable formulations for ocular drug delivery technology. This involves investigating hydrogels, implants, biodegradable microneedles, and polymeric nanocarriers such liposomes, nanoparticles, nanosuspensions, nanomicelles, and nanoemulsions. The amount of recent research in these fields is growing quickly. In order to provide new treatment options for ocular conditions, this review summarizes the developments in biodegradable formulations for ocular drug delivery over the past ten years, assesses the clinical application of various biodegradable formulations in treating ocular diseases, and attempts to highlight future trends and their potential for useful clinical use.

Keywords: Ocular drug delivery, Biodegradable formulations, Liposomes, Microneedles

Introduction
An anterior segment (cornea, conjunctiva, aqueous fluid, iris, ciliary body, lens) and a posterior segment (vitreous humor, sclera, retina, choroid, optic nerve) make up the delicate, immune-privileged human eye. Its distinct physiological and anatomical barriers prevent access to medicinal drugs while providing protection against poisons and bacteria. Topical, systemic, intravitreal, and periocular drug delivery strategies are available; patient-friendly solutions sometimes have limited bioavailability because of obstacles such the blood-retinal barrier and tear film. As a result, research has focused on developing novel ocular drug delivery methods that use biodegradable formulations for improved permeability and sustained release [1, 2].

A number of vision-threatening disorders, such as glaucoma, diabetic retinopathy, keratitis, conjunctivitis, age-related macular degeneration, dry eye disease, and retinal vascular occlusion, can affect the complex organ that is the eye. Innovative ocular medication delivery techniques that emphasize biodegradable formulations have emerged to address these illnesses. Polymeric micelles, liposomes, nanoparticles, dendrimers, nanosuspensions, microneedles, hydrogels and implants are all included in these formulations. They offer several benefits, including prolonged residence time, higher permeability, improved stability, tailored therapeutic release, and improved solubility, all of which improve medication efficacy. The application of these biodegradable medications in eye therapy, both *in vitro* and *in vivo*, is presently the subject of numerous investigations [3].

However, problems with medication transport to the interior structures of the eye, stability, sterilization, poor drug loading, expensive costs, and excipient irritation limit their practical use. Over the past ten years, there has been a spike in studies aimed at improving the clinical potential of biodegradable medications for ocular illnesses as a result of increased research efforts to solve these challenges.

Barriers In Ocular Drug Delivery
Barriers in the Anterior Segment
(a) Tear Film
Because of its high turnover rate and viscous mucus layer, which renews every five

minutes at a rate of 1-3 µL/min, the tear film acts as a barrier to drug delivery. Poor bioavailability results from increased tear production following topical medication delivery, which dilutes the medication and makes it easier for it to be washed out through the nasolacrimal duct. The tear film is made up of an inner mucus layer, an outer lipid layer, and a middle aqueous layer. Mucin forms a hydrophilic barrier on the ocular surface that prevents drug absorption by shielding the eye from pathogens and cellular debris [4, 5].

(b) Blood–Aqueous Barrier

The inner lining of Schlemm's canal, iris vessel endothelial cells, and non-pigmented ciliary epithelium make up the blood-aqueous barrier (BAB). Intravenous treatment for anterior segment disorders is not feasible because it controls solute flow between the anterior and posterior segments through tight junctions that limit the passage of molecules, such as hydrophilic medications and albumin generated from plasma. [6]

(c) Cornea

With five layers—epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium—with a thickness of about 500 µm, the cornea is a crucial barrier to topical medication absorption. Drug diffusion via the paracellular route is restricted by its epithelial layer, which has intercellular tight junctions. [7] Furthermore, cationic chemicals are more likely to penetrate the negatively charged epithelium than anionic ones. The structured collagen fibers that make up the stroma, which accounts for 90% of the cornea's thickness, prevent lipophilic drug penetration. Through selective transport, the endothelium helps to preserve corneal transparency and aqueous humor. All things considered, these traits pose serious obstacles to ocular medication administration. [8]

Barriers in the Posterior Segment

(a) Sclera and Bruch's–Choroid Complex

Collagen fibers, proteoglycans, and glycoproteins make up the sclera, the outermost covering of the eyeball, which preserves the shape of the eye and keeps foreign objects out. Its structure restricts the permeability of big and lipophilic molecules; transscleral permeability is influenced by the molecules' charge; positively charged molecules are less permeable because of the negatively charged proteoglycan matrix. Bruch's membrane supports the choroid, a vascular layer that nourishes the outer retina and is situated between the sclera and retina. Because they create sustained-release in the tissue contacts, this Bruch's–choroid complex poses more serious obstacles to drug delivery, especially for positively charged lipophilic medicines [9, 10].

(b) Vitreous humor

The vitreous humor, which has a volume of roughly 4 milliliters, is a transparent, gel-like material that sits between the lens and the retina. Water makes up 99% of its composition, coupled with non-collagenous proteins, several kinds of collagen, hyaluronic acid, and proteoglycans. Its major functions are to preserve the integrity of the eye and make it easier for nutrients to reach the retina. However, the viscosity of the gel restricts molecular diffusion, making it more difficult to move big, charged molecules, which could precipitate and impede the absorption of drugs [11, 12].

(c) Blood-Retinal Barrier

A physiological barrier called the blood-retinal barrier (BRB) controls the flow of water, ions, and proteins from the blood to the retina. Tight connections between retinal capillary endothelial cells constitute the inner BRB, while tight junctions between retinal pigment epithelial cells form the outer BRB. By selectively restricting the movement of chemicals, especially hydrophilic compounds and macromolecules, from the choroidal circulation to the eye, these junctions protect the retina and influence drug penetration into the ocular cavity [13, 14].

Conventional routes of ocular drug delivery

Table 1: Comparison of conventional routes of ocular drug delivery

Route of Administration	Targeted Ocular Segment	Advantages	Disadvantages
Topical Administration [15]	Anterior segment (cornea, conjunctiva, sclera, iris, ciliary body).	Treats common anterior segment diseases (e.g., conjunctivitis, glaucoma); better patient compliance.	Low bioavailability (<5% absorbed) due to tear dynamics and corneal barrier; difficult to produce therapeutic concentrations in the deeper posterior segment.
Systemic Administration [16]	Choroid; theoretically feasible for retina.	Drugs readily enter the choroid due to higher vasculature; rapid equilibration between blood and choroid extravascular space.	Blood-Aqueous Barrier (BAB) and Blood-Retinal Barrier (BRB) are major barriers; requires high dosage, leading to systemic side effects.
Periocular and Intraocular Injections [17]	Posterior segment.	Overcomes inefficiency of topical/systemic routes; effective for delivering high therapeutic concentrations (especially intravitreal).	Highly invasive; frequent injections required; low patient compliance; increased risk of complications (e.g., endophthalmitis, ocular hypertension, retinal detachment).

novEL biodegradable ocular drug delivery systems

Recent developments include the creation of biodegradable ocular drug delivery systems (DDSs), which improve ocular drug administration and bioavailability while guaranteeing constant drug levels at the target site. These systems allow for prolonged medication release over time because they are made to naturally break down and be removed from the body. By lowering the number of injections, this method improves compliance, lowers the risk of problems, and makes treatment more patient-friendly.

(I) Nanotechnology-Based Systems

(a) Liposomes and Niosomes

Liposomes are spherical structures made of cholesterol and phospholipids that help transport medications by encasing both lipophilic and hydrophilic substances. To improve pharmacokinetics, its design permits different drug loading

conditions and surface alterations. Despite their biocompatibility and ability to lessen medication toxicity, issues such poor stability, leakage, low loading capacity, and high production costs still exist. For the treatment of ocular diseases, these problems call for the creation of better liposome formulations [18, 19].

(b) Nanoparticles

Polymeric and lipid nanoparticles (NPs) range in size from 1 to 1000 nm. Cytotoxicity and production issues are among the problems that polymeric nanoparticles, which are made of a variety of natural and artificial materials, must deal with. Lipid NPs, on the other hand, are less hazardous and more stable since they use solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). While NLCs improve drug-loading capacity, SLNs provide efficient drug release and bioavailability. Drug-loaded NPs have the potential to replace conventional treatments for eye illnesses because of their high drug retention and minimal toxicity, according to recent studies. Their low capacity to transport water-soluble materials calls for more investigation [20, 21].

(c) Polymeric Micelles

The nature of amphiphilic polymers, which encapsulate hydrophobic medicines and increase solubility, makes recent developments in polymeric micelles (PMs) for ocular drug administration noteworthy. Stability and drug release depend on the choice of core-forming polymer, such as chitosan or PLGA. Although PMs are easy to use and improve medication penetration across ocular barriers, they have drawbacks such as poor drug loading and production difficulties. Although they provide better pharmacokinetics and sustained release, novel ocular nanosystems (ONSs) still need to optimize drug loading, release, and biocompatibility. To improve efficacy and patient compliance, future research should concentrate on co-delivery systems, sophisticated fabrication processes, and environmentally friendly synthesis procedures. [22, 23]

(d) Dendrimers

Dendrimers are innovative polymeric nanoarchitectures noted for their three-dimensional, branched, and symmetric structures, first synthesized by Fritz Vögtle in 1978. Their characteristics, such as nanoscopic size, narrow polydispersity, tunable surface functionality, and a high surface area-to-volume ratio, make them suitable for ocular drug delivery. The most studied are Polyamidoamine (PAMAM) dendrimers, available commercially due to their defined structure. However, clinical use is hindered by cytotoxicity issues, particularly with cationic dendrimers, which are more toxic than anionic and neutral types. This toxicity varies with the dendrimer generation, prompting researchers to explore modifications for reducing toxicity while maintaining efficacy. Despite these concerns, dendrimers remain a promising option for ocular drug delivery. [24, 25]

(II) Biodegradable Microneedles

An inventive development in the administration of eye medications, minimally invasive microneedle-based ocular drug delivery overcomes the drawbacks of conventional needles. Microneedles (MNs), which were initially intended for transdermal distribution, lessen patient discomfort and enable specific medication localization. Although non-biodegradable materials like ceramics and stainless steel have made it easier to fabricate MN, their biocompatibility problems might cause persistent irritation. Although they provide a regulated drug release mechanism, biodegradable substitutes, such as polylactic and polyglycolic acids, have trouble maintaining long-term efficacy for chronic ocular therapies. Research is required to maximize the safety and efficacy of the technology and to solve restrictions in the administration of medications to the posterior eye. [26, 27]

(III) Biodegradable Implants

As of right now, the FDA has authorized intraocular implants for intravitreally delivered sustained medication release to the retina. Both biodegradable and non-biodegradable implants are available; the latter offer greater accuracy and longer medication release. Trivaris®, Kenalog®, Iluvien®, Ozurdex®, Durysta®, and Dexycu® are a few examples; Ozurdex®, Dexycu®, and Durysta® are biodegradable. Durysta® controls intraocular pressure for four to six months, Dexycu® provides a single-dose, sustained-release alternative following cataract surgery, and Ozurdex® tackles macular edema with a six-month release profile. Furthermore, new biodegradable implants like OcuLiefTM and EyeLiefTM are being developed, suggesting a trend toward biodegradable technology in the treatment of ocular diseases. [28, 29]

Utilizing various biodegradable ocular drug delivery methods for ocular conditions

(a) Glaucoma

About 1% of people worldwide suffer from glaucoma, a major cause of blindness that is more common in people over 40. It results in increased intraocular pressure (IOP), which interferes with aqueous circulation and causes abnormalities in the visual field and optic nerve atrophy. Low medication bioavailability and patient non-compliance are problems with current topical therapies. Antiglaucoma drugs like timolol and latanoprost in biodegradable drug delivery systems (DDS) like liposomes and polymeric nanoparticles are examples of sustained drug delivery techniques that show potential for increased bioavailability and sustained release.

Table 2: Studies of biodegradable formulations for glaucoma

Study	Drug and System	Experimental Models	Description
Roy *et al*., 2020 [30]	Pilocarpine-loaded microneedle ocular patch using dissolvable PVA and PVPM	Ex vivo with excised human cornea and porcine eye	Pilocarpine penetration over the removed cornea was greatly enhanced by the patch. Within 30 minutes of patch administration, the availability in the pig eye globe's aqueous humor was higher than that of the solution formulation.
Bhalerao *et al*., 2020 [31]	Brinzolamide dimethyl sulfoxide in situ gelling solution	New Zealand white rabbits	Evaluated formulations significantly reduced intraocular pressure (IOP) from 25–28 mmHg to 12–14 mmHg, proving their safety and efficacy. Additionally, they outperformed the commercial Azopt® suspension (4.9 h) by showing a longer mean residence duration (7.4 to 17.7 h) and an improved area under the curve for IOP change from baseline.

Tan *et al*., 2017 [32]	Timolol maleate chitosan coated liposomes	New Zealand white rabbits	In comparison to commercial timolol maleate drops, the formulation demonstrated superior intraocular pressure (IOP) reduction, longer corneal retention time, and enhanced mucoadhesive qualities.
Huang *et al*., 2016 [33]	Thermosensitive in situ hydrogel of betaxolol hydrochloride	A rabbit model	The formulation's *in vitro* investigation revealed a longer release of betaxolol hydrochloride and an increase in viscosity. The enhanced bioavailability and a notable decrease in IOP were validated by the *in vivo* study's findings.

(b) Dry Eye Disease

Tear film instability, inflammation, and irregularities are all part of the multifactorial illness known as dry eye disease (DED), which affects the ocular surface. A variety of drugs are needed for management, such as immunosuppressants, lubricants, and anti-inflammatory drugs like corticosteroids. Biodegradable corticosteroid formulations have been the focus of research to increase therapy efficacy while reducing side effects. Numerous corticosteroid delivery methods, including hydrogels and nanosystems, have demonstrated potential in lowering inflammation. Notable advancements include a dendrimer-dexamethasone gel that effectively reduces ocular inflammation and a chitosan thermosensitive hydrogel with dexamethasone that showed sustained release. Other research has attempted to improve ocular bioavailability using various drug delivery techniques, such as PLGA nanoparticles, although many designs have limits in terms of practical usability and manufacturing difficulties. [34, 35]

(c) Conjunctivitis and Keratitis

Common ocular surface conditions including keratitis and conjunctivitis are brought on by a variety of infectious and non-infectious causes. Targeted pharmacological therapies, such as antibiotics, antivirals, antifungals, and anti-inflammatory medications, are frequently used in treatment. [36] However, problems including short residence time on the ocular surface and restricted solubility call for creative drug delivery methods. Studies have looked into biodegradable formulations, such as liposomal ciprofloxacin, which performed better than commercial medicines but lacked safety assessments. Although their efficacy against a broader spectrum of bacteria was not evaluated, polymeric nanoparticles (NPs), such as chitosan-based NPs for levofloxacin, showed improved eye retention. Furthermore, amphotericin B (AmB)-containing microneedle ocular patches were successful in treating fungal keratitis; however, there was no discussion of their long-term stability or direct comparison to current administration techniques. Further investigation is required to verify the safety and effectiveness of these innovative therapies. [37, 38]

(d) Age-Related Macular Degeneration (AMD)

In affluent nations, AMD is a major cause of blindness due to problems such as choroidal neovascularization (CNV). Anti-VEGF medications are still best administered intravitreally, however therapeutic small molecules have permeability problems. DDSs, or biodegradable drug delivery systems, can improve the penetration of medicinal agents. Studies show that liposomes, particularly the Liposome Aggregate Platform (LAP), can improve the retention of medications like flurbiprofen after injection; however, more research is needed to address any potential inflammatory reactions. Furthermore, sunitinib-loaded liposomes have demonstrated success in preventing neovascularization in animal models; however, in order to compare their performance with existing anti-VEGF treatments, investigations must more accurately reflect human pathophysiology.

The current research focuses on using polymeric nanoparticles (NPs) in conjunction with other delivery vehicles to improve drug penetration and duration in the treatment of ocular CNV. *in vitro*, Badiee *et al*. discovered that encasing bevacizumab in chitosan nanoparticles within a hyaluronic acid ocular implant produced sustained drug release for up to two months. [40] Wu *et al*. created a bilayer dissolving microneedle with ovalbumin-encapsulated PLGA NPs that can offer sustained protein release for more than two months ex vivo, overcoming the scleral barrier. [41] Additionally, employing polymeric NPs to co-administer dexamethasone with anti-VEGF drugs like bevacizumab and aflibercept has demonstrated strong anti-angiogenic effects and extended release. These findings point to a potentially effective treatment approach for CNV that combines the co-administration of many medications in a single injection with biodegradable formulations.

Conclusions

Biodegradable ocular drug delivery systems (DDSs) have advanced significantly over the past 10 years with the goal of enhancing drug stability, solubility, corneal permeability, and retention time. These technologies are incredibly adaptable and have a lot of room to grow, especially with biodegradable polymers that could revolutionize the way drugs are delivered to the eyes. To understand their methods of action, guarantee safety and quality control, and increase the effectiveness of these formulations, ongoing study is crucial. It is anticipated that the creation of novel ophthalmic DDSs in the future will be essential to improving ocular health.

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