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Frontiers in Ocular Drug Delivery System (ODDS)

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ABSTRACT: Ocular Drug Delivery System (ODDS) is a tough topic area in pharmaceutical science because the structure of the eye makes it hard for drugs to be absorbed properly. An ocular delivery system is a way or a tool that delivers medication directly to the eye to help overcome these challenges and make the treatment more effective. However, getting the medicine to work well is still hard because of things like tear washing it away quickly, blinking and the eye's limited ability to let drugs through the cornea. These factors make it hard to keep the drug in the eye for a long time and improve its effectiveness. The main goal is to find ways to get around these problems and improve how well the drug is absorbed.

In the past, a lot of research has focused on making better delivery systems that can get past these barriers and help drugs stay in the eye longer, making the treatment more effective and easier for patients to use. Recent developments have included using new kinds of nanotechnology-based carriers such as liposomes, niosomes, dendrimers, micelles, and biodegradable implants. These help improve how long the drug stays in the eye, how well it can pass through the eye tissues, and how it is released over time. These studies also talk about different nanostructured platforms and how they are tested and analysed. The types of formulation used include solutions, gels, and more advanced systems like nanoparticles and in-situ gels. Each product is checked for sterility, pH level, how it matches the body's fluid balance, and how stable it is to make sure it's safe and works well. The overall aim is to increase how long the drug stays in the eye, how well it gets into the tissues, and how willing patients are to use the treatment.

This review gives an update on the latest research in ocular drug delivery to help scientists think differently and come up with new and safe ways to deliver drugs. It also highlights the benefits/drawbacks/, and current trends in this field.

KEYWORDS: Ocular drug delivery, Ophthalmic formulations, In-situ gels, Nanoparticles, Ocular inserts, Sustained release.

I. INTRODUCTION

The eye is a delicate and highly specialized organ, and effective treatment of ocular disorders requires precise delivery of therapeutic agents to specific ocular tissues. Ocular drug delivery systems are designed to administer drugs to the anterior and posterior segments of the eye for the management of conditions such as glaucoma, conjunctivitis, uveitis, dry eye disease, and retinal disorders. Successful ocular therapy depends on achieving adequate drug concentration at the target site while minimizing systemic exposure.

Despite advances in pharmaceutical formulations, ocular drug delivery remains challenging due to the complex anatomy and protective mechanisms of the eye. Factors such as corneal barriers, tear film dynamics, blinking reflex, and nasolacrimal drainage significantly reduce drug retention on the ocular surface. As a result, conventional ocular dosage forms like eye drops and ointments exhibit poor ocular bioavailability, with only a small fraction of the administered dose reaching intraocular tissues.

Additionally, the blood–aqueous and blood–retinal barriers restrict the entry of drugs into deeper ocular regions, further limiting the effectiveness of traditional delivery approaches. Frequent administration of conventional formulations is often required to maintain therapeutic drug levels, which may lead to poor patient compliance and increased risk of local or systemic side effects.

To overcome these limitations, considerable research efforts have focused on the development of novel ocular drug delivery systems. Advanced approaches such as nanoparticles, liposomes, niosomes, microspheres, in situ gels, ocular inserts, and drug-loaded contact lenses have been explored to enhance drug residence time, improve bioavailability, and provide controlled or sustained drug release.

This review article highlights the recent advancements in ocular drug delivery systems, emphasizing their formulation strategies, therapeutic advantages, limitations, and potential applications in the treatment of various ocular diseases.

In recent years, the increasing prevalence of chronic ocular diseases and age-related eye disorders has further emphasized the need for effective and patient-friendly drug delivery approaches. Long-term conditions such as glaucoma and macular degeneration require sustained therapeutic levels over extended periods, making conventional dosage forms inadequate. Poor patient adherence due to frequent dosing schedules and discomfort associated with topical administration continues to challenge successful clinical outcomes [9,10].

Emerging ocular drug delivery technologies aim not only to improve therapeutic efficacy but also to enable targeted delivery to specific ocular tissues while reducing systemic absorption. The integration of nanotechnology, biodegradable polymers, and stimulus-responsive systems has opened new possibilities for precision ocular therapy. These advancements hold significant potential for improving treatment outcomes and expanding the scope of ocular drug delivery in both anterior and posterior segment diseases [11,12].

II. LITERATURE WORK

The eye is equipped with strong protective mechanisms such as tear secretion, blinking, nasolacrimal drainage, and multiple anatomical barriers that rapidly remove administered drugs and limit ocular absorption. In addition, physiological barriers like the blood–aqueous and blood–retinal barriers restrict drug access to deeper ocular tissues. The cornea plays a critical role in limiting drug permeation due to its lipophilic epithelial layer, which hinders hydrophilic drugs, while the hydrophilic stroma restricts lipophilic compounds. Rapid tear clearance, enzymatic degradation, and short precorneal residence time further reduce drug availability, often necessitating frequent administration and lowering patient compliance. Although topical delivery is widely used for treating anterior eye disorders, these barriers significantly reduce therapeutic effectiveness.

To address these challenges, multiple strategies have been developed to enhance ocular drug delivery and retention. These include the incorporation of viscosity enhancers, mucoadhesive agents, prodrug approaches, permeability enhancers, and in situ gelling systems to prolong ocular residence time. Advanced delivery systems such as nanoparticles, liposomes, nanoemulsions, dendrimers, polymeric micelles, and drug-eluting contact lenses improve drug solubility, stability, penetration, and enable sustained release, thereby reducing dosing frequency and improving patient adherence. The use of modern biomaterials, including biodegradable polymers, hydrogels, and stimuli-responsive materials, further supports controlled and targeted drug release.

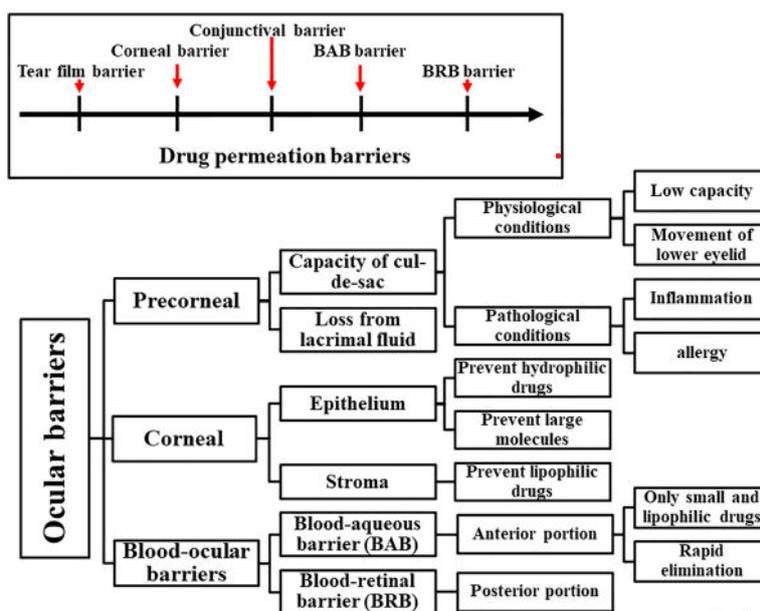
Despite significant progress, achieving effective non-invasive delivery to the posterior segment of the eye remains challenging due to multiple anatomical and physiological barriers. Recent research highlights the potential of nanotechnology-based carriers, surface-modified systems, in situ forming gels, and physical enhancement techniques such as iontophoresis and ultrasound-assisted delivery to improve drug penetration while avoiding invasive procedures. Emerging technologies including biodegradable implants, microneedle systems, gene-based therapies, and smart delivery platforms, supported by advances in bioengineering, nanofabrication, and artificial intelligence, are expected to further improve the safety, efficacy, and clinical outcomes of ocular drug delivery.

III. ANALYTICAL APPROACH

The methodology of ocular drug delivery represents an integrated scientific approach that combines pharmaceutical formulation principles with a thorough understanding of ocular anatomy, physiology, and drug transport pathways. Because the eye is protected by multiple defensive mechanisms—such as tear turnover, corneal and conjunctival barriers, nasolacrimal drainage, and blood–ocular barriers—drug penetration into ocular tissues is highly restricted. Consequently, ocular drug delivery systems are strategically developed to prolong drug residence on the ocular surface, enhance permeability across ocular tissues, and ensure controlled and site-specific drug release for effective therapy.

1. Preliminary Considerations in Ocular Drug Delivery

1.1 Barriers for Ocular Drug Delivery



The eye possesses multiple protective barriers that limit the entry of foreign substances, including therapeutic agents. These barriers play a crucial role in maintaining ocular integrity but significantly reduce drug bioavailability. The major barriers include precorneal barriers, the corneal barrier, and blood-ocular barriers.

1.2 Physiological Evaluation Of Drug Prior to formulation development, the physicochemical characteristics of the drug are carefully analyzed. Important parameters include molecular size, lipophilicity, aqueous solubility, ionization constant (pKa), and stability under different environmental conditions such as pH, light, and enzymatic activity. These properties significantly influence corneal permeability, drug retention, and overall formulation performance, thereby guiding the choice of delivery

2. Conventional Ocular Drug Delivery Systems

Conventional ocular drug delivery systems are mainly intended for diseases affecting the anterior segment of the eye and are commonly administered through topical routes. Although these systems are easy to use and cost-effective, they generally exhibit low ocular bioavailability due to rapid precorneal drug loss.

2.1 Ophthalmic Solutions

Ophthalmic solutions are prepared by dissolving the active pharmaceutical ingredient in sterile aqueous or oily vehicles. Formulation development includes optimizing pH to reduce irritation and enhance drug stability, maintaining isotonicity using suitable agents, and incorporating buffers and preservatives for stability and microbial protection in multidose preparations. Following instillation, the drug penetrates ocular tissues primarily by passive diffusion across the cornea. However, a major portion of the administered dose is eliminated through tear drainage and blinking. Short ocular residence time necessitates frequent dosing, which may reduce patient compliance.

2.2 Ophthalmic Suspensions

Ocular suspensions represent dispersions of hydrophobic drug in aqueous solvent. They have enhanced contact time because of drug retention in the conjunctival cul-de-sac. Particle size, solubility, and dissolution rate in the tear fluid are extremely important during the preparation process [102]. Generally, particle size 10 μm could result in ocular irritation and stimulated tearing [103]. Disadvantages of ocular suspension include poor stability. They cannot be stored in freezer as the particles tend to agglomerate and fail to disperse easily. A blurred vision after their administration could also result.

Improved ocular administration of posaconazole in polymer system of carbopol 974P and xanthan gum using high pressure homogenizing technique showed enhanced stability, antifungal activity, and prolonged retention [46].

2.3 Ophthalmic Emulsions

An emulsion based formulation approach offers an advantage to improve both solubility and bioavailability of drugs. There are two types of emulsions which are commercially exploited as vehicles for active pharmaceuticals: oil in water (o/w) and water in oil (w/o) emulsion systems^[26]. For ophthalmic drug delivery, o/w emulsion is common and widely preferred over w/o system. Several studies have demonstrated applicability of emulsions in improving precorneal residence time, drug corneal permeation, providing sustain drug release and thereby enhancing ocular bioavailability

2.4 Ophthalmic Ointments

Eye ointments are semisolid dosage form containing white petrolatum and mineral oil. They are administered to the lower eyelid only at bedtime due to its interference with vision. They are commonly used among young patients. They have anhydrous nature making them a good choice for lipophilic and moisture sensitive drugs. They have higher retention time and bioavailability in comparison with solutions [106]. Avaclyr® is an ocular ointment enclosing the antiviral acyclovir that was approved in 2019 for herpetic keratitis

3. Advanced (Standard) Ocular Drug Delivery Systems

Advanced ocular drug delivery systems are developed to address the limitations of conventional formulations by improving drug retention, enabling sustained release, and facilitating drug delivery to posterior ocular tissues.

3.1 In Situ Gelling Systems

Researchers have found the new concept of in situ gel in the early 1980s. Delivery of drug to ocular system through in situ gel is mainly for enhancing viscosity to decrease drug drainage from the cornea. The pourable gels are in liquid form when applied, after which they undergo a phase transition, when reaches to cul-de-sac of eye and converted into a visco-elastic gel giving rise to a response to changes environmentally, thereby increasing the bioavailability of the drug automatically. The major disadvantages of the in situ gels are that they get affected by temperature, pH or ions. Bazzaz et al. (2018) reported that in situ gelling system provides better and prolonged effect of a drug rather than conventional eye drops [60]

3.2 Ocular inserts

Ophthalmic inserts are solid patches, which, when placed in the conjunctival sac of the eye, slow down the rate of drug release. Ocular inserts also overcome the problem of frequent dosing by maintaining drug concentration in an effective manner and give rise to controlled, sustained and continuous drug delivery. Ocular Inserts also have various advantages like enhanced drug absorption due to increased contact time and minimized dose and application frequency. The major disadvantages of these inserts are patient noncompliance with frequent feeling like the entry of foreign body in the eye, difficulty in self-insertion feels and feeling of loss of the insert from eye.

3.3 Intravitreal Drug Delivery

Intravitreal injection is a delivery of medicine into the vitreous that is close to the retina at the back of the eye. A new approach for treatment of glaucoma includes a single intravitreal injection of vitamin E/poly-lactic-co-glycolic acid microspheres enclosing glial cell line derived neurotrophic factor. This approach provided a prolonged release for 6 months. Intravitreal injection of the biodegradable Rho kinase and protein kinase C inhibitor for handling diabetic macular edema and neovascular age-related macular degeneration exhibited prolonged release for about 6 months.

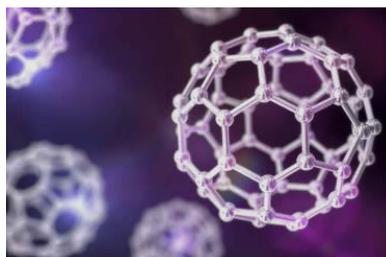
3.4 Implants

The aim of designing an intraocular implant is to prolong the activity of the drug, along with its controlled release by using a polymer or polymer system. An injectable delivery system of drug, like liposomes and nanoparticles, is easy to administer, but having limitation that after insertion, it becomes difficult to retract those particles during any complication, like toxic responses. Removal of ocular implants is easy and can be removed by surgical intervention. Implants can be categorized into two types based on the characteristics of the polymer(s) used: Nonbiodegradable implant, Biodegradable implants.

3.5 Nanotechnology-Based Drug Delivery Systems

Nanocarrier systems involve encapsulating drugs within nanoscale carriers such as nanoparticles, liposomes, niosomes, and nanoemulsions, dendrimers. Formulation optimization focuses on particle size, surface characteristics, and drug loading efficiency to maximize ocular penetration and retention.

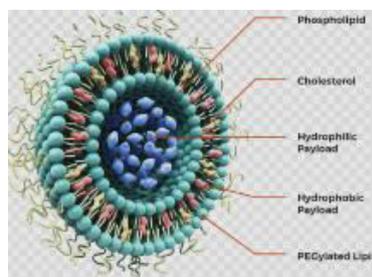
3.5.1 Nanoparticles



These are polymeric colloidal particles, size varying from 10 nm to 1 nm, where the drug is being dissolved, entrapped, encapsulated, or adsorbed [43]. It is used to deliver drug effectively. It consists of a number of biodegradable substances, like natural or synthetic polymers, lipids, phospholipids and metals. Conventional eye drops gave poor bioavailability (<5%) due to tear drainage, blinking and corneal barriers. It helps to increase drug residence time in the eyes, enhance corneal penetration and provide controlled and sustained drug release. To obtain nanoparticles, the drugs can be formulated in many ways as by integrating with the matrix or by attaching to the surface of biodegradable polymers used for the preparation.

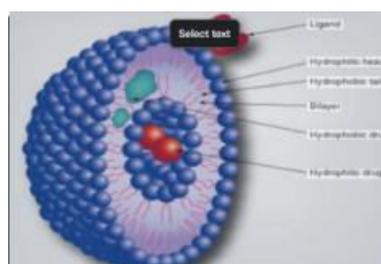
3.5.2 Liposomes

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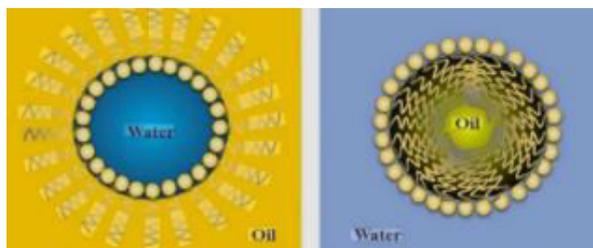
They were discovered in the mid-1960s [120]. Advantages of liposomes include safety, biodegradation, simple preparation techniques, and improved bioavailability [121]. They are spherical nanocarriers made of one or more concentric lipid bilayers. They could carry lipophilic drug in the lipid area, while the interior could entrap hydrophilic drugs. Changing the formation technique and their composition could alter their surface charge, sensitivity to ion or pH, or temperature changes and the resulted particle size [120]. Generally, the corneal epithelium has a negative charge; therefore, a positively charged liposomes would have high adherence, longer retention time, and better absorption. These outcomes will reduce the interval between doses and improve patient satisfaction [122].

3.5.3 Niosomes



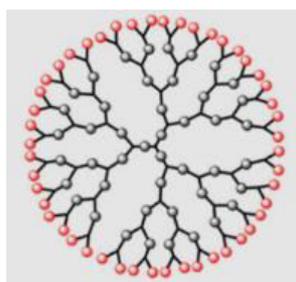
Niosomes are bilayered nanocarriers composed of selfaggregated non-ionic surfactants. They are biodegradable, biocompatible, enclose both hydrophilic and lipophilic drugs and non-immunogenic. They could prolong drug release and enhance its permeability and efficacy [161, 162]. Disadvantages of niosomes include chemical instability and possible hydrolysis, accumulation or loss of drug [18]. Cholesterol or its derivative is added to improve rigidity and stability of niosomes [8]. The resulted formula showed high drug entrapment, enhanced corneal permeation and activity [48]. Kaur et al. studied niosomal system composed of span 60, cholesterol, and chitosan. The finished product revealed higher activity, reduced side effects, and prolonged release [129]

3.5.4 Nanoemulsions



They are potential carriers for ocular delivery. Oils in water nanoemulsions are composed of dispersed oil phase that is stabilized by surfactants in an aqueous medium. They provide a reservoir for lipophilic drugs and interact with the lipids of tear film providing a sustained drug release [87, 163]. Surfactants are important for the interaction with the surface of the cornea, plus enhancing drug solubility [8]. Drawbacks of nanoemulsions include blurred vision if the particle size exceeds 100 nm due to development of milky formulation and reduced ocular tolerance due to high surfactant concentration [163]. Akhter et al. developed nanoemulsions system of cyclosporine A. Many oils, chitosan, Carbopol®, and Transcutol® P were incorporated.

3.5.5 Dendrimers



They are star-shaped or tree-shaped highly branched 3D structure, composed of repetitive molecules enclosing a central core [162]. They are suitable for delivery of both hydrophilic and lipophilic drugs due to their several terminal groups [161]. Drug is encapsulated inside the Dendrimer, it attract with corneal epithelium, enhance corneal permeability. Therefore provide controlled and sustained drug release. They showed increased residence time, prolonged activity, improved bioavailability, targeted delivery, and antimicrobial properties. They could transfer medications to both segments of the eye [8]. Lancina et al. developed brimonidine tartrate-loaded dendrimers using methoxy-polyethylene glycol.

IV. EXPERIMENTAL RESULT

Experimental investigations reported in the reviewed studies demonstrate that advanced ocular drug delivery systems significantly outperform conventional eye drops in terms of bioavailability, residence time, and therapeutic efficacy.

In vitro drug release studies revealed that formulations such as nanoparticles, liposomes, niosomes, and in situ gels exhibited a sustained and controlled release pattern. Unlike conventional formulations that showed rapid drug diffusion, these novel systems followed diffusion-based kinetic models such as Higuchi and Korsmeyer–Peppas, indicating

prolonged drug availability at the ocular surface. The controlled release behavior was primarily attributed to reduced particle size and polymeric encapsulation of the drug [1,2].

Ex vivo corneal permeation studies, commonly conducted using isolated goat or rabbit cornea, demonstrated enhanced drug permeation from nano-carriers and mucoadhesive systems. Increased permeation was associated with improved corneal contact time, bioadhesive properties, and temporary alteration of epithelial tight junctions, leading to higher transcorneal drug transport [3,4].

In vivo studies in rabbit models confirmed that novel ocular delivery systems achieved higher drug concentrations in the cornea and aqueous humor compared to conventional eye drops. These systems also showed prolonged precorneal retention and reduced dosing frequency, thereby improving patient compliance. In situ gelling systems and polymeric nanoparticles, in particular, demonstrated superior therapeutic outcomes in the management of glaucoma, infections, and inflammatory ocular conditions [5,6].

Overall, experimental results support that advanced ocular drug delivery systems offer a promising approach for improving ocular drug bioavailability while minimizing systemic exposure and adverse effects.

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