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Recent updates on drug delivery approaches for improved ocular delivery with an insight into nanostructured drug delivery carriers for anterior and posterior segment disorders

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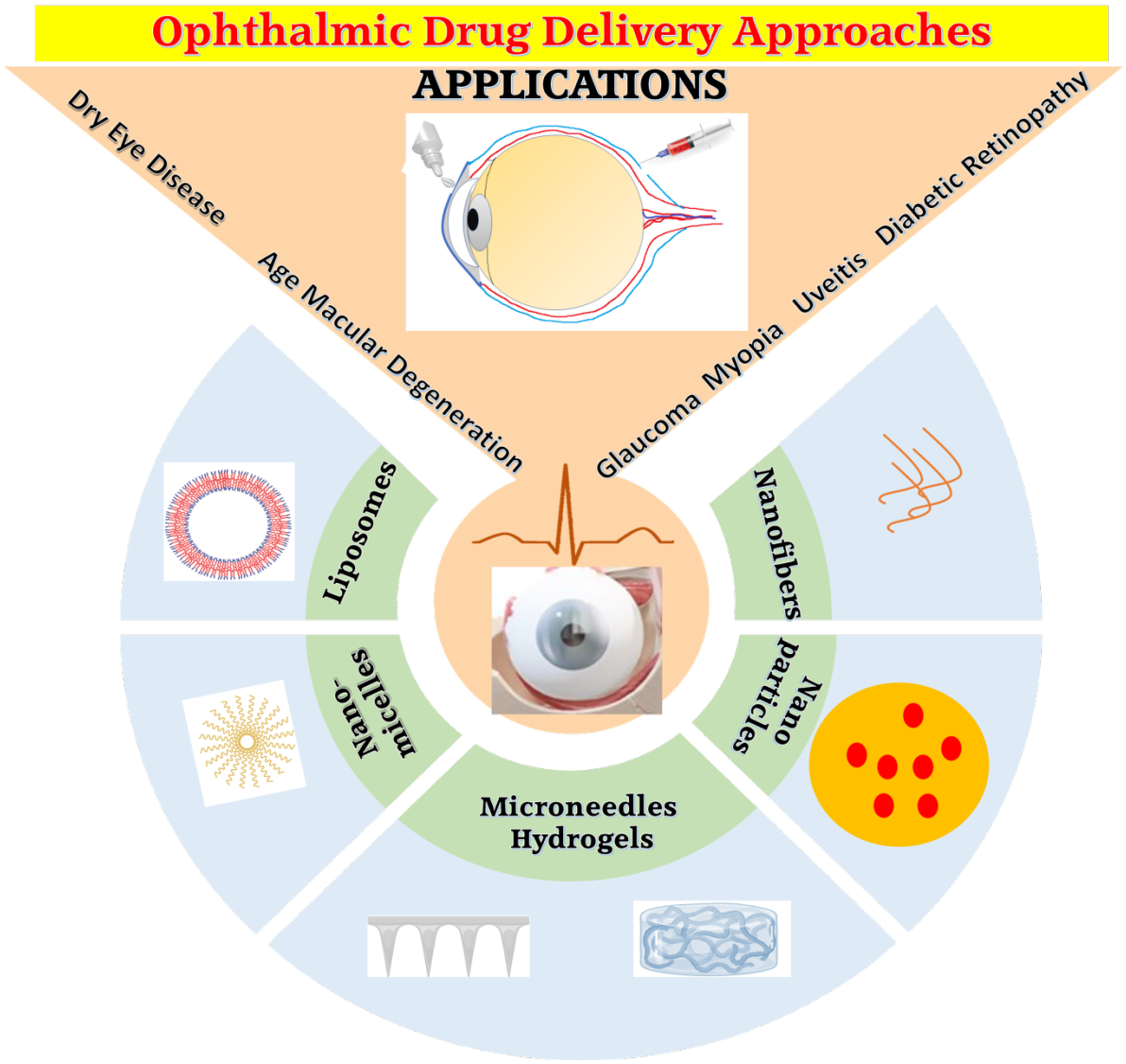
Abstract

Ocular diseases have a major impact on patient's vision and quality of life, with approximately 2.2 billion people have visual impairment worldwide according to the findings from the World Health Organization (WHO). The eye is a complex organ with unique morphology and physiology consisting of numerous ocular barriers which hinders the entry of exogenous substances and impedes drug absorption. This in turn has a substantial impact on effective drug delivery to treat ocular diseases, especially intraocular disorders which has consistently presented a challenge to eye care professionals. The most common method of delivering medications to the eye is topical instillation of eye drops. Although this approach is a viable option for treating many ocular diseases remains a major challenge for the effective treatment of posterior ocular conditions. Up till now, incessant efforts have been committed to design innovative drug delivery systems with the hopes of potential clinical application. Modern developments in nanocarrier's technology present a potential chance to overcome these obstacles by enabling targeted delivery of the loaded medication to the eyes with improved solubility, delayed release, higher penetration and increased retention. This review covers the anatomy of eye with associated ocular barriers, ocular diseases and administration routes. In addition it primarily focuses on the latest progress and contemporary applications of ophthalmic formulations providing specific insight on nanostructured drug delivery carriers reported over the past 5 years highlighting their values in achieving efficient ocular drug delivery to both anterior and posterior segments. Most importantly, we outlined in this review the macro and nanotechnology based ophthalmic drug formulations that are being patented or marketed so far for treating ocular diseases. Finally, based on current trends and therapeutic concepts, we highlighted the challenges faced by novel ocular drug delivery systems and provided prospective future developments for further research in these directions. We hope that this review will serve as a source of motivation and ideas for formulation scientists in improving the design of innovative ophthalmic formulations.

Graphical abstract



Keywords: Ocular diseases; ophthalmic barriers; ophthalmic routes; drug carriers; marketed products; patented products

Abbreviations

Age-related macular degeneration (AMD)

Active pharmaceutical ingredients (APIs)

Blood-aqueous barrier (BAB)

Blood-retinal barrier (BRB)

Bovine serum albumin (BSA)

Biodegradable implants (BI)

Chondroitin sulfate (CS)

Central retinal vein occlusion (CRVO)

Contact lenses (CLs)

Choroidal neovascularization (CNV)

Diabetic macular edema (DME)

Diabetic retinopathy (DR)

Dry Eye Disease (DED)

Drug delivery systems (DDSs)

Epithelial growth factor (EGF)

Endothelial growth factor (EnGF)

Electroretinograms (ERG)

Erythropoietin (EPO)

Ethylene vinyl acetate (EVA)

Fibroblast growth factor (FGF)

Fungal Keratitis (FK)

Food and Drug Administration (FDA)

Flurbiprofen sodium (FS)

Hyaluronic acid (HA)

Inner limiting membrane (ILM)

Inherited retinal diseases (IRD)

Intraocular pressure (IOP)

Ischemic optic neuropathy (ION)

Ketorolac tromethamine (KT)

Leber congenital amaurosis (LCA)

Muller glial cells (MGC)

Microneedles (MNs)

Microneedle scleral patch (MSP)

Microneedle corneal patch (MCP)

Nanoparticles (NPs)

Nanosuspensions (NSs)

Nanoemulsions (NEs)

Non-biodegradable implants (NBI)

Noninfectious posterior uveitis (NIPU)

Polyglycolic acid (PGA)

Platelet-derived growth factor (PDGF)

Polylactic acid (PLA)

Port Delivery System (PDS)

Pirfenidone (PFD)

Retinal pigment epithelium (RPE)

Retinal ganglion cells (RGCs)

Retinitis pigmentosa (RP)

Retinoblastoma (RB)

Rhodamine B (Rb)

Reactive oxygen specie (ROS)

Self-plugging Microneedle (SPM)

Simplex virus (HSV)

Traumatic optic neuropathy (TON)

Triamcinolone acetonide (TA)

Uveal melanoma (UM)

Vascular endothelial growth factor (VEGF)

World Health Organization (WHO)

1. Introduction

Millions of people around the world suffer from severe visual impairment or blindness caused by various eye diseases [1–3]. At least 2.2 billion people, according to the World Health Organization (WHO), have problems with their near or distant vision [4]. Furthermore, a Lancet Global Health analysis predicts that by 2050, there will be 600 million cases of moderate to severe vision impairment and 115 million cases of blindness, respectively, as the population ages. The most frequent causes of vision loss include uncorrected refractive error, inflammation of the cornea, sclera and iris, conjunctivitis [5], dry eye disease [6], allergies [7], retinopathy [8,9], age-related macular degeneration (AMD) [10], cataract [11], glaucoma [12] and diabetic macular edema (DME) [13–15]. Nearly 246 million people have subnormal vision, 285 million have vision impairments and 39 million are blind over age of 50, according to WHO reports [16,17]. More than 30% of blindness cases in India occur before the age of 17, and the majority occur in children under the age of five [18]. Elderly people frequently experience vision impairment in a variety of other ways [19]. Age-related macular degeneration (AMD), particularly in elderly patients, is responsible for 8.7% of blindness worldwide [20]. It is also important to note the extremely high annual expenditures of medicines around the world, which can reach up to US$ 250 billion. Moreover the incidence rate of ophthalmic diseases is also closely correlated with the socio-demographic index, age, life quality and gender [21].The majority of the aforementioned conditions demand the use of pharmaceuticals and their administration near, on the surface of or both inside the eyeball. Additionally it is frequently necessary to apply medications repeatedly over an extended period of time [22].

The eye is a highly specialized sensory organ that is separate from the systemic circulation and has unique pharmacodynamic and pharmacokinetic characteristics [23]. It is composed of an anterior and a posterior segment. The vitreous chamber, retina, choroid, sclera and optic nerve are located in the posterior segment. While cornea, conjunctiva, sclera, anterior chamber, iris, pupil, ciliary bodies and crystalline lens are located in the anterior segment. In other words, eye is composed of multiple layers of various attached tissues [24].

Vision impairment can result from problems in either segment. The most common conditions that impair vision in the posterior eye segment are age-related macular degeneration (AMD), diabetic retinopathy (DR) and glaucoma. While the anterior segment is more vulnerable to

conditions like cataracts, uveitis, allergic conjunctivitis and dry eye disease [25]. For diseases like wet AMD and DR, the development of new blood vessels from the existing vasculature is accounted for by angiogenesis. Anti-angiogenic and pro-angiogenic factors must be in balance for angiogenesis to occur physiologically in the human body [26]. When this balance is upset, the human body develops a pathological condition. Severe ocular angiogenesis is primarily caused by global ocular morbidity [27]. The angiogenic switch needs to be turned "on" in conditions that promote ocular angiogenesis in order for neovascularization to proceed [27]. Retinal vein occlusions, DR, corneal neovascularization, AMD, retinopathy of prematurity, choroidal and retinal neovascularization etc. are some of the complications it may cause. Endothelial growth factor (EnGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and others are pro-angiogenic growth factors that have been linked to the development of pathological vessels in ocular diseases [28]. With prompt diagnosis and treatment, majority of them can be completely or partially cured, but inappropriate or delayed therapy can result in irreversible changes [29].

A few significant to drug administration can be identified when taking into consideration the distinctive architecture of the eye. The most significant ones includes physiological processes such as nasolacrimal drainage and blinking, anatomical barriers, efflux pumps and metabolism in ocular tissues and few static barriers (tear film, corneal and blood aqueous barriers) can be seen in the eye's anterior portions [26, 30].

Drugs can be administered in a variety of ways, including topically, systemically, intravitreally, and periocularly to distinct areas of the eye. However due to different barriers such the tear film, cornea, sclera, blood-aqueous barrier and blood-retinal barrier, the most patient-friendly methods, such as topical and systemic routes frequently have low absorption [25,31]. After a medicine is administered through a specific route, each layer of ocular tissues may have unique features that act as barriers to drug penetration. The design of novel ocular drug delivery systems (DDSs) with biodegradable formulations for prolonged release and improved permeability has consequently become a crucial field of study. The fundamental goal for creating non-invasive ocular medication dosage forms is to enhance penetration across the sclera, cornea, and conjunctiva in order to increase bioavailability [30]. The length of time for which a drug retains at the application site affects the pace and extent of absorption in the case of externally applied

medications [32]. The sclera, which can cover up to 95% of the surface of the eye, is highly permeable to molecules smaller than 70 kDa. In contrast, the cornea only allows things with a mass of up to 1 kDa through [22]. Unfortunately, medication metabolism, tear protein binding or nasolacrimal drainage pathways frequently result in limited transscleral absorption [33]. Constant eyelid and ocular movement as well as irrigation with tear fluid both reduce the effectiveness of the treatment [34,35]. These factors lead to the yearly development of novel, technologically sophisticated ophthalmic drug delivery methods in addition to the quest for new active pharmaceutical ingredients (APIs) [36,37].

Eye drops [38–40], ointments [41,42] or gels [43,44] that contain the medicine in a dissolved or suspended form [45,46] are the most often used ophthalmic preparations. They are instilled to eyelid, conjunctival sac or surface of the eye by medical personnel or the patient themselves. Their biggest drawback is the frequent dosing requirement, which might be problematic. As a result, the therapy is less effective because the treatment plan is rarely followed [47,48]. In order to deliver the required concentration in the treated tissue for the specified time period, medicines are frequently added to suitable carriers or introduced into systems in addition to constructing the vehicle/base composition.

Innovative techniques for ocular drug administration have been designed in order to successfully treat ophthalmic diseases with a special emphasis on biodegradable formulations. Polymeric micelles, polymeric nanoparticles, liposomes, dendrimers, microemulsions, nanosuspensions, implants, microneedles and hydrogels are the principal types of these biodegradable DDSs. These formulations provide a number of advantages, including the targeted release of therapeutic substances, greater solubility and stability, higher permeability and prolonged residence duration, all of which improve the efficacy of the drugs. The therapeutic potential of biodegradable medicines in ocular therapy is currently the subject of numerous studies, both *in vitro* and *in vivo*. Despite the promise of these drug-loaded biodegradable formulations, their clinical use is constrained because of a number of issues, such as difficulties in local infusion delivery of the drugs to the inner structures of the eye, problems with stability, sterilization, low drug loading, high cost and potent excipient-induced irritation. As a result, during the past 10 years, studies in this area have exploded. These studies are aimed at addressing these problems and boosting the potential of biodegradable pharmaceuticals as a therapy option for ocular diseases.

In this review, we aim to summarize and provide an overview on evolution and contemporary applications of delivery carrier systems with specific insight on nanostructured drug carriers over the last five (5) years for effective ophthalmic drug delivery to anterior and posterior segments. Firstly, we discussed the anatomy of eye with specific emphasis on associated ocular barriers, key factors responsible for low ocular bioavailability, ophthalmic disorders and administration routes. Then, we discussed the various macro and nanotechnology based ophthalmic drug delivery approaches used in treating various ocular disease. Moreover, we also outlined here, the ophthalmic formulations that are being patented, marketed or studied in clinical trials for treating ocular diseases. Finally, in view of reports on current trends and therapeutic concepts, we highlighted the characteristic challenges faced by novel ophthalmic drug delivery systems and provided future prospective for further research in these directions. Although mostly current ophthalmic drug research is still in laboratory stage, we hope that this review will serve as a source of motivation and will provide new ideas for drug delivery researchers and pharmaceutical scientists in improving the design of innovative ophthalmic drug products.

2. Eye anatomy

Despite being one of the most easily accessible organs in the body, medication delivery to eye tissues is extremely difficult. Similar to the brain, eye is referred to as being ‘‘immune privileged” since it is part of the central nervous systems which is shielded from circulation. The extensive ocular barriers and the exact eye architecture make the eye a highly isolated organ from systemic circulation. As a result, treating ocular illnesses presents a number of challenges, particularly in the posterior portion.

The human eye, which is a complicated organ made up of delicate tissue structures grouped as closely adjacent layers. Fig. 1 indicates the anatomy of eye. Anatomically, the anterior and posterior eyes are separated by the ciliary body and lens. The tear film, cornea, pupil, iris, lens and ciliary body make up the anterior segment. Conjunctiva, sclera, choroid, retina, vitreous humor and optic nerve make up the posterior segment. Orbital glands and epithelial secretions regulate the composition and volume of tears. The cornea is the area in front of the eye where light enters and focus [49]. The iris, which is the colored part of the eye regulates how much light enters the eye. Pupil refers to the central opening in the middle of the iris. The pupil adjusts its size in response to amount of light present. The clear crystalline lens helps focus light onto the

retina. Ciliary body comprises ciliary muscles, stroma and the bilayered ciliary epithelia. Communication between the anterior and posterior segments is possible *via* ciliary body's capillaries [50]. Between the retina and the lens of the eye, there is a transparent, avascular connective tissue called vitreous humor. Collagen, hyaluronic acid, ions, and water make up 99.9% of its composition [51]. The frontal aspect of the sclera is protected by the conjunctiva, a thin transparent membrane that lines the interior of the eyelids. It is a mucous membrane made up of three layers: an exterior epithelium, a substantia propria that houses blood and lymphatic arteries as well as nerves, and a submucosa layer that is connected to the sclera [52]. The cornea continues into the sclera. Collagen and mucopolysaccharides are its main components. The circulatory layer known as the choroid is situated between the retina and the sclera. The retina is a thin layer of tissue that covers the back of the eye and is made up of neuronal and glial cells. It generates electrical impulses that are sent to the brain *via* the optic nerve [50].

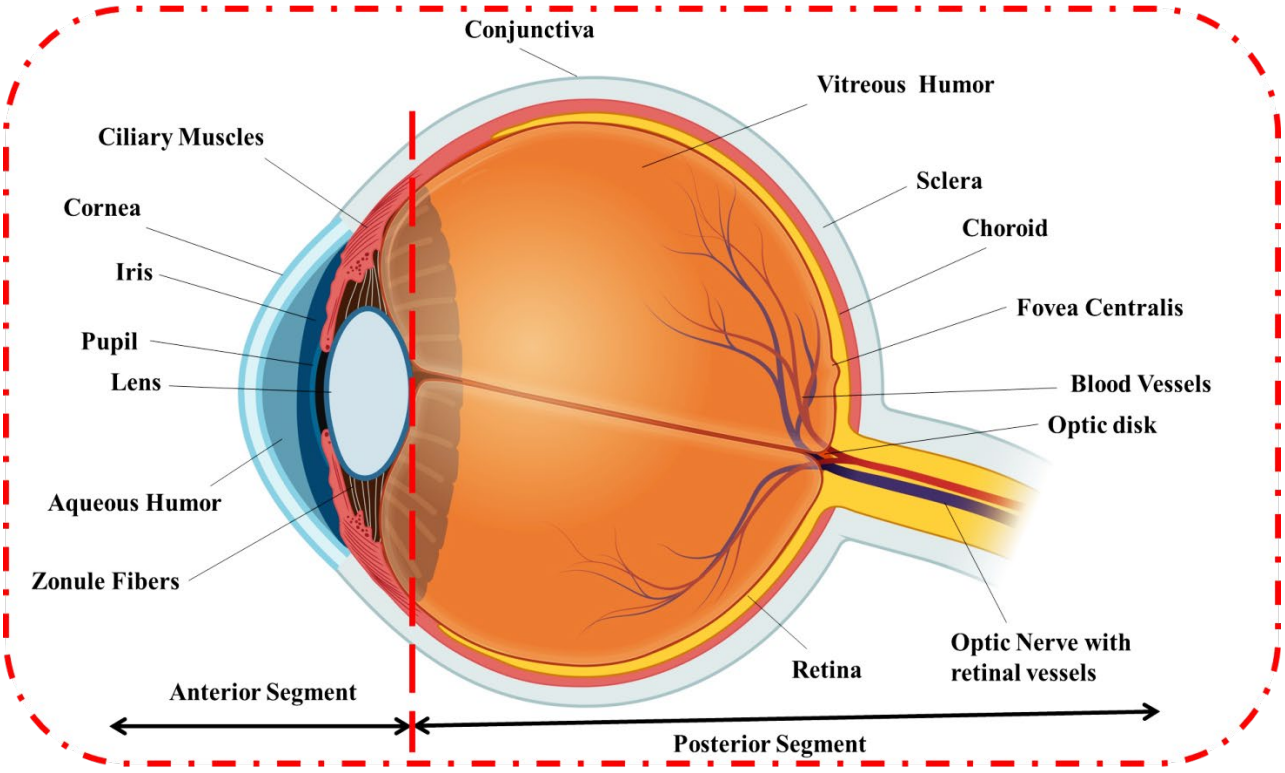


Fig. 1 The anatomy of eye. Created with Bio render.

3. Barriers affecting ocular drug delivery

The anatomy and structure of the eye are intricate but exact. However because of its distinct features, drugs administered may come across a number of barriers leading to low concentrations in the specified areas [53]. Barriers which affect delivery to eye can be divided into two segments;

3.1. Anterior segment barriers

3.1.1. Tear film

The initial permeability barrier that restricts ocular medications entry is the tear film, a precorneal film made up of three layers: an exterior thin lipid layer, a middle aqueous layer and an innermost mucous layer [54]. In terms of anatomy, the outer oil layer stops water from evaporating and lessens the absorption of drugs into the cornea and sclera [55]. Some endogenous proteins including globulin, albumin and lactoferrin can bind to and metabolize the supplied medicine in the intermediate aqueous layer reducing its bioavailability [55]. Water, mucin, lipids, salts, enzymes and other substances make up the inner layer, known as the mucus layer [56]. The mucus layer plays an important role as a barrier in drug delivery because its pore structure with negatively charged glycans and hydrophobic regions traps and adheres to foreign particulates followed by being washed by mucus turnover before reaching the corneal surface [57,58]. The mucus layer is the densest at the epithelial apex and gets more diluted as it extends outward into the tear fluid. The tear film is replaced every 5 minutes under physiological conditions by a tear flow of 1-3 µl/min [59]. The basal tear volume is about 7 µL, and this volume dramatically increases to 30 µL following topical administration resulting in an immediate drainage of excess fluid through the nasolacrimal duct and a loss of over 85% of the drug before it reaches the corneal surface. In addition, after topical administration, the increase in volume stimulates reflex tear production which dilutes the medication and facilitates its drainage into the nasolacrimal duct [60]. This ultimately results in poor bioavailability of pharmaceuticals which typically ranges from 0.1% to 5% applied topically [60,61].

3.1.2. The corneal barrier

The cornea is the most obvious mechanical and physiological barrier to substances that are both hydrophilic and hydrophobic. One of the main obstacles to the absorption of topical drugs is the cornea. It is a transparent, avascular tissue that is 500 μm thick and made up of five layers: the epithelium, Bowman's layer, stroma, Descemet's membrane and endothelium [62,63]. The rate-limiting layers for the trans-corneal penetration of medicines are the epithelium and stroma.

The exterior corneal stratified multilayer epithelium is a hydrophobic layer with tight connections between epithelial cells [64]. It serves as a barrier to the passage of drug molecules along the paracellular pathway by enclosing the intercellular space. Another factor for limited topical medication bioavailability is the presence of drug efflux pumps and drug-degrading enzymes such as cytochrome P450 in the epithelium [65]. Moreover as the corneal epithelium is physiologically negatively charged, cationic drugs bind and enter the cornea more readily than anionic ones [66]. Additionally, 90% of the thickness of the cornea is made up of the stroma, which is made up of highly structured collagen fibers whose highly hydrated structure serves as an essential barrier to the penetration of lipophilic substances [67]. Due to its selective carrier-mediated transport and secretory function, the corneal endothelium which is the innermost hexagonal cell monolayer contributes to the preservation of aqueous humor and corneal transparency [54].

3.1.3. Blood–aqueous barrier

The blood-aqueous barrier (BAB) composed of non-pigmented ciliary epithelium of the ciliary body, the endothelial cells of the iris arteries and the inner lining endothelium of the Schlemm's canal provide another barrier in anterior segment to the effective ocular drug delivery [68]. Through poorly permeable tight junctions, BAB regulates the flow of solutes between the anterior and posterior segments. Tight junctions serve as gatekeepers preventing hydrophilic medicines and plasma-derived albumin from entering the aqueous humor as well as the free transit of molecules from iris blood vessels. Therefore it is commonly thought that intravenous therapy for anterior segment illness is not practical [69]. Aqueous humor is secreted by the ciliary body which is situated behind the iris and nourishes the internal ocular structures.

Aqueous humor that has been secreted moves in the direction of the cornea, collects in the Schlemm's canal and then eventually empties into the episcleral blood vessels.

A dynamic barrier to the removal of therapeutic medicines from the ocular tissues is thus presented by aqueous humor flow. The high aqueous humor turnover (about 2-3 μL min^{-1}), further diminish the concentration of those medications [60]. Drugs come into contact with the iris and lens as they migrate gradually from the aqueous humor to the posterior segment.

Insufficient information is currently available to evaluate these constructions' barrier status. Evidence supports the expression of relevant active drug transporters in the ciliary body and iris, which further reduces drug permeation [70]. Additionally the ciliary body's melanin pigment binds to the drugs and the iris can prevent from reaching the posterior segment [71]. Regarding the lens, drug distribution is restricted in the lens by the cortex and nucleus created by intact and compact lens fibers [72].

3.2.Posterior segment barriers

3.2.1. Vitreous humor and inner limiting membrane

A clear, gel-like material called vitreous humor covers the gap between the lens and the retina [73]. The vitreous humor functions as the initial barrier to prevent drug permeability to the underlying retinal and choroidal tissues, after intravitreal administration, the most popular intraocular administration method that can produce drug concentrations in the posterior portion of the eye. The vitreous fluid's viscosity hinders the diffusion of larger, heavier therapeutic payloads like proteins but does not significantly impede the movement of smaller molecules [74]. Vitreous humor is highly hydrated three-dimensional structure with a volume of about 4 mL, mainly made up of water (99%), non-collagenous proteins, collagens, hyaluronic acid (HA), proteoglycans of chondroitin sulfate and heparan sulfate. Additionally, the vitreous humor's net anionic charge controls the diffusion of drug molecules. To be more precise, positively charged particles become trapped in the vitreous body while negatively charged particles diffuse freely [75]. Therefore, the molecular weight and charge of the injected medicine greatly affect its distribution in the vitreous and bioavailability in the retina. The inner limiting membrane (ILM), a membrane created by the footplates of the Müller glial cells, is the next structural barrier for molecular diffusion to the retina after the vitreous fluid [76]. The ILM forms a strong physical

barrier to most nanoparticles with an average pore size of 10–25 nm. However uptake and transcellular penetration *via* Müller cells may be an alternate method of entering the inner retina from the vitreous chamber [77].

3.2.2. Sclera and Bruch's choroid complex

The sclera which is eyeball's outermost layer connects the anterior and posterior regions of the eye [25]. Along with the cornea, sclera serves as significant barrier to drug transport to the eye due to its low permeability and thickness of 0.5-1 mm. The eyeball's outer shell, which is made up of a dense, hydrophilic collagenous connective tissue is composed of negatively charged proteoglycan matrix stacked and intersected with scleral collagen matrix in the inter-fibril gap [78]. The sclera's thickness appears to be important for transscleral medication transport [79]. Additionally the charge of the molecules has a significant impact on transscleral permeability. Positively charged molecules are less permeable across the sclera than negatively charged molecules, in contrast to penetration across the cornea, because the sclera's proteoglycan matrix is negatively charged which causes positively charged solutes to bind and obstruct their passage through the tissue [80].

The choroid is a prominent dynamic barrier covers most of the posterior outer portion of the eye and is situated between the sclera and the retina. It is highly vascularized and innervated, providing essential blood supply to the retina. The choroid is made up of a network of fenestrated capillaries that feed the outer retina with oxygenated blood. The choroid is made up of five layers; the choroid capillary layer, the two vascular layers, Suprachoroidal cavity and Bruch's membrane. Bruch's membrane, known as basement membrane of the retinal pigment epithelium (RPE) is a 2-4 μm thick collagenous membrane that lies between the choriocapillaris on the outside and the RPE on the inside. RPE functions as a metabolic barrier against drug permeability because it expresses a variety of enzymes (esterases, peptidases, dehydrogenases and cytochrome P450 enzymes) and efflux proteins (P-gp) [81]. Drug distribution through the transscleral route is significantly hindered by Bruch's-choroid complex than by the sclera itself. In the Bruch's choroid complex, the binding with solute particularly positively lipophilic medications creates slow-release drug depot [82]. Additionally Bruch's-choroid complex permeability with hydrophilic carboxyfluorescein and dextrans is influenced by the molecular size and exhibits an exponential decline with increasing molecular radius in bovine tissues [83].

3.2.3. Blood retinal barrier

A physiological barrier called the blood-retinal barrier (BRB) controls how proteins, ions, and water travel from the systemic circulation to the retina [84]. This barrier in the posterior part can be divided into inner and outer BRB subsets. The outer BRB is made up of tight connections between retinal pigment epithelial cells that are situated between photoreceptors and choroidal capillaries. While the inner BRB is made up of tight junctions between retinal capillary endothelial cells that preferentially protects the retina from exogenous blood-borne chemicals especially macromolecules and hydrophilic compounds [54]. Due to the features of the retinal microvascular endothelium, such as its lack of fenestrations and the expression of specialized intercellular junction proteins, the intercellular junctions of the retinal microvasculature are strong structural barriers against molecular diffusion to and from the retina [85]. Only 1% to 2% of drug administered can reach the retina and vitreous region due to the outer BRB [85]. Fig. 2 refers to various ophthalmic barriers to drug delivery.

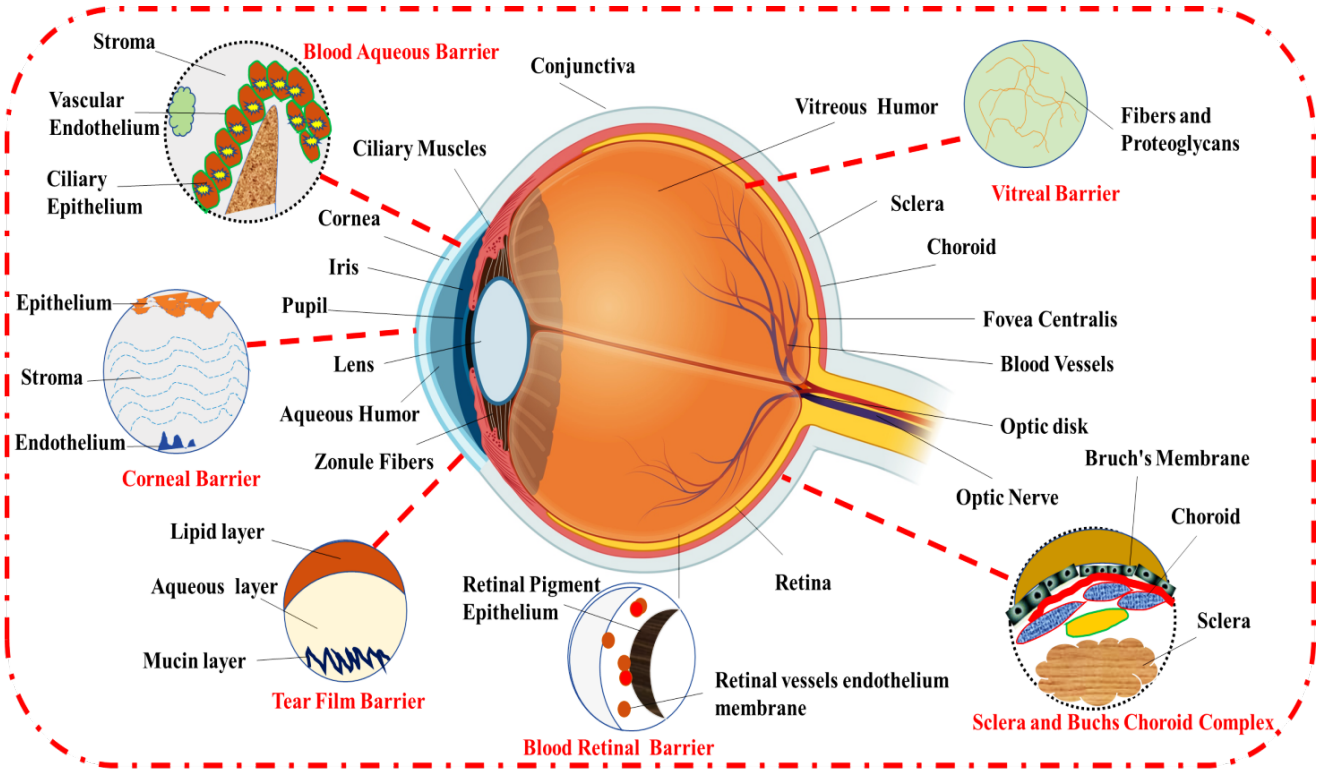


Fig. 2 Various ophthalmic barriers most notably precorneal barrier such as tear film and others including corneal barrier, BRB, sclera and Buchs choroid complex, BAB etc to effective drug delivery. Designed with Bio render.

4. Ophthalmic diseases

4.1.Glaucoma

Glaucoma is a chronic progressive optic neuropathy marked by irreversible degeneration of retinal ganglion cells (RGCs) and their axons, resulting in loss of peripheral and eventually central vision in advanced stage.

Glaucoma, a progressive vision loss eye disease is the world's second largest cause of blindness after cataracts [86]. The number of glaucoma sufferers is expected to rise to 111.8 million by 2040 [87]. In the early stage, it is usually asymptomatic and progresses gradually to irreversible blindness in the later stages. It causes blindness due to the progressive degeneration of the optic nerve axon and the death of RGCs [88]. It is frequently associated with increased intraocular pressure (IOP) mediated primarily by the impeded drainage of the aqueous humor [89]. Age, race, diabetes, heredity, nearsightedness, migraine and retinal vascular caliber are all risk factors for glaucoma. Glaucoma is classified into two types: open angle glaucoma (OAG) and angle closure glaucoma (ACG). OAG is usually accompanied by wide open angle, TM/SL should be visible, while for ACG, the AC is usually very narrow, sometimes it is obstructed because of synechia [88]. Glaucoma is more prevalent in women, accounting for 55% of open angle glaucoma, 70% of angle closure glaucoma and 59% of all kinds of glaucoma in 2010 [94]. The level of IOP is primarily determined by the production and drainage of aqueous humor secretion Aqueous humor contains numerous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. As a result of aging, their level decreases which may lead to higher IOP. Changes in the balance of oxidants and antioxidants influence the course of glaucoma [90]. Although glaucoma is a complex condition, current therapy focuses mostly on reducing IOP in order to slow or delay further vision loss [91]. Prostaglandin analogues, beta blockers, alpha-agonists, carbonic anhydrase inhibitors and parasympathomimetics are examples of conventional medications that work by lowering aqueous humor production or facilitating aqueous humor drainage [92]. Recently, cell softening therapy has brought forward two new effective medicines, rhokinase inhibitors and actin depolymerizers to enhance fluid drainage by treating dysfunction of pressure-regulating outflow structures.

4.2.Cataract

Cataract is the leading cause of eyesight loss worldwide. Cataract complications account for 40-60% of blindness worldwide [93]. Cataract is described as the formation of cloudiness/opacification in the crystalline lens. According to the National Programme for Control of Blindness and Visual Impairment, cataract is the leading cause of avoidable blindness in India (62.6%) [94]. UV radiation exposure, diabetes, poor nutrition, genetic determinism and smoking are all risk factors. Cataracts are classified into three types: cortical, nuclear and posterior subcapsular. Crystalline protein regulates the clarity and transparency of the lens [95]. Cataracts are primarily induced by glycation, oxidative stress and exposure to lipophilic chemicals which cause an increase in calcium levels in the lens as well as crystalline buildup. Hyperglycemia and hydroxyl radicals cause oxidative damage. Cataract can also be triggered by mutations in crystalline and its related genes. Surgical removal of opaque lenses is now the treatment of choice. However prophylactic anti-cataract therapy may reduce the need for surgical treatment. Anti-cataract compounds are multifunctional antioxidants that can combat free radicals [95]. Supplements that may slow down cataract formation/progression are also used as an anti-cataract agents [96].

4.3.Age related macular degeneration (AMD)

AMD is the third leading cause of severe permanent vision loss worldwide and it is more common in people over the age of 50. AMD is responsible for around 8.7% of all blindness worldwide [97]. AMD affected almost 196 million people in 2020 and the figure is anticipated to rise to 288 million by 2040 [98]. It is a multifactorial degenerative condition affecting the eye's posterior region. Aging, smoking, poor diet, high blood pressure and immobility are all risk factors. It is clinically classified as either early or late AMD. Early AMD clinical signs include changes in retinal pigmentation [99]. Late AMD is classified as dry (atropic or non-exudative) or wet (neovascular or emulative). The major feature of AMD is irregular angiogenesis (the formation of new blood vessels) in the retinal pigment epithelium, formation of drusen (yellow deposits under the retina), atrophy and Bruch’s membrane separation [100]. Many cellular growth factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), and epithelial growth factor (EGF) are elevated during angiogenesis due to abnormalities in associated metabolic processes. There is currently no cure for AMD, however effective

treatments may slow rate of progression [99]. High zinc and antioxidant vitamin supplementation can decrease disease progression from the early to late stages [101]. Juxtascleral injections of anecortave cortisone exhibited extended release in the choroid and retina for 6 months in a new strategy to AMD treatment [102]. In a novel approach to AMD treatment, juxtascleral injections of anecortave cortisone displayed prolonged release in the choroid and retina for 6 months [102]. Intravitreal injections of anti-vascular endothelial growth factors (VEGF) such as bevacizumab and aflibercept, successfully treat neovascular AMD; however, they remain invasive [103].

4.4.Conjunctivitis

A common ocular surface condition known as conjunctivitis, which is characterized by conjunctival inflammation can be brought on by either infectious or non-infectious agents, including allergens, toxins, immune-mediated processes and neoplastic processes. Non-infectious conjunctivitis is caused by allergens and irritants whereas infectious conjunctivitis is caused by microbial infection. All ages, races and genders are impacted [104]. Conjunctivitis symptoms include eye redness, irritation, tears and increased secretions. Nearly 40% of people worldwide have allergic conjunctivitis [105]. Topical administration of antibiotic (infectious) or anti-inflammatory (non-infectious) medicines i the mainstay for treatment.

4.5.Diabetic retinopathy (DR)

A chronic consequence of diabetes, diabetic retinopathy is the main factor in blindness and visual loss worldwide [106]. When retinal detachment occurs, it may cause blurred vision, floaters in the eyes, distorted vision and even loss of eyesight in some cases [107]. This specific vascular problem is associated with both types of diabetes mellitus. After 20 years of diabetes, retinopathy affects around 60% of type II individuals and 100% of type I patients. The development of DR is mediated by the elevated levels of proinflammatory mediators resulting from hyperglycemic condition, which lead to oxidative stress and inflammation. In USA, it is the third main cause of blindness. If diabetes mellitus is detected and treated early, along with proper management of blood pressure and blood glaucoma level, DR can be preventable [108]. Both of its proliferative and non-proliferative types of DR ultimately cause the retina's cells to deteriorate over time. Nowadays, vitrectomy, laser photocoagulation and pharmaceutical therapies are used to treat DR. Clinically, retinal circulation can be improved with laser treatment if it is

administered in a timely manner, preventing vitreous hemorrhage and retinal neovascularization. Laser photocoagulation prevents blindness by sealing the blood vessels that are leaking, however also leaves a laser scar. A vitrectomy is a surgical treatment to remove the vitreous gel and blood from leaky capillaries in the back of the eye, however this only offers temporary relief and does not stop additional leakage of blood [90]. Intravitreal injection of corticosteroid is one type of pharmaceutical therapy used to alleviate macula edema. Sustained release corticosteroids that block inflammatory pathways are also implanted. The use of anti-VEGF medications (Ranibizumab and Aflibercept) in contemporary care reduces blood loss and edema by stopping the expression of VEGF [109]. Novel drug delivery techniques are necessary to offer alternative approaches for the treatment of DR because of the limited bioavailability of medications, potential side effects and inherent risks associated with surgical intervention.

4.6.Fungal keratitis (FK)

Keratitis is an inflammation of the cornea. Since a healthy cornea would not permit any fungal infection, fungal keratitis only develops in corneas that have undergone trauma. Without appropriate and quick treatment, keratitis may result in corneal opacity, conjunctival scarring, and even eyeball atrophy. Candida albicans, Candida glabrata, Candida tropicalis, Candida krusei and Candida parapsilosis are only a few of the fungi that can cause keratitis [110]. Based on the etiological cause, keratitis can be categorized as infectious or non-infectious with bacterial, protozoal (Acanthamoeba), fungal and viral keratitis being the subcategories of the infectious form [111]. In third-world developing nations, 40% of infectious keratitis is caused by fungi. Ocular (trauma, contact lenses, previous corneal surgery and topical corticosteroids) or systemic (diabetes, HIV positive and leprosy) risk factors are both possible. Fungal keratitis causes corneal ulceration, stromal inflammatory infiltration and poor wound healing [112]. Fungal keratitis is treated with oral or topically applied antifungal medications. When medications are ineffective, corneal surgery may be necessary. Even after surgery, vision may not always be recovered in certain circumstances. At the moment, the first-line regimens essentially consist of using antibiotic eye drops topically. However the limited antimicrobial activities of broad-spectrum antibiotics, drug resistance, time consuming laboratory tests to screen the sensitive antibiotics and low bioavailability of eye drops all work against the

therapeutic effectiveness of conventional antibiotic eye drops-based pathogen eradication regimens [113].

4.7. Dry eye disease (DED)

Dry keratoconjunctivitis, also known as dry eye disease is a multifactorial ocular surface condition that is characterized by an imbalance of tear film homeostasis, persistent cycle of ocular surface inflammation, tear film instability and hyperosmolarity ultimately resulting in damage to the ocular surface [114,115]. According to 2017 statistics [116,117] the morbidity of DED which affects about 350 million people worldwide and has an estimated global prevalence of 5–50%. DED is currently on the rise due to the increased use of electronic devices, the aggravation of environmental pollution and the wearing rate of contact lenses. Ocular irritability, pain, soreness, foreign body sensation and impaired vision are among the symptoms of DED. The DED significantly impact patients' quality of life, potentially leading to psychological depression which places a heavy financial burden on society [118,119]. However the pathophysiology of DED is still not completely understood. The majority of research points to inflammation as the primary etiology [120]. The inflammatory response in DED consists of a rapid but broad innate immune response and a slower but more targeted adaptive immune responses [121]. Restoring tear film equilibrium and ending the DED vicious cycle are the major objectives of treatment for DED. For the treatment of DED, common treatments include topical secretagogues, corticosteroids, immunosuppressants and artificial tears. However, these treatments have drawbacks, such as undesirable side effects, ocular discomfort, poor patient compliance, cataract and glaucoma [122]. It is crucial to use novel medication delivery techniques to get over ocular obstacles and increase drug absorption.

4.8.Uveitis

Inflammation may impact the uveal tract, which includes the iris, ciliary body and choroid. Uveitis is the term used to describe inflammation of the papilla, retina and uvea [123]. Uveitis is the fifth or sixth most common cause of blindness worldwide and significant contributor to visual impairment, accounting for 10-15% of blindness in affluent nations [124,125] Uveitis typically affects younger people than other vision threatening disorders like cataracts and AMD, as 60-80% of patients are between 20 and 50 years old [126]. Visual impairment at a young age has a stronger influence on life quality and can result in long-term disability. Uveitis can be

further divided into anterior, middle, posterior, and panuveitis depending on where the predominant location of inflammation occurs [127]. Currently, the first-line therapeutic treatment for uveitis is still the topical and systemic administration of corticosteroids (dexamethasone, triamcinolone acetonide, etc.).

The severe adverse effects of corticosteroids on the target organs should not be overlooked. Topical ophthalmic treatments such as eye drops, suspensions, gels, and ointments are still constrained by poor patient compliance and inadequate bioavailability. Despite that, topical treatment is still widely used because it is noninvasive, simple to administer and affordable. Therefore, improving delivery techniques to increase bioavailability and decrease injection frequency is essential for treating uveitis [128].

4.9. Eye tumor

Numerous malignancies, which typically spread from other regions of the body can develop in the eye [129, 130]. Retinoblastoma (RB) and uveal melanoma (UM) are two prevalent intraocular primary tumor forms [131] that we shall exclusively describe here. RB is an aggressive ocular tumor that can develop in young children and newborns. It occurs in 1/15,000 to 1/20,000 live births globally. Both genders are affected. This is primarily caused by a mutation in the retinoblastoma protein-coding tumor suppressor gene RB1. Either unilateral (60%) or bilateral (40%) cases are possible. Loss of vision, subsequent monocular tumors and even death are among the potential outcomes for RB [132]. Despite some progress in RB management with current chemotherapy has made, there are still significant drawbacks such as insufficient pharmacokinetic characteristics, multidrug resistance, poor therapeutic effectiveness, nonspecific targeting and the requirement for adjuvant therapy [133].

The most common primary intraocular cancer is uveal melanoma (UM). The tumor metastasizes in around 50% of UM cases which ultimately results in the patient's death [134]. There is still a need for efficient treatments despite decades of progress in the diagnosis and local treatment of UM.

Treating approaches mainly used for retinoblastoma include surgery, systemic chemotherapy, cryotherapy and radiotherapy. According to recent research, the formation of angiogenic blood

vessels and the release of compensatory proangiogenic factors are crucial stages in the treatment of retinoblastoma [135].

4.10. Endophthalmitis

Endophthalmitis is a serious bacterial or fungal vitreous and/or aqueous infection that can impair vision permanently in the affected eye. Intravitreal antibiotic injections are the primary form of treatment, while vitrectomy (surgical debridement of the vitreous) may be advantageous in some circumstances [136]. In addition, silicone oil, intravitreal steroids, systemic and topical antibiotics are efficient supplementary therapy [137]. In order to achieve an efficient therapeutic concentration of antibiotics in the eye, frequent intravitreal delivery is required. However the intravitreal injection may cause subconjunctival bleeding, corneal abrasion, traumatic cataracts, retinal detachment etc. Additionally, several of the most prevalent pathogenic organisms can create biofilms which can significantly hinder the effectiveness of intravitreal antibiotics [138]. Various alternative delivery carriers need to be created and made in order to increase drug bioavailability and decrease the frequency of administration.

4.11. Inherited retinal disease

Retinitis pigmentosa (RP), Stargardt disease and Leber congenital amaurosis (LCA) are only few examples of the inherited retinal diseases (IRD), which account for a significant share of blindness globally. They are often brought on by changes in the genes that express the proteins necessary for the survival, growth and survival of retinal cells [139].

About 2.5 million people worldwide suffer with inherited retinopathy or RP. Nearly 70 genes and more than 3,000 genetic mutations have connections [140]. It is characterized by bone spicules (pigmented deposits) that are brought on by the loss of photoreceptors. Patients may have nyctalopia at first, followed by a progressive loss of peripheral vision and finally tunnel vision [141].

The prevalence of Stargardt disease which is characterized by central vision loss is 1: 6,000-7,000 worldwide [142, 143]. The buildup of lipofuscin and bisretinoid substances within the RPE cell layer is the fundus expression of Stargardt disease. One of those deposits, A2E, is a major component of lipofuscin and the buildup of A2E is a widely recognized sign of the course of

Stargardt disease [144]. All cases of Stargardt disease are linked to ABCA4, an ATP-binding cassette transporter that is essential for removing excess all trans-retinal and 11-cis-retinal from photoreceptor cells and preventing the buildup of hazardous retinoid compounds [140].

The prevalence of LCA, a rare genetic retinopathy is 1:80,000 people globally. As a result of gene mutation, LCA is characterized by severe and early vision loss, sensory nystagmus, amaurotic pupils and missing electrical signals on electroretinograms (ERG) [145]. RPE65 is the most representative of these pathogenic genes and is implicated in 6% of all LCA cases [143].

No pharmacological medications have been implemented into clinical practice to stop the progression of RP, Stargardt disease and LCA, despite the fact that a number of therapeutic options including drug discovery and gene therapy are being considered. The majority of efforts have been focused on neuroprotection as a means of reducing the disease's course [146]. There have been numerous attempts to close the gap between the enormous number of unmet medical demands and the ineffectiveness of traditional medications.

4.12. Optic neuropathy (ON)

Glaucoma, ischemic optic neuropathy (ION) and trauma to the posterior segment are the three main causes of RGC injury, a prevalent acute optic neuropathy in the elderly. ION is defined as all optic neuropathy brought on by ischemia, with an annual incidence estimated at 2.3 to 10.2 cases per 100,000 people aged 50 or older [147]. Traumatic optic neuropathy (TON) is a condition that is frequently brought on by falls, car accidents and assaults. Depending on the circumstances, TON may result from a sharp trauma (direct injury) that directly damages the optic nerve or from transmitted forces after a concussive blow to the head or orbit (indirect injury). Indirect TON is the most prevalent type of TON and affects 2.3% of all patients who have head trauma [148]. Neurotrophic factors, growth factors, antioxidants and anti-inflammatory drugs are the primary types of pharmaceutical medications [149]. As discussed in the "Glaucoma" section, the primary treatment for glaucoma is to lower IOP, which serves as a highly effective neuroprotectant. However, because there is normal tension glaucoma and an unmet need for optic nerve protection, supplemental neuroprotective therapy has gained a lot of interest. As a result, numerous medications, including neurotrophic factors and memantine are being researched [150]. Corticosteroids are the main clinical treatment for ION, which can

enhance visual functions [148]. Erythropoietin (EPO), corticosteroids and levodopa plus carbidopa [151] have all been used to treat TON. However, their therapeutic benefits are constrained by the ineffectiveness of retinal administration, short half-life and poor absorption etc.

5. Ocular drug delivery administration routes

The key to treating eye illnesses is effective medication concentration at the site of the lesion. To bypass the current ocular obstacles and achieve effective medication concentration in target positions accordingly, several administration methods such as systemic, topical, intraocular and periocular administration have been created. Table 1 indicates some of the examples of ophthalmic drug products administered *via* various routes to eye with their expected reported outcomes.

5.1.Topical administration

Since topical treatment is a non-invasive administration approach, it is still the recommended option for treating ocular problems. More than 90% of the ophthalmic products available today fall within this category [152]. However, due to limited corneal penetration and brief residence duration, there is minimal bioavailability (1%). Due to the rapid tear turnover rate, blinking, lacrimation and nasolacrimal drainage, pre-corneal drug loss is still the main problem for topical administration. The frequent and high dose concentration required for topical application could have negative side effects. Additionally frequent dosage may affect a patient's compliance [153]. Patients who are disabled or elderly should avoid using the topical route [154]. Due to the obstinate presence of the anatomical corneal barrier, topical treatment is also less successful for treating posterior eye problems even with repeated dosing [46]. Moreover, it's important to consider the impact of side effects like ocular irritation, steroid-related problems and preservative degradation [155].

5.2. Systemic administration

Drug delivery into the ocular tissues by systemic administration such as intravenous and oral dosage is still very difficult for the 3 major reasons. First, drugs taken orally must first endure the abrasive conditions of the gastrointestinal system and first-pass metabolism. Second, there is

significantly less drug buildup in the eye since it has a much smaller blood supply than the rest of the body. Last and more importantly, the BAB limits the access of medicines' to the target tissues. As previously indicated BAB limits the entry of drugs from the systemic circulation into the eye's anterior region, while both inner and outer BRB permit highly restricted drug entry to posterior segment of the eye [156,157]. As a result, in order to obtain the intended therapeutic efficacy, a large dose and frequent drug administration are necessary which may lead to systemic side effects and poor patient compliance.

5.3. Intraocular administrations

Intraocular administrations can be made mainly *via* the following routes;

5.3.1. Intracameral injections

Intracameral injections include injecting an antibiotic directly into the anterior part of the eyeball. It is typically done after cataract surgery to prevent endophthalmitis brought on by an eye infection that can happen after cataract surgery. The use of hydrogel functionalized with vinyl sulfone and thiol groups in intracameral injection for the treatment of glaucoma was recently described [158].

5.3.2. Intravitreal injections/implants

A medication injection into the vitreous, which is near the retina at the back of the eye, is known as an intravitreal injection. A single intravitreal injection of vitamin E/poly-lactic-co-glycolic acid microspheres containing glial cell line-derived neurotrophic factor is part of a novel glaucoma treatment strategy. For six months, this strategy offered a lasting release. Similar outcomes were attained after polymer-free dexamethasone dimer implants were injected intravitreally [159]. For treating diabetic macular edema and neovascular age-related macular degeneration, intravitreal injection of the biodegradable Rho kinase and protein kinase C inhibitor displayed extended release for about 6 months [160].

5.3.3. Juxtascleral injections

When topical treatment is ineffective for treating some posterior segment disorders, juxtascleral injections are employed. Trauma, diabetic-related diseases and cystoid macula edema are all

treated *via* this route. Juxtascleral injections of anecortave cortisone that exhibited extended release for 6 months in the choroid and retina are one new method for treating AMD [161].

5.3.4. Retrobulbar injection

The retrobulbar method entails injecting a needle through the eyelid and orbital fascia to deliver the drug into the retrobulbar space, which is located behind the globe. Amphotericin B administered retrobulbarly shown greater antifungal activity than administered intravenously [162]. Chlorpromazine is injected retrobulbarly to treat painful, blind eyes [163]. Triamcinolone is injected retrobulbarly to treat macular edema brought on by retinal vein blockage [164].

5.3.5. Subconjunctival injection

When topical drug treatment results in relatively little drug penetration into the anterior segment of the eye, subconjunctival injection is routinely employed. For the treatment of uveitis, subconjunctival injections of steroids made as PEGylated liposomes demonstrated prolonged anti-inflammatory effect and targeted the necessary ocular tissue for at least one month [165]. Subconjunctival injection of brinzolamide in PLGA nanoparticle form demonstrated good management of IOP for 10 days [166]. In mice with graft versus host disease, subconjunctival injection of human mesenchymal stromal cells provided significant reduction in corneal inflammation and squamous metaplasia [167].

5.3.6. Periocular administrations

Due to the ability of injecting higher quantities (up to 1 mL as opposed to 100 µL intravitreally), periocular administrations can have longer duration of effect than intravitreal injections [168]. However, there is a relatively low risk of ocular pain, infection, endophthalmitis or hemorrhage. The most typical periocular administration, subconjunctival injection is used in clinical practice to give pharmaceuticals such as local anesthetics and anti-inflammatory agents to the anterior part of the eye. It is inserted between the bulbar conjunctiva and sclera. However due to their considerable absorption by the lymphatic and blood circulation systems rather than intraocular distribution, subconjunctival drugs frequently have a limited bioavailability. Therefore multiple injections are required, which pose operational risks such as subconjunctival hemorrhage and conjunctival edema [169]. The remainder of the periocular administrations, such as the sub-

tenon, retrobulbar, peribulbar and posterior juxtascleral administrations are mostly utilized for anesthetic during ocular surgery. Fig. 3 refers to scheme of approaches in ocular drug administration using various routes for effective drug delivery.

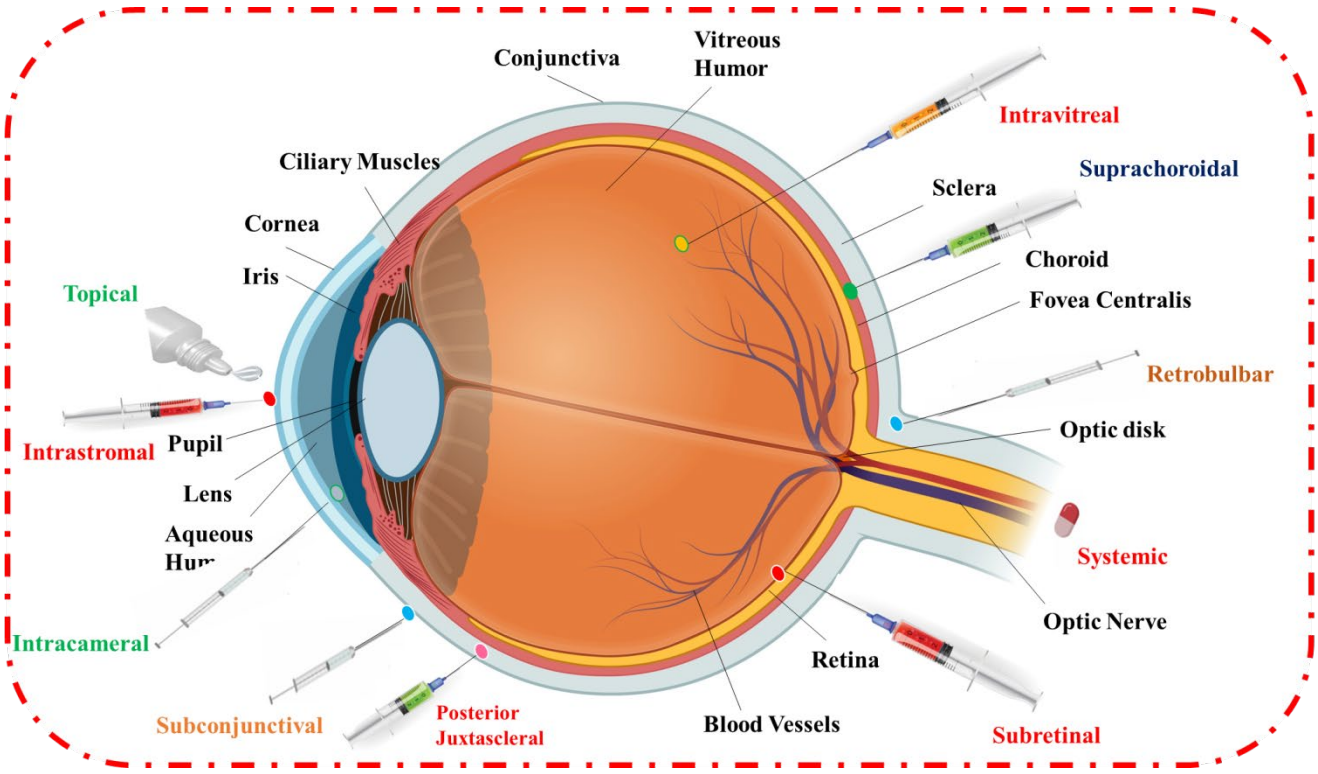


Fig. 3 Scheme of drug delivery approaches in ophthalmic drug administration using various routes for enhanced bioavailability and therapeutic effect. Created with Bio render.

Table 1 Examples of various pharmaceutical agents with their route of administration and expected outcome in different ophthalmic diseases

Administration Route	Model Drug	Target Outcome	References
Topical	Dexamethasone	Improved retention time and extended release	[170]
Topical	Fluconazole	Highest drug entrapment, permeation, and activity	[171]
Topical	Posaconazole	Improved and prolonged antifungal activity	[172]
Topical	Sertaconazole nitrate	Improved corneal uptake and retention	[173]
Topical	Dorzolamide hydrochloride	controlled *ex-vivo* permeation, increased stability and improved bioavailability	[174]
Topical	Ketoconazole	High corneal permeation, prolonged ocular retention and bioavailability	[175]
Topical	Agomelatine	Prolonged drug retention and sustained drug effect	[176]
Topical	Hesperetin	Highest permeation and bioavailability	[177]
Topical	Rifampicin	Improved stability and	[178]

		higher antimicrobial activity	
Topical	Coenzyme Q10	Prolonged effect and improved efficacy	[179]
Topical	Cyclosporine	Improved drug retention, permeation, and effect	[180]
Topical	Voriconazole	Increased bioavailability, stability and duration of action	[181,182]
Topical	Terconazole	Enhanced drug retention, permeation and safety	[183]
Topical	Gatifloxacin	Improved safety, permeation, and effect	[184]
Intravitreal injections	Vancomycin	Prolonged drug retention and sustained release	[185]
Intravitreal injections	Rho kinase and protein kinase C inhibitor	Extended release for 6 months	[160]
Intravitreal injections	Dexamethasone	Extended release for 6 months	[160]
Intravitreal injections	Methotrexate	Reduced intraocular inflammation, pain and macular edema	[186]
Retrobulbar injection	Amphotericin B	Enhanced antifungal efficacy	[162]
Retrobulbar injection	Triamcinolone	Treating macular edema resulted from	[164]

		branch retinal vein occlusion	
Retrobulbar injection	Chlorpromazine	Treating blind inflamed eyes	[163]
Juxtascleral injections	Adeno-associated viruses	retinal gene treatment	[187]
Juxtascleral injections	Anecortave cortisone	Extended release for 6 months	[161]
Juxtascleral injections	Anti-VEGF	Depot formation on the episcleral surface for treatment of macular degeneration and diabetic retinopathy	[188]
Subconjunctival injection	Dorzolamide	Prolonged reduction in IOP for 35 days	[189]
Subconjunctival injection	Steroids	Sustained anti-inflammatory effect	[165]
Subconjunctival injection	Human mesenchymal stromal cells	lowering in corneal inflammation and squamous metaplasia	[167]
Subconjunctival injection	Brinzolamide	Successful IOP management for 10 days	[166]

6. Innovative ocular drug delivery approaches

To overcome ophthalmic drug delivery barriers and increase drug bioavailability in eye vicinity, various novel drug delivery systems and carriers have been designed and used. This section highlights various drug delivery carriers reported in last 5 years for effective ophthalmic

delivery. Fig. 4 refers to the general illustration of different drug delivery carriers used in ophthalmic drug delivery.

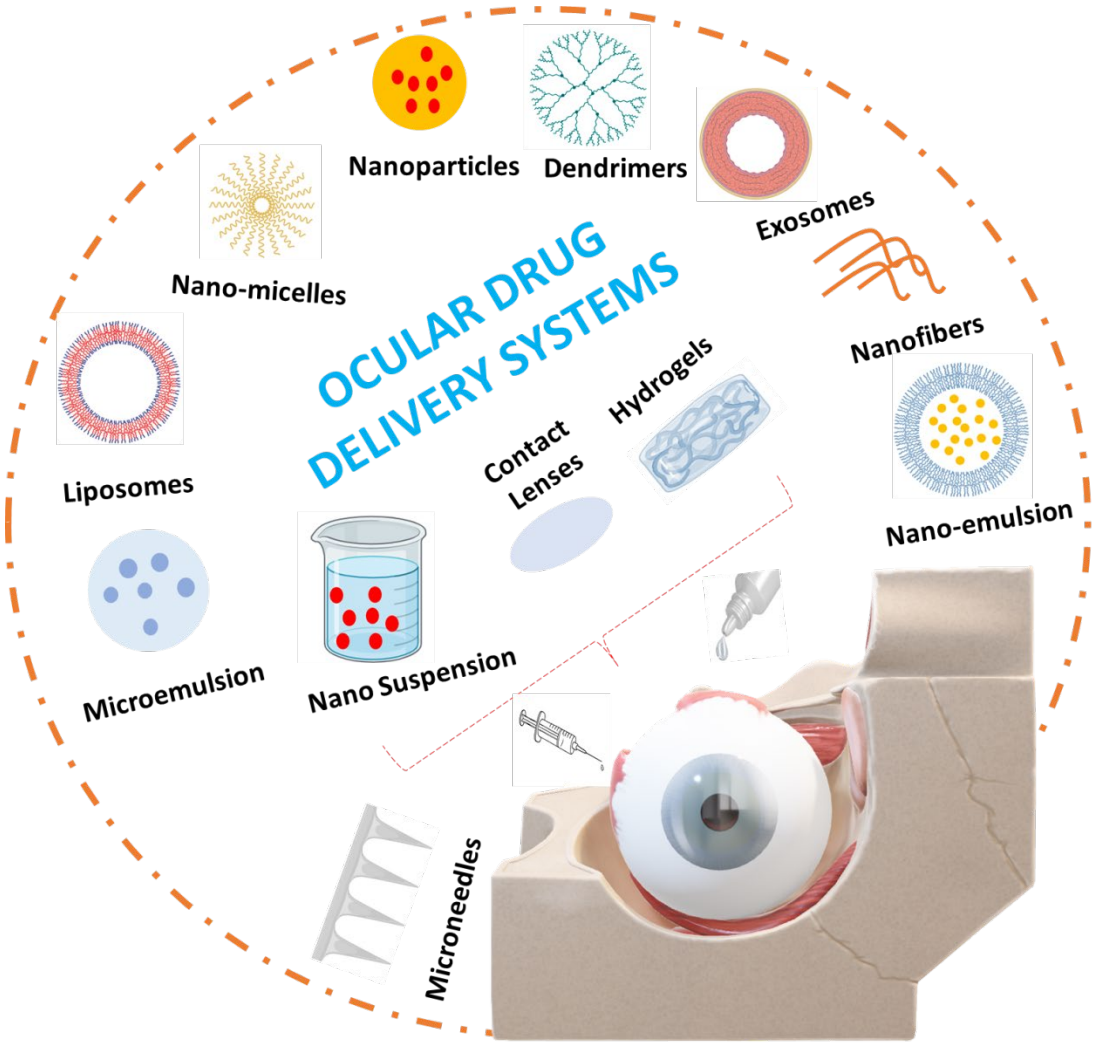


Fig. 4 General illustration of various drug delivery carriers for effective ocular drug delivery. Designed with MS Power point.

6.1. *In situ* hydrogels

Hydrogels due to their high water contents capacity and mechanical qualities and that imitate the extracellular matrix and soft tissues offer potential applications in drug delivery and tissue engineering [190]. Hydrogels can be tailored to resemble biological matrices owing to possession of some known characteristics such as high hydrophilicity, high hydration and closely

matched mechanical properties [191]. These characteristics of hydrogels allow to protect the physicochemical properties of biological drug for extended time period. Additionally, when present in the vitreous humor some ocular medications notably biologics, demonstrate low stability and/or a short half-life. Drug stability and release time can both be increased by encasing these biologics in hydrogels. Hydrogels can combine different medications into a single platform, streamlining the treatment routine and enhancing patient compliance which may be necessary for some eye illnesses such as retinal diseases. Due to its synergistic benefits, combination therapy has become a key tactic for improving therapeutic outcomes.

In situ gel is a unique method for delivering drugs to the eye that are initially in solution form before being administered then transform into gel form and released the loaded drug when exposed to external stimuli like pH, temperature etc [192].

This establishes bioadhesive network which extend medication retention and enabling sustained release and alternatively decreases the need for frequent dosage and boosts patient adherence. For the treatment of ocular illnesses*, in situ* gel systems have been shown to be successful as a vehicle for the delivery of drug-containing nanoparticles (NPs), nanosuspensions (NSs), nanoemulsions (NEs) and liposomes using a variety of administration methods [192]. A number of mechanisms, including physical change in biomaterials like an exchange of solvent and cross-linking between solvent/swelling are involved in the conversion of the solution to *in situ* gel. This trigger is brought on by physiological factors such body temperature, chemical interactions, and the pH of body fluids.

The use of combined treatment approach of hydrogels and nanotechnology has substantially increased in treating eye illnesses [193]. To further extend the retention duration of medications on the ocular surface and increase their bioavailability, several nanoformulations, including NPs, nanomicelles, microneedles (MNs) and nanofibers have been combined to construct composite systems [194].

Fang *et al*, combined Soluplus micelles with cyclodextrin solutions to create polypseudorotaxane hydrogel for the treatment of anterior uveitis [195]. The hydrogel in comparison to drug solutions in the endotoxin-induced rabbit uveitis model showed better results in terms of drug retention ability, corneal permeability, intraocular bioavailability and anti-inflammatory activity.

The results showed that hydrogels made of Ɣ-cyclodextrins have a great deal of potential for treating anterior uveitis. Jung *et al*, created an *in situ* formed hydrogel based on hyaluronic acid cross-linked to poly (ethylene glycol) diacrylate containing Bev which was gradually released following Bev injection. The Bev-hyaluronic acid *in-situ* hydrogel delivered Bev for more than 6 months was well tolerated in the rabbit eye and can be employed to treat posterior ocular disorders [196]. Gao *et al*, have created an injectable antibody-loaded supramolecular nanofiber hydrogel by combining betamethasone phosphate with $CaCl_2$ and anti-VEGF for treatment of AMD. This betamethasone phosphate-based hydrogel can decrease CNV for prolonged time by releasing anti-VEGF to prevent retinal vascular development and eliminate ROS to lessen local inflammation. Notably, anti-VEGF in hydrogel can last longer as compared to standard administration and can be administered less frequently which will increase patient compliance [197]. Overall, pre-clinical research using rabbit eye models has demonstrated that anti-VEGF-loaded hydrogel is well biocompatible following intravitreal injection and has sustained release qualities. To enhance *in vivo* dispersion across the vitreous and delivery to retinal cells, an injectable hydrogel filled with retinal-targeted biodegradable hybrid NPs with a hyaluronic acid coating has been designed by Ottonelli *et al*, By utilizing both the targeting capability and protective impact of NPs while delaying their release, it has been demonstrated to significantly improve the administration of sensitive therapeutic compounds to the retina [198]. An aflibercept loaded microsphere and hydrogel combination method was shown by Kim *et al*, to be a successful treatment for up to 6 months post-injection in a laser-induced CNV model in nonhuman primate models [199].

A biodegradable microparticles and nanoparticle-hydrogel DDS was recently created to achieve the simultaneous release of dexamethasone and aflibercept by Rudeen *et al*. Dexamethasone and aflibercept can be released simultaneously for up to six months *via* Combo-DDS. For patients with wet AMD, this may obviate the requirement for separate anti-VEGF and corticosteroid treatment regimens [200]. While hydrogels have a number of benefits as DDSs for the ocular posterior segment, further study is still required to improve their efficacy and guarantee long-term stability. However hydrogels have significant potential for delivering medicines to these important ocular regions, which could revolutionize the way that retinal and posterior segment diseases are treated.

In summary, the use of hydrogels in conjunction with nanotechnology broadens the scope of biological applications and creates new avenues for ocular medication administration.

6.2. Ocular Implants

Intraocular/intravitreal implants are relatively recent routes of administration intended to be implanted into the eye to provide a sustained release mechanism of the medication in the vitreous and to offer a long-term therapeutic impact in a monitored and regulated manner. They do not require repeated intravitreal injections and can bypass the BRB, avoid burst release, reduce the dose and administer medicines at a consistent pace directly to the ocular site. These implants improve patient compliance while also having longer half-life and lower peak plasma level [201,202]. Drug release from implants occurs in three phases—an initial burst, a middle diffusive phase and a final burst. Non-biodegradables and biodegradables are the two main types of materials employed in the development of these implants.

Scleral, intra-scleral (disc) and intravitreal implants (encapsulated cells) are examples of non-biodegradable implants (NBI) that do not undergo structural modifications and require two surgical procedures—one for insertion and another for removal or replacement. Because of their bigger size, they need a bigger incision to be implanted. They are constructed of polyvinyl alcohol, polysulfone capillary fiber or ethylene vinyl acetate (EVA) respectively.

Injectable microparticles, intravitreal implants (injectable rods), intra and epi-scleral implants (discs) and scleral implants (plugs) are among other biodegradable implants (BI) which deteriorate and fall apart over time. Only one surgical procedure is required for insertion because every implant component is eliminated on its own in BI [202]. They are created from polycaprolactones, polyglycolic acid, polylactic acid or polyglycolic acid (PGA).

Till now, Food and Drug Administration (FDA) has only approved intraocular implants as a means of delivering small molecular medications to the retina intravitreally for sustained release.

Regarding the current NBIs, the initial insert Vitrasert® (Bausch and Lomb, Rochester, NY, USA) was developed and authorized in 1996 using ganciclovir to treat CMV retinitis. It has been shown to minimize recurrences in patients with viral retinitis, regulate inflammation, and enhance visual acuity [203]. The FDA approved Retisert (Bausch & Lomb, Rochester, NY,

USA) in 2005 for the treatment of chronic non-infectious uveitis. It is an intravitreal NBI of the corticosteroid fluocinolone acetonide. Chronic noninfectious posterior uveitis (NIPU) is one of the principal indications for this insert, but it has also been proven beneficial in treating DME and macular edema (ME) brought on by central retinal vein occlusion (RVO) [204,205]. Yutiq (EyePoint Pharmaceuticals, Inc., MA, USA) is another intravitreal NBI of FA that was approved by the FDA in 2018 for the treatment of chronic NIPU [206]. I-vation is an NBI that treats DME by releasing triamcinolone acetonide (TA) (SurModics, Eden Prairie, MN, USA) [207,208]. A novel intraocular drug delivery system, Ranibizumab port delivery system (PDS) is designed to administer ranibizumab, an anti-vascular endothelial growth factor (VEGF) antibody, continuously to treat neovascular AMD (nAMD). It consists of an ocular implant and four auxiliary devices that are used for ranibizumab initial filling, refilling exchange, surgical implantation and explantation [209].

Biodegradable implants include Durysta®, Ozurdex®, and Dexycu®. With release profile of up to six months, Ozurdex® was given approval in 2009 for the treatment of macular edema brought on by retinal vascular blockage. As of 2018, Dexycu® is the only single-dose, sustained-release intracameral steroid that has received FDA approval. After cataract surgery, it offers anti-inflammatory efficacy starting on day 1 and lasting for 30 days. Durysta® got approval in 2020 for use as an intracameral injection to lower intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension for a period of 4 to 6 months [210,211]. New photosensitive biodegradable implants are also under developing stage, including OcuLief™ and EyeLief™ by Re-Vana Therapeutics Ltd. (Belfast, UK).

6.3. Microneedles

Microneedles (MNs) based systems have attracted a lot of attention recently as a substitute, non-invasive method for delivering medications to the eye in order to minimize tissue damage, reduce disruption of membrane continuity, eliminate the risk of pathogen infections and improve overall safety. This is due to intensive research and advancements in microtechnology. It has received extensive research for the transdermal delivery of numerous therapeutic pharmaceuticals (such as diabetes, obesity and vaccination medications) [212]. Different MNs, including solid MNs, hollow MNs and dissolved MNs have been studied and utilized [213].

Research has recently concentrated on microneedle systems/patches for ocular drug administration and effectively applied to the cornea or sclera concurrently with the development of single-microneedle technologies [214]. Ocular microneedles are DDSs that demonstrate passive molecule delivery through arrays of solid MNs coated with medication formulations that disintegrate quickly after implantation. They enable passive therapeutic drug diffusion, removing conjunctival clearance, bypassing epithelial tissue transport barriers and reducing retinal damage. The most typical divisions of microneedles are those based on shape, material used to create the systems, manufacturing process, drug loading mechanism and drug delivery method [215]. Many studies have been done recently on the use of MNs as DDSs to the posterior region of the eye. Globally, a prominent cause of vision loss is fungal keratitis (FK), an infectious corneal condition. To treat FK, Shi *et al*, created a patch with dissolving microneedles made of polylactic acid (PLA) and hyaluronic acid. One of these, 30% PLA-hyaluronic acid MN patch, reversibly penetrating the corneal epithelial layer, allowed the cornea to fully heal in just 12 hours. More significantly, it showed that in the rabbit model of FK, the therapeutic impact of self-implantation of drug-loaded MN patches as a controlled release reservoir for local drug delivery is much superior than that of eye drops. Because of its effective and quick corneal healing capabilities, the MN patch acts as an ocular drug delivery device which may also provide a novel therapy option for FK [216].

For the ocular administration of live microorganisms, Cui *et al*, developed cryo-MNs. Conventionally for eye infections, antibiotics eye drops are generally treatment of choice. However the evolution of antibiotic-resistant bacteria led to casting shadow on future of antibiotic based bacterial infections treatment. Authors in this system provided the predatory Bdellovibrio bacteriovorus, which could effectively stop the growth of gram-negative bacteria in cell studies. The infection was decreased in a rat eye infection model by almost six times after 2.5 days of therapy and corneal thickness and morphology were unchanged. This provides new information about the secure and efficient transport of novel antimicrobial drugs to the impermeable ocular surface [217]. A self-plugging MN (SPM) was created by Lee *et al*, to administer drugs into the eye while also sealing the scleral tissues. SPMs were created using a thermal stretching method and then coated with a biocompatible hydrogel and a drug-loaded polymer carrier. *In vitro* and *ex vivo* investigations were used to describe and explain each functional layer of the coating. Within 24 hours, the 10 mm-long SPM progressively released

almost 95% of the coated medication. Additionally, a pig model was used to show SPM's capacity for quick closure and sustained intraocular administration [218].

Roy *et al,* described two different types of patches i.e. microneedle scleral patch (MSP) and the microneedle corneal patch (MCP) for the delivery of triamcinolone acetonide (TA). *Ex vivo* tests on a pig eyeball revealed that, compared to MCP and TA nanosuspension, MSP obtained much higher TA concentrations in the vitreous humor and choroidoretinal complex after 5 minutes of treatment [219]. Amer and Chen created microneedle arrays based on PVA hydrogel for the delivery of immunoglobin G1, a model protein used to simulate bevacizumab, a drug used to treat AMD. The *in vitro* experiments revealed that the drug released more slowly than it did after injection. In comparison to single injections, the MN-based arrays exhibit a significantly more uniform drug release profile [220]. Wu and colleagues created bilayers microneedles arrays filled with nanoparticles for the sustained delivery of proteins to the posterior ocular area. The sclera could be punctured by the MNs due to their sufficient mechanical stability, releasing the nanoparticles (NPs) in less than three minutes. The delayed release of the drug was caused by the gradual dissolution of the NP-forming matrices [221]. Due to the low long-term efficacy brought on by the quick dissolving of biodegradable composites, the clinical application of MNs for ocular medication delivery is still difficult. Given that treating chronic eye disorders necessitates sustained medication administration over an extended period of time, this limitation is particularly troublesome. Most importantly the aforementioned barriers could restrict the distribution of medications to the posterior portion of the eye following intrascleral or suprachoroidal microneedle injection. In order to fully comprehend the potential advantages of MNs for ocular applications, additional research is required to look into the injection and retraction forces and overall safety of the technology.

6.4. Contact Lens

In recent years, evaluation of contact lenses (CLs) as administration routes has increased [222]. Using CLs as active ingredient carriers is a relatively novel approach that is still being studied and enhanced. Depending on the design material, there are two primary categories of contact lenses: rigid gas-permeable lenses and soft hydrogel or silicone hydrogel polymer lenses. Polymeric carriers, such as implants made of polymer and drug-containing polymer nanoparticles are used in therapeutic contact lenses [223]. Studies have recently concentrated on

methods to increase the bioavailability of various CLs based DDSs and prolong the drug residence period. The dosing schedule, bioavailability and extended drug residence duration in the eye are benefits of adopting CL as control-released drug systems [224,225]. CLs as a reservoir of drugs has been applied as promising treatment method for chronic eye conditions (like glaucoma), ocular allergies, the controlled release of antimicrobial peptides onto the ocular surface and the administration of antiviral, antifungal, anti-inflammatory and/or immunosuppressive drugs [226–228]. Therapeutic CL have the potential to reduce drug dosage requirements, administration frequency and systemic drug absorption [229].

For individuals who find wearing contact lenses unusual, some factors like water contents, oxygen permeability, transparency and mechanical properties present difficulties [230]. Drug delivery in the eye has been transformed by the use of nanotechnology and CLs.

To manage the distribution of pirfenidone (PFD) and treat corneal fibrosis and inflammation, a product with commercial approval named the silicon hydrogel ACUVUE® OASYS®, has been modified [231]. The 1-DAY ACUVUE® TruEye™ lens and ACUVUE® Oasys® soaked with vitamin E were both utilized by the same authors. These CL have been used to assess the drug release patterns of flurbiprofen sodium (FS) and ketorolac tromethamine (KT), which have demonstrated improved drug delivery dosages for the treatment of ocular inflammatory disorders[232]. The most typical, easiest and most affordable way of production is to submerge contact lenses in drug-containing NPs (~100 nm) which have demonstrated a better drug delivery dose in treating inflammatory ocular diseases [233]. Jiao *et al*, created a novel antibacterial and antioxidant contact lens using a polyacrylamide semi interpenetrating network hydrogel that contained quaternary ammonium chitosan and tannic acid. As per antibacterial test, the CL had good bactericidal impact on Escherichia coli and Staphylococcus aureus. Tannic acid has the potential to mitigate oxidative stress and shield cells from the harmful effects of reactive oxygen species. Therefore, a viable treatment alternative for ocular infections and inflammatory illnesses is this drug-free, antibacterial and antioxidant contact lens [234]. In order to treat keratitis, MY Sahadan *et al*, created a silicone hydrogel CL coated with phomopsidione nanoparticles (NPs) enabling a 48-hour sustained release of the drug [235]. To treat glaucoma, Ding et al. created a contact lens with integrated microtubes. This device can lengthen the time until a medicine is released from the body for 45 days, reduce side effects and improve drug bioavailability. More

crucially, as IOP varies, the contact lens' curvature shifts, causing more medication to release. As a result, the contact lens becomes an adaptive drug-release device that may offer dynamic and adaptable anti-glaucoma treatment [236]. Acyclovir and valacyclovir-loaded CLs based on methacrylic acid (MAA) have been utilized to treat ocular keratitis brought on by the herpes simplex virus (HSV) [233]. Additionally, silicone hydrogel soft CLs loaded with latanoprost or brinzolamide have been formed, allowing for continual medication delivery and serving as an effective alternative to eye drops for the treatment of glaucoma [237,238].

Naringenin (NAR), a flavonoid anti-inflammatory and antioxidant utilized to treat posterior eye segment diseases such AMD, has recently been reported through the application of soft hydrogel CLs [239].

Recently, it was demonstrated that it may be possible to administer ionic medications directly to the vitreous using a drug-loaded CL in conjunction with electrodes positioned diametrically opposite and beyond the limbus on cadaver rabbit eyes. With the advantages of being safer and less invasive, the incorporation of an electric field with numerous electrodes on a single lens can efficiently deliver ionic medicines to the posterior region at levels comparable to existing approaches [240].

It can be difficult to achieve a constant and regulated release profile, which could result in erratic medication concentrations at the target site. Drug release and bioavailability may be influenced by elements like tear film composition, blinking habits and lens movement on the eye. Some medications, particularly those with complex formulation or bigger molecules, might not be appropriate for delivery *via* contact lenses. In some circumstances, this restriction may limit this method of administration's adaptability. The number of medications that can be given using this method may be constrained by the various drugs' compatibility with contact lens materials and their capacity to retain stability throughout storage and wear. To increase the viability and dependability of CLs for treatments of the ocular posterior segment and the retina, research and technical improvements are continuously tackling these issues. These drawbacks may be eliminated with additional innovation and improvement, resulting in more efficient and patient-friendly ocular medication delivery techniques. Although the contact lens-based mode of administration for treatments of the ocular posterior segment and the retina has great potential,

more work needs to be done in these areas to address issues with drug loading, release kinetics and biocompatibility.

6.5. Nanostructured platform for ocular drug delivery

Novel drug delivery systems have been designed to bypass ocular drug delivery obstacles and boost drug bioavailability. The development of nanocarriers presents numerous benefits such as removing ocular obstacles and fostering transcorneal permeability, extending drug residency period, lowering the dosage frequency, improving patient compliance, decreasing drug degradation and sustained/controlled drug or gene delivery [241]. A number of ocular obstacles prevent a medicine from having a sufficient bioavailability [242]. The most important aspect for nanomedicines is the drug's particle size that needs to be appropriate and controlled. In order to achieve ocular medication delivery, it should also be less irritating, more biocompatible and have high bioavailability [243]. Moreover drugs can only be effectively delivered into the anterior portion of the eye through topical application and only a very little concentration of the drug will reach the posterior segment. But systemic administration will aid to deliver a modest drug concentration to the target site of ocular tissues. However, the dosage required to achieve therapeutic efficacy may result in a number of drug-related adverse effects. Therefore the use of drug delivery systems based on nanotechnology, such as liposomes, niosomes, solid lipid nanoparticles, nanosuspensions, nanoemulsions, nanomicelles and biodegradable microspheres, could aid in resolving a number of problems with toxicity and bioavailability of many medications. By overcoming the ocular barriers, medications that are designed to deliver to a specific target site for treating numerous eye diseases may be able to treat more conditions.

By overcoming various ocular barriers including the blood-retinal barrier in the eye, these nanotechnology-based drug delivery devices can also assist in prolonging the release of medications. This could further enhance the bioavailability of several medications, boosting their therapeutic potency [243]. Below we have briefly discussed nano based drug carriers reported for last five years for ophthalmic delivery *via* different routes. Table 2 indicates nano based drug carriers with their comparative advantages and disadvantages.

6.5.1. Liposomes

Liposomes are lipid vesicles with a core water compartment under diameter of 0.025 to 10 μm and one or more phospholipid bilayers. They can be used to encapsulate medications that are hydrophilic or lipophilic and are frequently employed in the treatment of retinal disorders. Due to their size, amphiphilic characteristics and biocompatibility, liposomes are attractive drug delivery platforms. The size, surface charge, method of preparation and lipid/cholesterol components of the liposomes all have a substantial impact on how they behave. For instance, the first AMD medication approved by the FDA is verteporfin liposome [244]. Additionally, liposomes can stick to the cornea, making them effective delivery systems for medications with poor absorption rates, high molecular weights and low solubilities. They can be used to transport various medications into the ocular tissues due to their particular surface charge. The corneal epithelium's negatively charged mucin layer is compatible with the positive charge on the liposomes, which enables them to attach to it. Tavakoli *et al*, examined how these liposomes' particle size, surface charge and surface coating affect their ability to penetrate the retina in an in vitro bovine explant system. The studies show that whereas large liposomes (>100 nm) cannot penetrate the retina, small liposomes (50 nm) may cross emphasizing the significance of particle size. The dispersal of retinal liposomes is additionally aided by PEGylation and anionic surface charge [245]. Recently one study has been conducted by Wong *et al*, reporting aptamer functionalized mucin targeting liposomes containing Cyclosporine A for effective treatment in dry eye disease. Their results show that aptamer linked liposomes showed good uptake by cornea cells which in turn will increase the residence time of the liposomes. Moreover the CsA loaded liposomes showed good anti-inflammatory activity by noticing a down regulation in inflammatory cytokines e.g. TNF, IL in *invitro* dry eye cells model [246]. A liposomal system was created by Cheng *et al*, using dicetylphosphate, chitosan, cholesterol and soybean phosphatidylcholine. This formula demonstrated enhanced activity and greater corneal permeability [247]. According to one study, tacrolimus (FK506)-loaded cationic liposome eye drops were effective in treating dry eyes. The diameter of tacrolimus liposomes is roughly 300 nm and their surface charge is +30 mV. Tacrolimus levels in the cornea can be increased and ocular retention time can be extended *via* interactions between cationic liposomes and the anionic eye surface. Inflammatory variables linked to DED and ROS have been demonstrated to be reduced by FK506 liposomes, which have excellent effect for treating eye diseases [248].

Additionally, Qiao H *et al*, created liposomal eye drops loaded with Rebamipide to improve ocular retention in treatment of dry eye disease. As per results, in comparison to free drug suspension, liposomes showed higher retention in cornea. Moreover in invivo analysis, liposomes displayed higher drug concentrations in corneal and aqueous humor which shows its higher uptake and retention. Additionally the invivo biodistribution analysis showed that Rebamipide concentration reached to maximum after 10 minutes of liposomes administration [249]. J. Navarro-Partida *et al*, reported triamcinolone acetonide loaded liposomes for topical applications and treatment of DME. Results indicated that formulations did not show any inflammation and showed good ocular tolerability. Moreover in patients with DME, TALF reduces central foveal thickness and improved visual acuity in the phase I clinical trial [250].

Gu *et al*, created novel nanocomposite eye drops by hybridizing glycylsarcosine (GS)-anchored layered double hydroxides (LDH) with liposomes loaded with dexamethasone made up of soybean phospholipids and cholesterol. GS is a traditional PepT-1 substrate that was altered on LDH and is used to target PepT-1 on the ocular surface. By electrostatic adsorption, LDH, a type of positive carrier can improve precorneal retention [251].

Although liposomes offer several benefits, their usage is constrained by their low drug loading capacity, short shelf life and difficult sterilization.

6.5.2. Dendrimers

Another cutting-edge method for delivering medications to the eye is using dendrimers. Dendrimers are the macromolecular compounds that resemble trees in that they have symmetric branches that encircle a central core. Dendrimers are repeating molecular structures with a central core that are often tree or star-shaped, nanoscale (about 2-100 nm), symmetric and hyperbranched [252,253]. They excel in drug conjugation, surface group functionalization and drug encapsulation. Dendrimers are also extremely adaptable in their functionality and can be created into multifunctional biological macromolecules by altering the surface for different applications. These molecules have been extensively used in the delivery of hydrophilic and lipophilic drugs, nucleic acids (gene, miRNA/siRNA), macromolecules and other biomedical applications [254]. Kambhampati *et al,* demonstrates the effect of systemic hydroxyl-terminated polyamidoamine dendrimer-triamcinolone acetonide conjugate (D-TA) in clinically relevant rat

model of AMD. Their results shows that the diseased mi/ma and RPE specifically uptake the systemic conjugate (D-TA) without attachment of any specific ligand. With minimal adverse effects on healthy ocular tissue and other organs, D-TA significantly suppresses pro-inflammatory cytokines and pro-angiogenic factors, attenuates inflammation in the choroid and retina by limiting macrophage infiltration in the pathological area and significantly reduces choroidal neovascularization [255]. Dendrimer gel particles (DHPs), which combine the benefits of dendrimers, hydrogels and NPs were recently created by Wang and colleagues. By encapsulating two anti-glaucoma medications—brimonidine tartrate and timolol maleate in dendrimer gel particles of various sizes, their delivery effectiveness and efficiency were evaluated. The findings demonstrated that in terms of cytocompatibility, degradability, drug release kinetics and corneal permeability, nano-in-nano DHP (nDHP, 200 nm) outperformed μDHP3 (3 μm) and μDHP10 (9 μm). Drug corneal permeability was raised by nDHP 17-fold as compared to standard drug solutions. According to these findings, nDHPs can be employed for precise medication administration, which opens up new opportunities for combining different nanotechnologies [256].

The main goal of recent investigations on dendrimers for topical instillation and drug delivery to the posterior portion of the eye was to increase their penetration capacity. Penetratin modification on dendrimers is a useful tactic as a potent promoter of ocular penetration [257]. In comparison to PAMAM without modifications, Yang *et al*, created a novel penetratin and cyclic arginine-glycine-aspartate (RGD) co-modified PEGylation mine (PAMAM) G4.0 as a nanocarrier with a significantly improved permeability of 1.5 times and extended retinal retention time of more than 12 h [258].

In conclusion, dendrimers are efficient carriers for ophthalmic applications because they offer workable answers to the solubility, dispersion and targeting issues associated with ocular drug delivery. However number of formulation processes, challenges with large-scale production, cytotoxicity and low drug loading prevent the clinical translation of this technology [259].

6.5.3. Nanomicelles

Nanomicelles are core-shell nanocarriers that spontaneously assemble from amphiphilic copolymers with hydrophobic groups at the center and hydrophilic groups at the outside [260].

The particle size typically ranges from 10 to 100 nm and can be categorized into three groups: polymers, surfactants and multi-ion composite nanomicelles [261]. In addition, the creation of polymer micelles is fueled by hydrophobic interactions, hydrogen bonds, electrostatic interactions, etc. They could be globular, cylindric or star-shaped. They could trap medicines that were both lipophilic and hydrophilic. They are easier to prepare, less poisonous, more bioavailable, more stable and more able to permeate the body. They could deliver medications to the anterior and posterior parts of the eye [262].

An immunomodulatory medication used to treat DED is cyclosporine. Ghezzi *et al*, created micelles for the administration of cyclosporine using tocopherol polyethene glycol 1000 succinate (TPGS) and Solutol®HS15 due to its relatively large molecular weight and poor permeability [263]. Meanwhile, the results of employing fatty acids for the production of micelles and drug loading were used to evaluate the addition of linolenic acid. Analyses were done on the influence of TPGS as a corneal permeability promoter and irreversible alterations in tissue permeability. It was shown that TPGS micelles, which are roughly 13 nm in size and loaded with 5 mg/mL cyclosporine, improved drug retention in the cornea and sclera and had good tolerance for ocular applications [264].

Liu *et al*, synthesized nanomicelles using hydroxypropyl methylcellulose and amino-terminated poly(ethylene glycol)-block poly(D,L)-lactic acid. The nanomicelles significantly increased tacrolimus ocular penetration and extended release [265]. Additionally, XU *et al*, created hydrogen-castor oil 40/octyl alcohol 40 (HCO-40/OC-40) hybrid nanomicelles and chitosan oligosaccharide-valine-stearic acid (CSO-VV-SA) nanomicelles for topical ocular drug administration. Human corneal and conjunctival epithelial cells were not significantly harmed by either type of nanomicelle. Rabbit tears contained dexamethasone in both nanomicelles for a duration of more than 3 hours [266].

Hyaluronic acid was employed by Terreni *et al*, to prolong the release, boost penetration and raise the action of cyclosporine A [267]. Anti-VEGF is traditionally injected intravitreal into the posterior segment of the eye to treat retinal disorders. A nano-micelle drug delivery system made of polypropylene glycol, polyethene glycol and fragments of polycaprolactone (PCL) was created by Zhao X *et al*. Aflibercept is locally delivered to the posterior part of the eye through the corneal-scleral pathways by the copolymer EPC (nEPC). In a mouse model of laser-induced

choroidal neovascularization (CNV), animal tests have demonstrated that aflibercept loaded EPCs (nEPCs + A) may enter the cornea in an *ex vivo* porcine eye model and carry aflibercept to the retina to promote CNV regression. Additionally, nEPCs + A demonstrated strong inherent anti-angiogenic qualities and good biocompatibility. These results imply that nEPCs could make good candidates for other therapeutic uses [268].

6.5.4. Nanosuspensions

Nanosuspensions (NSs), a form of biphasic colloidal dispersions system of nanoscale poorly water-soluble drug particles with a diameter of less than 1 μm, suspended in an aqueous medium surrounded by polymer or stabilizer [269,270]. NSs are suitable for the ocular delivery of medications that are poorly water-soluble. Nanosuspension doesn't need a carrier material, in contrast to traditional matrix-framed nano-systems. It is often stabilized by surfactants or polymers and includes only 100 percent pure medication NPs in the nanometer range [271]. They benefit from longer residence times, prolonged drug release and improved drug solubility. Using an ion-pairing technique, Josyula *et al*, created an insoluble moxifloxacin-pamoate (MOX-PAM) complex that was later transformed into mucus-penetrating nanosuspension eye drops (MOX-PAM NS) to increase the bioavailability of moxifloxacin hydrochloride. In healthy rats, MOX-PAM NS considerably increased ocular drug absorption compared to Vigamox® (commercial formulation), had higher C_{max} and had superior antibacterial properties. In a rat model of ocular Staphylococcus aureus infection, treatment with MOXPAM NS administered once daily was comparable to that with Vigamox® provided three times daily. These findings indicated the significant clinical and translational importance of nanosuspension [272]. Additionally, nanosuspensions can be used in conjunction with different delivery methods. Synthetic corticosteroids like triamcinolone acetonide (TA) are commonly used to treat a variety of inflammatory diseases. A hybrid nanosuspension and dissolving MNs system was created in one study by Wu Y *et al,* to deliver the hydrophobic medication TA transscleral in an efficient and least invasive manner. The TA NS-loaded MNs dissolved quickly and were powerful enough to pierce the removed porcine sclera at an insertion depth more than 80% of the needle height. Remarkably, the transscleral deposition revealed that following 5-minute application of NS-laden MN, the amount of TA deposited in the sclera was greater than that of MN loaded with a common medication [273].

Despite these positive nanosuspension outcomes, there are still stability problems with nanosuspensions. The stability characteristics of steric and electrostatic stabilizers, the largest possible particle size and physical stability are crucial elements that require more research [274].

6.5.5. Nanoemulsions

Nanoemulsions range in size from 20 to 500 nm are transparent or translucent systems that are thermodynamically unstable but kinetically stable [275,276]. They could serve as ocular delivery vesicles. Oils in water nanoemulsions are made up of a dispersed oil phase that is stabilized in an aqueous medium by surfactants. They function as a storage space for medications that are lipid soluble and interact with the lipids in the tear film to produce a sustained drug release [277]. Surfactants are crucial for interacting with the corneal surface and for improving medication solubility [278]. The disadvantages of nanoemulsions include lower ocular tolerance from high surfactant concentrations and impaired vision if the particle size is more than 100 nm [277]. In addition, NEs have benefits over conventional drug administration techniques in terms of extended anterior corneal retention time, sustained drug release, high penetration ability, improved ocular bioavailability and simplicity of sterilizing [279,280]. In addition, it can be used to treat a variety of eye conditions, including DED [281], fungal keratitis [282], herpes simplex infection [283], glaucoma [284] and others. Dukovski *et al*, used lecithin as the anionic and chitosan as the cationic surfactant to create a functional cationic ophthalmic NE that contains 0.05% (w/w) chitosan and nonsteroidal anti-inflammatory medications. The treatment of DED may be possible owing to NPs' ability to maintain the tear film, prolong the medication retention time on the ocular surface and act on inflammatory components in an *ex vivo* porcine cornea model [281].

Youssef *et al*, created a ciprofloxacin-loaded nanoemulsion (CIP-NE) using oleic acid and Labrafac® lipophilic WL 1349 as the oil phase, Tween® 80 and Poloxamer 188 as surfactants,. According to studies on *in vitro* release and *ex vivo* trans-corneal permeation, the CIP-NE formulation may be used as a promising nanocarrier to improve the therapeutic efficacy of bacterial keratitis [285]. These studies showed sustained release and increased penetration compared with commercial ciprofloxacin. In another study, Ismail *et al* employed the travoprost nanoemulsion as a new carrier, displaying acceptable nanodroplet size, zeta potential, refractive index, pH, controlled release and adequate stability under accelerated conditions. Travoprost

nanoemulsion offered a better bioavailability, a shorter half-life and sustained IOP reduction for 60 hours when compared to Travatan® eye drops. Consequently, travoprost nanoemulsion is an effective ocular delivery system for the treatment of glaucoma [286].

To cure AMD, Ge *et al*, created a lutein nanoemulsion that had been modified by penetratin. The nanoemulsion was loaded with lutein to increase its water solubility. The nanoemulsion was supplemented with stearyl penetratin to improve penetration by a noninvasive administration method. The penetratin nanoemulsion was made as an ion-responsive *in situ* gel in order to increase corneal retention duration and allow penetratin to take full action. The nanoemulsion was quickly transported to the posterior part of the eye and dispersed throughout the retinal region with penetratin aid. In the dry AMD rodent model, this approach demonstrated good efficiency in protecting the retinal cells from apoptosis and ROS-induced damage [287]. To further investigate the mechanism of small-molecule medicines, nanoemulsions can also be perfect nanocarriers. To transport a hydrophobic small chemical, a runt-related transcription factor 1 (RUNX1) inhibitor called Ro5-3335 to the retina, Delgado-Tirado *et al*, created an aqueous phase nanoemulsion delivery method using surfactants as the encapsulating matrix. Following topical application Ro5-3335 was found in the vitreous cavity and it significantly slowed the advancement of proliferative vitreoretinopathy in the rabbit model [288,289]. In animal models, this kind of technology also worked well for treating choroidal and ocular neovascularization.

NEs still have several disadvantages, such as eye discomfort and low viscosity, despite the fact that they can be employed in ocular preparations. Additionally, because NEs are thermodynamically unstable, they can disintegrate over time *via* a variety of physicochemical processes, including coalescence, gravitational separation, flocculation and Oswald maturation.

6.5.6. Nanoparticles (NPs)

Nanoparticles (NPs) are spherical-shaped colloidal particles ranging between 1 and 1000 nm in size [290]. NPs are mainly divided into two categories; lipid NPs and polymeric. Polymeric nanoparticles (NPs) that are biodegradable are solid colloidal particles that are derived from natural sources like chitosan, albumin, alginate and dextran or from synthetic sources like polylactic acid (PLA), polyglycolide (PGA), poly lactic-coglycolic acid (PLGA), polyaspartic

acid, poly-alkyl cyanoacrylate and polyethyleneimine (PEI) [290,291]. Mucoadhesive nanosystems made of hydrophilic polymers, such as polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) extend the residence time of NPs in the anterior corneal and ocular mucosal regions [292]. Additionally the effective ocular absorption of NPs is greatly influenced by their surface charge. Cationic NPs have a longer retention period on the ocular surface than anionic NPs due to the negatively charged surfaces of corneal and conjunctival tissues [293]. With the benefits of being: (1) smaller and less irritating (2) offering sustained drug release to avoid repeated dosing (3) preventing non-specific uptake or premature degradation (4) offering better absorption and improving intracellular penetration and (5) targeted delivery to desired tissues, NPs have been used extensively to date to deliver drugs to the targeted tissue in the eye [293,294]. Since PLGA is a synthetic polymer and can be modified by changing its molecular weight, terminal groups and lactide-to-glycoside ratio, it is very suitable for controlling drug release when utilized to create NPs for ocular delivery [295]. Numerous drug delivery products containing PLGA have been approved by the FDA.

In one study, Bev, an anti-VEGF medication that is frequently used to treat diabetic retina, was delivered to the posterior chamber of the eye using chitosan-coated polylactide-glycolic acid nanoparticles (CS-PLGA NPs). With higher concentrations of Bev in the posterior ocular tissues, CSPLGA NPs demonstrated superior permeability compared to the conventional drug solution, as demonstrated by confocal laser scanning microscopy and pharmacokinetics. When compared to local and intravitreal injections, the subconjunctival injection of CSPLGA NPs dramatically decreased the level of VEGF in the retina for a period of 12 weeks in the retinopathy model. Consequently, it may be possible to target the retina using CS-PLGA NPs for medication delivery [296]. Kim *et al*, used an iontophoretic technique to inject NPs containing latanoprost into the eye to treat glaucoma. These PLGA nanoparticles offered the advantages of sustained release of latanoprost and extended drug residence time. *In vivo*, NPs demonstrated the longest-lasting pharmacological impact. When compared to Xalatan®, a commercial latanoprost eye drop, it increased its efficacy by about 23 times and lasted for more than seven days. This provides a new approach to extend the duration of medication's effectiveness and lowering the frequency of drug administration in the treatment of glaucoma [297]. In diabetic retinopathy, Radwan *et al*, examined the viability of topical instillation of bovine serum albumin (BSA) nanoparticles coated with hyaluronic acid (HA) carrying apatinib, a specific inhibitor of VEGF

receptor 2. Prolonged precorneal retention is suggested owing to HA's mucoadhesive properties and interactions with hyaluronan receptors on corneal epithelial cells. Furthermore, *via* receptor-mediated endocytosis, the HA coating improved the transport of apatinib to specifically target CD44 receptor-positive retinal cells [298]. With the use of cell-penetrating peptides, polymer nanoparticles can also be employed as carriers for the transport of genes to the retina. A potential method for non-invasive gene delivery therapies for the treatment of retinoblastoma was made possible by non-viral vector nanostructure reported by Jiang K *et al* [299]. The purpose of the octopus-shaped 8-valent penetratin (VP) was to efficiently transport siRNA or antisense oligonucleotides (ASOs) into animals exhibiting retinoblastoma. It is made up of a biocompatible multi-arm PEG core and multiple outspread penetratin tentacles. Following topical instillation in the model of retinal tumor-bearing mice, 8VP effectively and non-toxically suppressed the intraocular tumor's protein expression while enabling quick and extended distribution of nucleic acids in the retina *via* noncorneal channel. Similarly, Nguyen *et al*, created hollow polylactic acid NPs and creatively examined how shell thickness affected the creation of long-acting medication carriers for the efficient treatment of glaucoma. A medium-thickness shell (~40 nm) demonstrated the most effective pilocarpine release and sustained relief of high IOP for over 56 days in the rabbit glaucoma model. This may preserve the corneal endothelium's structural integrity and attenuate retinal and optic nerve degeneration. This study suggests that the shell thickness effect may be useful in the creation of long-acting drug delivery devices for the treatment of many chronic eye diseases [300].

Alternatively lipid NPs' reliance on non-toxic, biodegradable lipid components reduces the possibility of toxicity. In addition to being more stable and economical, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have a solid matrix that enables controlled drug release. Since SLNs avoid using organic solvents, use physiological lipids and facilitate large-scale synthesis, drugs are more bioavailable, better protected and have superior release control.

Solid lipid nanoparticles (SLNs) are colloidal carrier systems with a particle size range of 10 nm to 500 nm that are composed of lipids distributed in an aqueous surfactant solution. They are best fitted for delivering hydrophobic medications. It has been demonstrated that SLNs have enhanced retinal permeability and prolonged drug release at the ocular location. Ahmed *et al*, created etoposide-loaded SLNs for intravitreal delivery to treat retinal disorders using the melt

emulsification and ultrasonication techniques. In the vitreous cavity, the produced formulation demonstrated biphasic drug release with an initial burst release and a sustained release that lasted for seven days. Histopathological investigations showed that the retinal area had less toxicity [301].

Schnichels *et al*, studied lipid DNA NPs functionalized for brimonidine loading *via* hydrophobic interactions with double-stranded micelles and particular aptamers. Comparing the animals treated with two types of DNA NPs once daily for five weeks, the IOP reduction was found in 74% (SEM: ± 3%) and 54% (SEM: ± 1%) of the animals respectively, compared to 36% (SEM: ± 3%) of the animals treated with the original brimonidine [302].

In order to create distinct nanostructures in the matrix, NLCs are created by controlling the mixing of liquid oil and solid lipids. Using NLCs can help overcome the drawbacks of SLNs, such as their restricted ability to load drugs and their tendency to expel drugs while being stored [303]. In Table 3 and Table 4, we have reported recent studies for last 5 years on different ophthalmic formulations highlighting their potential in various anterior and posterior segment ophthalmic disorders respectively. Fig. 5 indicates the general illustration of drug release mechanisms and permeation from nano drug carriers through corneal barrier.

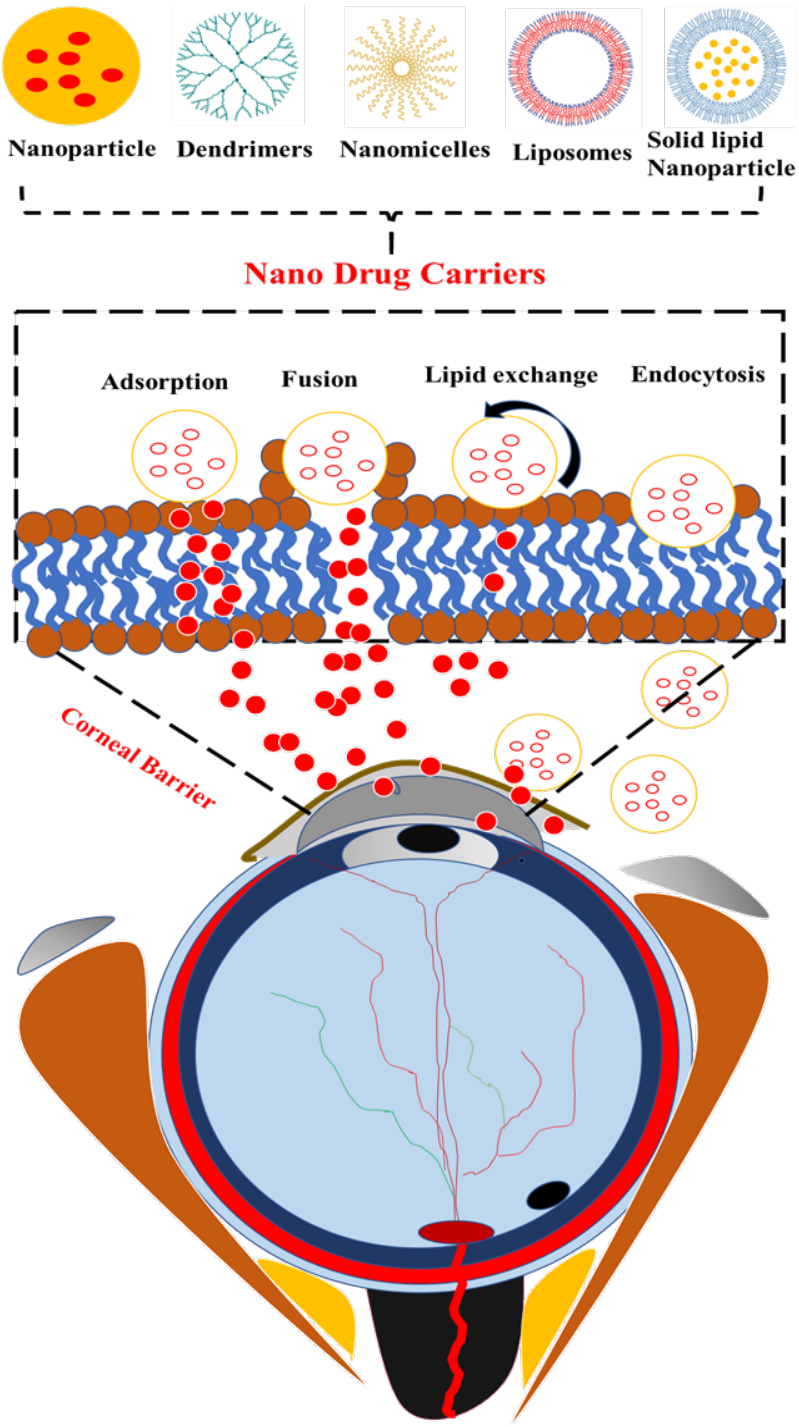


Fig. 5 General illustration of mechanisms responsible for drug release from nano drug carriers and permeation through corneal barrier.

Drug carriers	Advantages	Disadvantages	Ref

Table 2 Nanostructured drug candidates with their comparative advantages and disadvantages

Liposomes	Lipid vesicles with 0.025 to 10 µm in size range. Hydrophilic and hydrophobic drugs can be encapsulated. High corneal permeability Not-toxic and biocompatible Low dosing frequency	High production cost Low stability leading to less scalability potential Loaded drug leakage	[249]
Dendrimers	✓ Star shaped highly branched macromolecules with 2-100 nm size. ✓ Can encapsulate hydrophilic and hydrophobic drugs. ✓ High drug loading ability and controlled release. ✓ Multi-functionality by altering the particle surface.	✓ Difficult scalability owing to multiple synthesis steps ✓ Can induce chemical drug modification and lead to toxicity issues. ✓ Encapsulation efficiency is low and storage problems	[258]
Nanomicelles	✓ Core-shell nanocarriers with size range of 200 nm and suitable for hydrophobic drug solubilization. ✓ Good ocular barriers permeation and improved ocular drug transport. ✓ Good carriers for active drug targeting. ✓ Low cytotoxicity and biocompatible	✓ Problems of drug leakage and burst release owing to deformation and disassembly. ✓ Low loading efficiency ✓ High cost leading to low scalability.	[264]
Nanosuspensions	✓ Colloidal dispersion of hydrophobic drugs with size	✓ Aggregated particles owing to physical	[275]

	range of 10-1000 nm stabilized by surfactant. ✓ High drug solubility leading to increased ocular bioavailability. ✓ Increased retention time and prolonged drug release of hydrophobic drugs. ✓ Suitable for ophthalmic drug delivery	stability ✓ Precipitations of particles	
Nanoemulsions	✓ Translucent systems with size range of 20-500 nm and kinetically stable. ✓ Surfactant presence stabilizes the carriers and improves their corneal permeability. ✓ Sustained drug release due to lipid interaction in tear film.	✓ Chance of ocular irritation owing to requirement of high surfactant concentrations. ✓ May cause impaired vision owing to larger particle size.	[282]
Nanoparticles	✓ Spherical-shaped colloidal particles with size range of less than 400 nm are good candidates for ophthalmic drug delivery. ✓ Improved efficacy due to target specific ocular drug delivery. ✓ Sustained drug effect and low drug degradation. ✓ High intracellular penetration.	✓ Low loading efficiency and particles agglomeration. ✓ High particles surface area leading to burst release of drug. ✓ Inefficiency of scale-up methods.	[297]
Solid lipid nanoparticles	✓ Non-toxic drug carrier candidates.	✓ Drug leakage on long storage.	[298]

	✓ Easy surface engineering ✓ Long term stability and prevention of lipophilic drug degradation. ✓ Scalability of large production	✓ Inadequate loading efficiency.	
Nanostructured lipid carriers	✓ Solid- and liquid lipid combinations with size range of 50-1000 nm. ✓ Biocompatible and high bioavailability in ocular tissues. ✓ Inadequate drug leakage on storage.	✓ Cytotoxicity may encounter based on nature of lipid matrix used and concentrations.	[298]
Niosomes	✓ Non-ionic surfactant components with 20-1000 nm size range. ✓ Bioadhesive, biodegradable and biocompatible. ✓ Controlled and targeted ocular drug delivery and improved bioavailability.	✓ Low loading efficiency ✓ Encapsulated drug leaching. ✓ Particles agglomeration ✓ Specialized equipment's and large scale up cost.	[30]
Cubosomes	✓ Self-assembled crystalline liquid nanoparticles with size range of less than 500 nm. ✓ Suitable candidates for hydrophilic, hydrophobic and amphiphilic drug candidates. ✓ High loading capacity ✓ Improved permeability, ocular residency and bioavailability of drugs.	✓ Low encapsulation of hydrophilic drugs to hydrophobic drugs.	[30]

Table 3 Recent studies on ophthalmic formulations for anterior section disorders for last 5 years

Ocular disease	Delivery carrier	Active Drug	Experimental animal model	Description	Ref, Year
					2024
DED	F127 hydrogels	Copper-selenide	Male C57BL/6J mice	F127 hydrogel containing copper nanoparticles showed good ocular adherence. Moreover formulations exhibited improved anti-inflammatory, antioxidant and anti-apoptotic effects.	[304], 2024
					2023
Fungal keratitis	Phospholipid-mixed micelles	Posaconazole	*Invitro*	Formulations showed excellent stability and sustained drug release for a month. Moreover in comparison to drug suspension, formulations exhibited improved *invitro* antifungal activity.	[305]
DED	Aptamer linked-Liposomes	Cyclosporine A	Male SD rats	Aptamer linked liposomes increased the retention time and showed reduction in pro-inflammatory cytokines levels.	[246]
					2022
DED	Cationic liposomes	Tacrolimus	Male New Zealand rabbits	Improved ocular retention and corneal tacrolimus level. Exhibited anti-oxidative and anti-inflammatory effects	[248]
DED	Polyhedral oligomeric silsesquioxane hybrid thermoresponsive hydrogels	FK506	Female C57BL/6 mice	Hydrogel showed cytocompatibility with cornea cells. Improved retention and good therapeutic efficiency of FK506 compared to its commercial product.	[306]
Corneal edema/swelling	Micro and nano-emulsions	Indomethacin	Carrageenan-induced rats edema model	Nanoemulsions loaded with indomethacin showed more efficient effect compared to	[307]

				microemulsions in progression of edema	
DED	Proglycosomes Nano-vesicles	Tacrolimus	New Zealand rabbits	Formulations subsided the ocular inflammation and slowed the epithelial damage rate. Formulations exhibited increased tear secretion in comparison to tacrolimus solution only.	[308]
DED	Cyclodextrin Nanoparticles	Fluorometholone	New Zealand white rabbits	CD nanoformulations showed enhanced corneal penetration with no toxicity. Moreover formulations displayed good therapeutic effects in BAK induced DED model.	[309]
DED	Nanoparticles	Melatonin/ tavilermide	Female BALB/c mice	Formulations showed the synergetic effect of anti-oxidative and anti-apoptotic and can be used in DED conditions.	[310]
DED	Nanogels	Lysine	Rabbit model	Lys-nanogels prolonged the retention time and improved the ocular bioavailability. Moreover formulations showed improved therapeutic effect by decreasing the inflammation and ROS generation.	[311]
Fungal keratitis	Polymer nanomicelles	Voriconazole	Rabbit model	Designed nanomicelles showed strong mucoadhesion and corneal penetration. Moreover nanomicelles showed improved antifungal effect in rabbits as compared to free drug solution.	[312]
Keratitis	Gelatin-polyacrylic acid NPs laden *in situ* gelling solution	Oxytetracycline	White albino rabbits	Optimized formulations showed good antibacterial effect against Pseudomonas aeruginosa invitro and on a rabbit eye conjunctivitis model. Moreover formulations showed sustained effect in comparison to commercial	[313]

				product.	
					2021
DED	Nanocapsules in thermoresponsive *insitu* gel	Cyclosporine A	New Zealand Male colored rabbits	Extended ocular retention and improved CsA tissues level. Increased tear production in comparison to commercial product.	[314]
DED	Chitosan Nanoparticles in implanted PVA contact lens	Hyaluronic acid	*Invitro* study	Showed cytocompatibility to corneal cells. Ring implanted contact lens exhibited controlled hyaluronic acid release up to 14 days.	[315]
DED	Thermoresponsive *insitu* gel	Levocarnitine	New Zealand rabbits	Formulation showed high tear production and conjunctival goblet cells. Down-regulated the corneal cells apoptotic rate and improve the degree of corneal damage.	[316]
DED	Cationic nanosuspensions	Cyclosporine A	New Zealand male adult albino rabbits	Cationic nanosuspension achieved higher CsA concentrations in anterior ocular tissues in comparison to mucus penetrating particles *via* topical instillation.	[317]
Corneal abrasion	Nanofibers	Moxifloxacin HCl/ pirfenidone	Rabbit model	Formulations displayed improved antimicrobial activity and anti-scarring effect in comparison to commercial Mox eye drops. Formulations also showed sustained drug release for 24 hours.	[318]
					2020
DED	Nonspherical microcrystals	Tacrolimus	Mouse DE model	Tacrolimus loaded formulations showed superior therapeutic performance with respect to anti-inflammatory effect in comparison to commercial TAC eye drops. The instillation is also reduced for formulations.	[319]
DED	Solid	Rebamipide	Adult rabbits	In comparison to	[320]

	nanoparticle			commercial rebamipide ophthalmic suspension, the formulations showed sustained drug effect. In N-acetylcysteine-treated rabbits, increased mucin level of drug found with improved tear film healing.	
Ocular inflammation	PLGA nanoparticles	Dexibuprofen	New Zealand albino rabbits	Formulations exhibited sustained dexibuprofen effect *invitro* and *ex-vivo*. They also showed improved *invivo* anti-inflammatory effect.	[321]
Ocular tuberculosis	Cationic nanoemulsion	Rifampicin	*Invitro*	Formulations showed increased mucoadhesion leading to improved retention time on mucin. *Invitro* antibacterial test showed improved antimicrobial efficacy of rifampicin loaded in cationic nanoemulsions.	[182]
DED	Contact lens	Ceria nanoparticles	Female BALB/c mice	CeNP-CL showed intrinsic extracellular ROS-scavenging properties compared to commercial eye drops. CeNP-CLs on the eyes in a mouse model showed protective effect.	[322]
					2019
Ocular topical inflammation	Chitosan-deoxycholate self-assembled NPs	Prednisolone acetate	Female guinea pig eyes	Optimized nanoparticles formulations showed two fold increase in drug release in simulated tear fluid. Moreover formulations showed good anti-inflammatory effect on guinea pig eyes.	[323]
Ocular inflammation	PLGA nanoparticles in dry tablet	Dexamethasone	New Zealand White male rabbits	Formulations exhibited increased retention and ocular bioavailability in rabbit in comparison to Maxidex®.	[324]
Ocular	PLGA	Fluorometholone	New Zealand	Improved retention and	[325]

inflammatory condition	NPs *insitu* forming gels		male albino rabbits	bioavailability was shown by formulations. Moreover optimized formulations showed good anti-inflammatory effect in rabbits.

Table 4 Recent studies on ophthalmic formulations for posterior section disorders for last 5 years

Ocular disease	Delivery carrier	Active Drug	Experimental animal model	Description	Ref, Year
					2024
Neovascularization	Nanoparticles	RNA	Adult SKH1 hairless mice	After subconjunctival injection, cell internalization of the larger RNA nanoparticles in the retina and retinal pigment epithelium were found by confocal analysis. Moreover aptamers linked nanoparticles showed higher antiangiogenic effects.	[326]
					2023
AMD	Nanoparticles	Platinum	Dark albino Sprague-Dawley rats	Intravitreally injected formulations showed improved post treatment ERG responses to light stimuli and inhibited the inflammatory response to degeneration in retina.	[327]
Neurodegenerative ocular diseases	Nanofibers implants	Melatonin	*Invitro*	Optimized nanofiber implants exhibited sustained drug release and promising alternative treatment in degenerative ocular disease.	[328]
					2022
AMD	Nanoparticles	Cerium oxide	Mouse model *DKOrd8*	Topical administration of formulations showed reduced oxidative stress in ARPE19 cells and inhibiting neovascularization *invitro*. While anti-inflammatory	[329]

				and anti-degenerative effect in retinal degenerative mouse model.	
Neovascularization	Liposomes	Sunitinib	Laser induced CNV mouse model	After intravitreal injection, liposomes containing Sunitinib showed improved established Neovascularization in laser induced CNV mouse model.	[330]
Neovascularization	Lipoprotein-inspired nanoparticle	Verteporfin	Male Japanese white rabbits	Formulations showed significant reduction in VEGF and proinflammatory intercellular adhesion molecule-1 proteins level after single dose topical instillation *invivo*.	[331]
Wet AMD	Micro and nano-particles in hydrogels	Dexamethasone/ aflibercept	*Invitro*	Combinatorial formulations showed extended drug release and anti-VEGF effect can be used in wet AMD patients.	[200]
AMD	Nanoparticles	Cerium oxide	Sprague Dawley (SD) albino rats	After intravitreal injection, formulations showed significant reduction in vascular endothelial growth factor (VEGF) protein levels and neovascularization in animal model.	[332]
Fundus Neovascularization	Self-assemble nanotransforrs	Glycopeptide /Doxorubicin	Mouse OIR model	After topical application, nanotransforrs showed high penetration, successfully targeted M2 macrophages in the fundus and reduced the pathological neovascularization in animal model.	[333]
DR	Lipid-polymer hybrid nanoparticles	Melatonin	*Invitro*	The optimized nanoformulations demonstrated good mucoadhesion and sustained release. Moreover in invitro DR model, formulations showed enhanced neuroprotective and	[334]

				antioxidant activities.	
Glaucoma	Nanofibers	Brinzolamide	*Ex-vivo* with sheep corneas	Formulations showed linear permeation with precise dosing. They demonstrated high stability and compatibility.	[335]
Glaucoma	*Insitu* gelling nanofiber films	Timolol maleate	Rabbit model	Formulations showed good cytocompatibility and doesn't induce any ocular irritation. Topical administration in rabbits induced faster drug action and sustained effect in IOP lowering for 24 hours.	[336]
					2021
Neovascularization	Bilayer dissolving microneedle	Ovalbumin-encapsulated PLGA nanoparticles	*Ex vivo* (excised porcine sclera)	MNs holding ovalbumin nanoparticles showed sustained protein release for 2 months and showed successful penetration *via* scleral barrier. This treatment strategy can be effectively used for neovascular diseases.	[221]
Diabetic retinopathy	Hyaluronic-coated Albumin Nanoparticles	Apatinib	Male wistar rats	Topically applied formulations showed high mucoadhesion and biodistribution in posterior eye tissues. Moreover formulations exhibited *invivo* therapeutic effect in diabetic rat model.	[337]
Uveitis	Soluplus® nanomicelles	Everolimus	*Ex-vivo* with goat cornea	Formulations showed improved corneal penetration, longer systemic nano circulation *via* topical application and promising nanocarrier for uveitis.	[338]
Glaucoma	Graphene oxide-loaded silicone hydrogel contact lenses	Bimatoprost	New Zealand white rabbits	These contact lenses showed no Ocular irritation with significant improvement in mean residence time and drug release. In comparison to eye drops, improved bioavailability was noted in	[339]

				rabbits tears.	
AMD	Nanomicelles	Artemisinin	*Ex-vivo* with albino rabbits	Formulations presented good corneal permeation with acceptable level of hemolytic potential. Moreover in comparison to free drug, formulations exhibited remarkable anti-angiogenic activity.	[340]
Glaucoma	Nanomicelles	Nimodipine	New Zealand rabbits	Developed formulations showed increase *invitro* permeability and anti-oxidant activity. Moreover improved in vivo permeation, IOP reduction and miosis was reported with micelles treatment.	[341]
					2020
DME	Liposomes	Bromfenac	New Zealand rabbits	After intravitreal injection, liposomes did not exhibit any retinal toxicity and no significant changes were recorded in ERG measurements after 3 months.	[342]
Retinal inflammation/ AMD/DR	Liposome aggregate platform system	Flurbiprofen/ calcein	Adult pigmented rabbits	After intravitreal injection, liposomes system improved the flurbiprofen retention in ocular tissues with decreased inflammatory reactions towards calcein.	[343]
AMD	Solid lipid nanoparticles	Atorvastatin	Rabbits model	Formulations showed increased mucoadhesion and uptake and were tracked in ARPE-19 cells. Moreover formulations exhibited increased bioavailability in aqueous and vitreous humor *invivo*.	[44]
Glaucoma	Nanosuspension	Acetazolamide	New Zealand rabbits model	The formulations showed enhanced stability, saturation solubility and sustained effect. Additionally nanoformulations exhibited	[344]

				significant reduction in IOP with decreases doses in comparison to free drug solution.	
Glaucoma	*Insitu* gelling niosome	Latanoprost	Rabbits model	*Insitu* gels carrying drug loaded niosomes increased the encapsulation efficiency and retention time. Moreover formulations showed no toxicity and were able to reduce IOP for 3 days in rabbits model.	[345]
					2019
Glaucoma	Micelles-laden contact lenses	Latanoprost/Timolol	Male Nippon albino rabbits	Micelles laden contact lenses showed improved and sustained drug release in tear fluids. Moreover in rabbits, formulations showed improved residence duration and bioavailability of drugs with sustained reduction in the IOP for over 168 hours.	[346]
DR/AMD	PLGA Nanoparticles	Fenofibrate	Male Brown Norway mice	Intravitreal injection of nanoformulations showed sustained drug level in rats eye for 60 days. Moreover lesser retinal vascular leakage and retinal leukostasis and improved retinal dysfunctions was noted with formulations. Developed formulations shows promising treatment approach for DR and AMD.	[347]

7. Potential clinically approved ocular formulations on market and under clinical trials

7.1. Currently accepted therapies in the clinic

For the treatment of anterior and posterior ocular diseases, extensive research has been conducted on nanocarriers such as nanoparticles and nanomicelles. They have started engaging

in clinical trials and demonstrated beneficial outcomes in patients. As per the most recent estimates available on Market Research, the global pharmaceutical drug market for ophthalmics is expected to reach 40.7 billion dollars in 2020 and 65.90 billion dollars by 2030. The development of nanotechnology for the treatment of eye diseases seems promise given the growing number of products available, where formulations based on polymers and lipids are expected to boost market expansion going forward. Many promising ocular nanoformulations approved by the FDA and European Medicines Agency (EMA) have been introduced on the market in recent decades. DED and retinal disorders associated with ocular fundus neovascularization are the subjects of the greatest number of ophthalmic nanoformulations and clinical trials. Although CsA has a number of drawbacks and difficulties, it is widely used in DED. For instance, in 2002, FDA approved Restasis®, the first cyclosporine A (CsA) oil-in-water emulsion to treat DED [348]. It employed polysorbate-80 as an emulsifier and 0.5 mg/ml CsA was dissolved in castor oil. However, there are still side effects associated with Restasis® including epiphora, ocular discomfort and injection pain [349]. Cequa® is a nano-micellar formulation containing 0.09% CsA and is intended to enhance drug penetration and delivery to ocular tissues. In 2018, the FDA authorized Cequa® as a therapy for DED. The micellar formulation consists of octoxynol-40 and polyoxygenated hydrogenated castor oil, which can concurrently produce thermally stable micelles by hydrogen bonding. With improved stability and less manufacturing deadlock, Cequa® offers advantages over most other colloidal CsA formulations, making it more cost-effective. It was recently introduced to the market and has demonstrated strong biocompatibility and high therapeutic performance [350]. Visudyne®, a verteporfin-loaded liposomal system used as a photosensitizing agent in conjunction with laser light treatment for CNV secondary to AMD, was the first FDA-approved nano-based medication delivery system. After injecting visudyne® intravenously, a red laser is aimed through the pupil and into the eye ten minutes later. It absorbs light, gets excited and transfers energy to surrounding oxygen to create singlet oxygen. By causing damage to the freshly formed bleeding blood vessels, this reactive oxygen can halt and even reverse the progressive loss of vision [351, 352]. Even after two decades of approval, this medication is still widely utilized and is the only intravenous nano-based drug delivery method available for the treatment of retinal disorders [353, 354]. Macugen®, a polyethylene glycol (PEG) aptamer loaded with pegaptanib sodium is the first licensed drug delivery system based on nanotechnology for the treatment of neovascular

AMD. As the first medication in a new class of eye medications, it targets VEGF exclusively. VEGF is a protein that signals aberrant blood vessel formation and leaking in neovascular AMD [355, 356].

After intravitreally injecting 0.3 mg of Macugen®, approximately 1190 patients with all subtypes of neovascular AMD participated in two pivotal phase II/III, randomized, multicenter, double-blind clinical trials. At 54 weeks, 70% of patients experienced less vision loss than 55% of the placebo group [357]. After 2 years, patients who received 0.3 mg of Macugen® experienced a nearly 50% improvement compared to those who received placebo injections. The fact that Macugen® is the first aptamer therapy authorized for use in humans so highlights its noteworthy distinction and provides insight into potential uses for aptamers in the future.

In order to relieve inflammation brought on by illness or trauma, Triesence® is injected into the eye. Usually, it is administered following the unsuccessful use of steroid eye drops to relieve symptoms. Triesence is also used during a certain type of eye surgery (vitrectomy). Similarly AzaSite® is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of microorganisms such as Haemophilus influenzae, Staphylococcus aureus etc. Cationorm® is a hydrating and lubricating emulsion which protects the ocular surface and relieves the discomfort and irritation due to dry eye caused by prolonged use of contact lenses or environmental condition. EYSUVIS® is the first and only FDA-approved corticosteroid for short-term (up to two weeks) dry eye treatment.

OZODROP® IVT is a protective, lubricating, moisturizing and soothing ophthalmic solution for the ocular surface used for protection before and after eye surgery, treatment of symptoms related to inflammation and promoting reparative processes after surgical or traumatic stress.

The potential of other nanocarriers, like nanomicellar and nanoemulsion to treat a range of eye conditions have been extensively studied. Table 5 refers to different FDA approved formulations available commercially for various ophthalmic disorders.

Table 5 Clinically approved formulations for ophthalmic diseases

Formulation	Product	Active Drug	Approved application	Administration route	Approval year to market

Nanoemulsion	Restasis	0.05% Cyclosporine	DED	Topical	2002
Nanoparticles	Triesence®	Triamcinolone acetonide	DED/Vitrectomy/Uveitis	Intravitreal	2007
Nanoemulsion	Ikervis	Cyclosporine	DED	Topical	2015
Micelles	AzaSite®	Azithromycin	DED, keratitis; eye inflammation	Topical	2007
Nanoemulsion	Cationorm®	Medical device	DED	Topical	2008
Micelles	Cequa®	0.09% Cyclosporine	DED	Topical	2018
Polymeric nanoparticles	Eysuvis®	0.25% Loteprednol etabonate	DED	Topical	2020
Liposomal drops	Artelac Rebalance®	Vitamin B12	DED	Topical	NA
Nanoemulsion	Cyclokat®	0.1% Cyclosporine	DED	Topical	NA
Nanoemulsion	Lacrinmune®	Cyclosporine	DED	Topical	NA
Liposomes	Lacrisek®	Vitamin E and Vitamin A-palmitate	DED	Topical	NA
Nanoemulsion	Cyporin-N®	0.05% Cyclosporine	DED	Topical	NA
Liposomes	Visudyne®	15 mg Verteporfin	Wet age macular degeneration	Intravenous	2000
Aptamer-nanoparticles	Macugen®	Pegaptanib	Wet age macular degeneration	Intravitreal	2004
Liposomes	Ozodrop®	0.5% Ozonized oil	Post cataract surgery infection	Topical	NA
Nanoemulsion	Durezol®	0.05% Difluprednate	Postoperative Eye inflammation and pain	Topical	2008
Solution	BromSite®	Bromfenac	Postoperative Eye inflammation and pain	Topical	2016
Polymeric nanoparticles	Inveltys™	1% Loteprednol etabonate	Postoperative Eye inflammation and pain	Topical	2018
Implant	Retisert®	Fluclorolone	Uveitis and macular edema	Intravitreal	2005
Polymeric nanoparticles	Trivaris™	80 mg/ml Triamcinolone acetonide	Uveitis	Intravitreal	2008
Nanosuspension	Tobradex	Tobramycin	hOcular pain,	Topical	2009

	ST®	Dexamethasone	redness and bacterial infection		
Nanosuspension	Besivance®	Besifloxacin	Ocular pain, redness and bacterial infection	Topical	2009
Micelles	Xelpros™	0.005% Latanoprost	Glaucoma (open angle)	Topical	2018
Liposomes	Abelcet®	5 mg mL^{-1} Amphotericin B	Endophthalmitis	Intravenous	1995
Liposomes	Amphotec®	50 and 100 mg vial Amphotericin B Cholesteryl Sulfate	Endophthalmitis	Intravenous	1996
Liposomes	AmBisome®	50 mg vial Amphotericin B	Endophthalmitis	Intravenous	1997
Nanoemulsion	Verkazia®	Cyclosporine	Vernal keratoconjunctivitis	Topical	2021
Polymeric hydrogel	Timoptic-XE	Timolol maleate	Ocular hypertension or open-angle glaucoma	Topical	2018

7.2. Investigational nano ocular formulations

Apart from formulations on market, few innovative nano-based eye drops are presently being studied in clinical studies to determine their efficacy and safety in treating ocular problems. More nanocarriers, including ocular nanomedicines are anticipated to hit the market in the near future despite the fact that the regulatory process for nanocarriers has moved slowly over the previous two decades. Between June 2020 and May 2021, a phase III clinical trial (NCT04246801) was carried out to investigate the benefits of clobetasol propionate nanoemulsion eye drops (SVT-15473) on the alleviation of pain and inflammation in patients following cataract surgery. The purpose of this study was to evaluate the safety and effectiveness of a 0.05% clobetasol propionate ophthalmic nanoemulsion compared to a placebo when given four times a day for 14 days following unilateral cataract surgery. The study involved 210 people in total. In order to treat the pain and inflammation associated with cataract surgery, participants experienced postoperative inflammation on the first day after routine cataract surgery and who meet all other eligibility requirements were randomly assigned in a 2:1 ratio to one of two study groups to

receive either clobetasol propionate ophthalmic nanoemulsion 0.05 % (N=140) or a placebo (N=70). A nanoemulsion technique called Impact-SVT® nanoemulsion (emulsion with nanometricsized particles) was used to create SVT-15473 droplets), to enhance drug-mucus absorption and bioadhesion and to lessen ocular discomfort [358]. Twenty-two hospitals across the United States provided 212 newly cataract-operated patients for this experiment. For this novel nano based delivery technology, the company recently submitted a New Drug Application (NDA) to the FDA for approval with positive outcomes. A unique nanoemulsion drug-delivery technique called IMPACT-SVT enhanced drug penetration and bioadhesion, making it possible to utilize topical drops of a "superpotent" corticosteroid called “Clobetasol”. In terms of ocular surface covering and absorption, the research medication had advantages, although its effect on IOP was minimal. The company reported that upon application, there is no discomfort or clouded eyesight. The therapy has shown no rebound impact in the next two weeks after a typical 14-day course of treatment, therefore a taper is not necessary. In addition, a randomized, double masked, vehicle-controlled phase II study using loteprednol etabonate nanoparticle eye drop for the treatment of meibomian gland illness was completed at roughly 8 centers in the United States (NCT02218489). This study's main goal was to compare the safety and effectiveness of KPI-121 ocular suspension to the vehicle (placebo) in individuals exhibiting symptoms of inflammatory meibomian gland disease. KPI-121 drug product is a sterile, aqueous, submicron suspension of loteprednol etabonate. Over the course of the 28-day study, 1-2 drops of the product will be administered four times a day (QID) to each eye. To treat cataracts, a recent Phase II clinical trial (NCT03001466) engaged in testing the therapeutic effect of a urea-loaded nanoparticulate system was conducted. Pluronic® F-127 copolymer-based polymeric nanoparticles were employed to increase the effectiveness of urea. The trial, conducted between December 2014 and April 2016, involved all 51 patients with cataracts from The Assiut University Hospital's outpatient clinic. Two groups of these patients were chosen at random. Eleven cases (22 eyes) in Group I (control) utilized eye drops containing Balance Salt Solution (BSS). Group II consisted of 40 cases (67 eyes) that received treatment with the urea NPs solution eye drops. The differences in the patients' visual acuity at six months were measured [359]. In one another clinical trial's main findings demonstrated that, INVELTYS, when taken twice a day for two weeks, safely and efficiently reduced postoperative ocular inflammation Mucus-penetrating particles that allow the drug to effectively permeate the tear film and facilitate drug release into

the targeted tissues may be responsible for the reported results [360]. A multi-center cohort open-labeled study (NCT02371746) has been initiated to assess the safety and effectiveness of ENV 515 (travoprost XR) in the management of glaucoma and ocular hypertension. This study was conducted over the course of 28 days, 6 months and 12 months with optional 6 months extension. Clinical trials are currently underway for AR-13503 (NCT03835884) and AR-1105 (NCT03739593), intravitreal implants created with PRINT technology to treat AMD and DR. AR-13503 is a 24-week, two-stage, first-in-human research. A multicenter, open-label study of the safety and tolerability of a single intravitreal administration of AR-13503 SR Implant at increasing doses is Stage 1, and a multicenter, single-masked, randomized, parallel group study of the safety and initial response of AR-13503 SR Implant alone and in combination with aflibercept versus aflibercept alone is Stage 2. AR-1105 trial will assess the effectiveness, safety and tolerance of the dexamethasone implant in treating macular edema (ME) caused by retinal vein occlusion (RVO). A longer-lasting intravitreal implant with a low dosage of dexamethasone may lead to fewer retreatments and may reduce the frequency of steroid-related side effects.

Despite the fact that nano-based drug delivery systems can pass through the biological barrier and accumulate in the ocular tissues when used for topical instillation, a few have been approved for commercial use. The clinical transition of topical instillation in the treatment of posterior segment disorders has not been the subject of many clinical investigations.

In a recent Phase II clinical trial (NCT02466399), an open-label, randomized, multi-center, active-controlled parallel-comparison of POLAT-001 to latanoprost ophthalmic solution in patients with ocular hypertension and primary open-angle glaucoma was studies *via* subconjunctival injection. In this trial, 80 people with high IOP and open-angle glaucoma were enrolled. After three months of treatment, the variations in IOP were assessed to evaluate the safety and effectiveness of latanoprost eye drops and liposome latanoprost (POLAT-001).

Another in phase II/III clinical research (NCT05066997), highlighting the use of dexamethasone nanoparticle eye drops (OCS-01) to treat diabetic macular edema (DME). The OCS-01 ocular suspension contains 1.5% dexamethasone and is made using OPTIREACH technology, which improves drug permeability and bioavailability in eye tissues by taking use of special properties of drug/cyclodextrin nanoparticles. The study eye received 1 DexNP eye drop 3 times a day (every 8 hours) for 12 weeks in comparison to vehicle administration. These cyclodextrin

nanoparticles have demonstrated the ability to increase drug concentrations in ocular tissues, especially for the treatment of diabetic macular degeneration (DME) as demonstrated by animal research and early clinical trials. In 133 DME patients, the trial fulfilled its pre-established efficacy goals and showed that OCS-01 eye drops were more effective than vehicle eye drops, which were the same as the active treatment but did not contain dexamethasone, in lowering central macular thickness and enhancing visual acuity [361]. Table 6 shows some recent patents on ophthalmic delivery products and those in various clinical trial phases in the past few years.

In order to improve patient and population health, translational and implementation sciences seek to prioritize and direct efforts to increase the effectiveness and pace of scientific innovation across the translational science continuum. To increase the applicability and effect of scientific innovation, important ideas and procedures from translational and implementation science can be applied to clinical trial research, especially pragmatic trials. Although the need to expedite the translation of knowledge into clinical practice has gained more attention, protocolized intervention trials for the generation of evidence are frequently designed with little regard for evidence translation, making it difficult to incorporate innovation into workable and sustainable health care programs and policies in real-world settings. Clinical research can progress the conversion of scientific innovation into better patient care and public health by incorporating translational and implementation science concepts and practices. The "bench-to-bedside" migration of discoveries from the controlled research laboratory to ordinary clinical or community settings is thus reflected in the translational science continuum. The National Institutes of Health and other organizations have made investments in the clinical and translational sciences with the goal of accelerating translational research at every stage of translation. The difficulties or translational blocks that arise between animal and first-in-human studies, efficacy and effectiveness trials and the identification of evidence-based practice and its application in routine care have been described as appearing between particular phases of the translational continuum. The professional and scientific silos that divide each research phase are one of the reasons for these obstacles, which prevent or impede the advancement of basic scientific discoveries to public health impacts. Translational science uses team science and transdisciplinary research to find and fix these translational barriers and to develop efficiencies that will hasten the incorporation of biomedical innovation into applications that enhance population health. To this aim, the scientific tenets of translational science stress developing

generalizable solutions to enduring problems in putting innovation into practice, as well as solving unmet patient, clinic, community, or demographic needs. Utilizing the ideas and methods of implementation science, national funding agencies are promoting transdisciplinary team science more and more in order to increase the return on funds for clinical research investments. While implementation tactics are typically employed in later stages of translation, they can be used at any point in the translation process to help bring innovations or interventions to market. So in summary efforts to transfer scientific innovation from clinical research across the translational continuum into normal clinical practice and larger public health effect can be guided by transdisciplinary team science and the integration of implementation science ideas and methods. It is possible to support translation of innovation, increase adoption, and promote implementation and sustainability of evidence-based practices in clinical research by identifying and characterizing multilevel barriers to and facilitators of the adoption of evidence-based practices into routine clinical care, as well as by developing, applying, and evaluating implementation strategies to address said barriers.

Table 6 Ophthalmic formulations under clinical trials in different phases and status

Formulation	Product	Active Drug	Route	Indication	Phase	Trial ID	Status
Nanoparticles Intracameral implant	ENV515	Travoprost	Topical	Ocular hypertension, open-angle glaucoma	II	NCT02371746	Completed
Nanoemulsion	Catioprost	0.005% Latanoprost	Topical	Glaucoma	II	NCT01254370	Completed
Liposomes	POLAT-001	Latanoprost	Subconjunctival injection	Glaucoma	II	NCT02466399	Completed
Nanoemulsion	OCU-310	0.2% Brimonidine tartrate	Topical	DED	III	NCT03785340	Completed
Nanoemulsion	Nanodrop (PRO-176)	Propylene glycol	Topical	DED	I and II	NCT04111965	Not recruiting yet
Nanoemulsion	TJCS eye drops	Cyclosporine	Topical	DED	III	NCT02461719	Completed
Micelles	AXR-159 ophthalmic	AXR-159	Topical	DED	II	NCT03598699	Completed

Nanoemulsion	TJO-087	0.05% Cyclosporine	Topical	DED	III	NCT05 245604	Completed
Nanoparticles	Haporine-S	Cyclosporine	Topical	DED	III	NCT01 804361	Completed
Nanoemulsion	NOVA22007	Cyclosporine	Topical	DED	III	NCT00 814515	Completed
Nanocrystals	NCX 4251	Fluticasone propionate	Topical	Blepharitis	II	NCT03 926026	Completed
Nanoparticles	DexNP (OCS-01)	Dexamethasone	Topical	Pain and inflammation Post cataract surgery	II	NCT04 130802	Completed
Nanoemulsion	OCU300	Brimonidine tartrate	Topical	Ocular graft disease	III	NCT03 591874	Terminated
Nanomicellar	LX211	Voclosporin	Oral	Non-infectious uveitis	III	NCT00 404612	Completed
Micelles	ISV-303	Bromfenac	Topical	Inflammation following cataract surgery	III	NCT01 576952	Completed
Micelles	ISV-305	dexamethasone	Topical	Inflammation following cataract surgery	III	NCT03 192137	Completed
Nanoparticles	Urea-loaded nanoparticles eye drops	Urea	Topical	Cataract	II	NCT03 001466	Completed
Polymeric nanoparticles	KPI-121	Loteprednol etabonate	Topical	Retinal vein occlusion, macula edema	II	NCT02 245516	Completed
Nanoparticles	TLC399 (ProDex	Dexamethasone	Intravit real	Retinal vein occlusion, macula edema	II	NCT03 093701	Completed
Polymeric nanoparticles	DexNP (OCS-01)	Dexamethasone	Topical	Diabetic macular edema	II and III	NCT05 066997	Recruiting
Nanoparticles	Dexamethaso ne cyclodextrin Eye drops	Dexamethasone	Topical	Diabetic macular edema	II and III	NCT01 523314	Unknown
Liposomes	Coenzyme Q10	Coenzyme Q10	Oral	Ataxia-oculomotor	III	NCT02 333305	Completed

				apraxia 1			
Nanoparticles	Nab-paclitaxel	Paclitaxel	Intravenous	Intraocular melanoma	II	NCT00738361	Completed
Liposomes	Marqibo	Vincristine sulfate	Intravenous	Metastatic malignant uveal melanoma	II	NCT00506142	Completed
Antibody biopolymer conjugate	KSI-301	VEGF antibody	Intravitreal	wet AMD	III	NCT04964089	Completed
Polymeric nanoparticles	GB-102	Sunitinib	Intravitreal	wet AMD	II	NCT03953079	Completed
Dendrimers	D-4517.2	TKI	Subcutaneous	wet AMD	II	NCT05387837	Completed
Albumin-stabilized nanoparticles	Taxol	Paclitaxel	Intravenous	Uveal Melanoma	II	NCT01200342	Terminated

8. Challenges and future perspectives

In this review, we first elaborated the anatomy and different ocular barriers which posts significant challenges in effective drug delivery and treatment specifically to posterior eye segment. While traditional medications have shown some success in treating ocular disorders, there are still several drawbacks, including inadequate bioavailability, low permeability and ineffective dispersion. The effectiveness of existing treatments can be greatly increased by using innovative drug delivery techniques such liposomes, contact lenses, aqueous gels, nanomicelles, NPs, nanosuspensions, microemulsions, dendrimers and MNs. There are still a number of obstacles to overcome in the development of innovative ocular medication delivery methods, despite considerable advances. Among these is the complexity of production technology and procedures, which restricts the application of nanotechnology-based ocular medication delivery systems in clinical settings. Nanocarriers' stability and safety are the main issues which need to be improved. The capacity of the nano-formulation to self-aggregate at low drug concentrations affects drug entrapment and ultimately results in poor formulation stability, which is the cause of the low therapeutic efficacy. The swelling mechanism of nano-formulation presents another difficulty. Particle size rises when swelling happens, although this constraint can be addressed by managing the swelling mechanism with capping agents or pH-sensitive coatings applied over the

formulation. Additionally several nanoformulations did not fulfill FDA quality standards, and manufacturing challenges rendered the formulation of medications based on nanoapproaches unsuitable for mass production. Therefore, in order to overcome these related obstacles and do so at a reasonable cost, future research should concentrate on the aforementioned issues and on the large-scale production of nanoformulations in accordance with USFDA criteria. A large number of novel medication delivery methods lack thorough *in vivo* assessments in human eyes and are instead predominantly evaluated *in vitro* or on animals. Many new nanocarriers are being developed to increase ocular permeability and bioavailability, but more research is still needed to determine how these nanocarriers distribute throughout the tissues of the eye, particularly the retina, following topical application. In order to improve the medication's bioavailability and efficacy while lowering its toxicity to normal ocular tissues, actively targeted therapies will be able to enhance drug concentration in particular areas, such as the retinal pigment epithelium (RPE), photoreceptors, retinal or choroidal neovascular [362]. It is still difficult to design formulations that will adequately and uniformly distribute the drug throughout retinal lesions by maintaining a good balance between rates of drug release, absorption, and selective target binding. Ocular medication delivery is currently unmet by basic functional nano-based delivery methods. The current tendency is toward materials that are multi-component and complex, blurring the lines between conventional classifications, even while the complexity may increase the costs and challenges associated with large-scale manufacture for prospective clinical translation. In addition to being more intricately designed, delivery systems are also intended to be multifunctional, combining therapeutic and diagnostic capabilities to allow for visual tracking while treating eye diseases [363-365]. Current preclinical and clinical results for nanocarriers have offered hope for safer and more efficient medication delivery to treat disorders of the anterior segment. However, it remains challenging to target nanocarriers to the posterior region, thus an appropriate delivery method that can get pass the ocular barriers is required to administer medicines. Aside from use of nano-drug delivery systems, other approaches to treat ocular disorders include controlled medication release from implants, nano wafers and 3D printed hydrogel technologies. Commercializing nanomedicine requires addressing its safety, scalability and reproducibility. The majority of naturally occurring and biodegradable polymers are thought to be safe for drug delivery; nonetheless, comprehensive toxicity tests must be carried out prior to commercial acceptance. A few nanocarrier preparation methods have been studied for large-

scale and scale-up manufacturing, but more methods that are easy to use, workable and produce nanomedicines that are approved by regulators need to be explored. More work has to be put into creating cutting-edge non-invasive ODDS that can penetrate beyond ocular barriers, extend the duration of the drug's release and maintain therapeutic concentration at target location. In order to more accurately forecast the safety and effectiveness of delivery vectors, more *in vitro* and *in vivo* studies should be conducted, animal models of eye disorders more similar to those in humans should be produced, and therapeutic impact evaluation techniques should be further enhanced. Compared to traditional ocular medication delivery methods, nanotechnology offers the ability to offer unique functionality and improve therapeutic efficacy. Around 34.32 billion USD in revenue is anticipated to be generated by the global market for ophthalmic pharmaceuticals by the end of 2024, with a compound yearly growth rate of almost 4.7% between 2018 and 2024. The market was valued at nearly USD 25 billion in 2017. In summary, novel drug-delivery systems have undeniable advantages for ocular applications and innovative nano medicines will be increasingly used in clinical practice in the future.

9. Conclusion

Numerous ocular barriers in anterior and posterior segments of the eye, making the successful management of ophthalmic diseases a challenging task. Nevertheless, significant emphasis has been paid to the use of innovative formulations for targeted drug delivery to the anterior and posterior portions of the eye in order to address the drawbacks of conventional formulations. Significant progress has been achieved in the last 10 years in the development of biodegradable ocular DDSs, with the aim of enhancing key characteristics such as drug stability, solubility, corneal permeability and retention time for improved bioavailability, performance, patient satisfaction and compliance. In particular, with the development of innovative vehicles designed for regulated and sustained drug administration to treat vision-threatening disorders, the use of biodegradable polymers in the design of these systems holds the promise of revolutionizing ocular drug delivery. Target-specific and controlled medication delivery to ocular tissues for the treatment of ophthalmic disease has been made possible by advances in nanomedicine. Additionally, the easy-to-scale-up and reproducible technological advancements increase hope for the economical commercialization of nanomedicines. Challenges remain in the clinical application of these nanocarriers despite multiple successful laboratory trials. The heterogeneity

of these nanocarriers, which may lead to therapeutic instability is one of the main obstacles. Furthermore, the immunological response and toxicity are important issues that must be addressed. For improved clinical translation, it is vital to investigate reliable production methods and standardize analytical instruments and methodologies. In general, the utilization of nanomedicines in ocular formulations exhibits great potential; nonetheless additional efforts are required to surmount the obstacles linked to their practical implementation. With further investigation and advancement, these nanocarriers hold great promise for revolutionize the management of ocular illnesses. The design of innovative ophthalmic DDSs remains a future focus and is anticipated to be essential to enhancing ocular health.

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