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Review article

Nanotechnology based drug delivery systems for the treatment of anterior segment eye diseases

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ABSTRACT

Diseases affecting the anterior segment of the eye are the primary causes of vision impairment and blindness globally. Drug administration through the topical ocular route is widely accepted because of its user/patient friendliness - ease of administration and convenience. However, it remains a significant challenge to efficiently deliver drugs to the eye through this route because of various structural and physiological constraints that restrict the distribution of therapeutic molecules into the ocular tissues. The bioavailability of topically applied ocular medications such as eye drops is typically less than 5%. Developing novel delivery systems to increase the retention time on the ocular surfaces and permeation through the cornea is one of the approaches adopted to boost the bioavailability of topically administered medications. Drug delivery systems based on nanotechnology such as micelles, nanosuspensions, nanoparticles, nanoemulsions, liposomes, dendrimers, niosomes, cubosomes and nanowafers have been investigated as effective alternatives to conventional ocular delivery systems in treating diseases of the anterior segment of the eye. This review discussed different nanotechnology-based delivery systems that are currently investigated for treating and managing diseases affecting the anterior ocular tissues. We also looked at the challenges in translating these systems into clinical use and the prospects of nanocarriers as a vehicle for the delivery of phytoactive compounds to the anterior segment of the eye.

1. Introduction

The eye is a very delicate and important organ of the body with unique protective physiology and anatomy (Fig. 1). It makes one conscious of the environment and also sends information to the brain and serves as a link between the brain and the outside of the body. Because the eye is active once someone is awake, it is exposed to a lot of environmental hazards and disease-causing agents, which on damage or infection, may affect the quality of vision or even complete loss of vision.

According to the World Health Organization, vision impairment affects at least 2.2 billion people globally, and almost 50% of these cases are preventable [2]. Anterior segment eye diseases (ASED), including uncorrected refractive errors, cataracts, glaucoma, corneal opacity and trachoma, are among the seven leading causes of vision impairment and account for more than 70% of the causes of blindness [3,4]. Vision impairment constitutes a vast socioeconomic burden not just for the individual but the whole society. Other ASED such as dry eye diseases and conjunctivitis, though not vision-threatening, significantly affect the quality of life. Hence, they pose a serious global health challenge.

Drug delivery to the anterior one-third part of the eye (conjunctiva,

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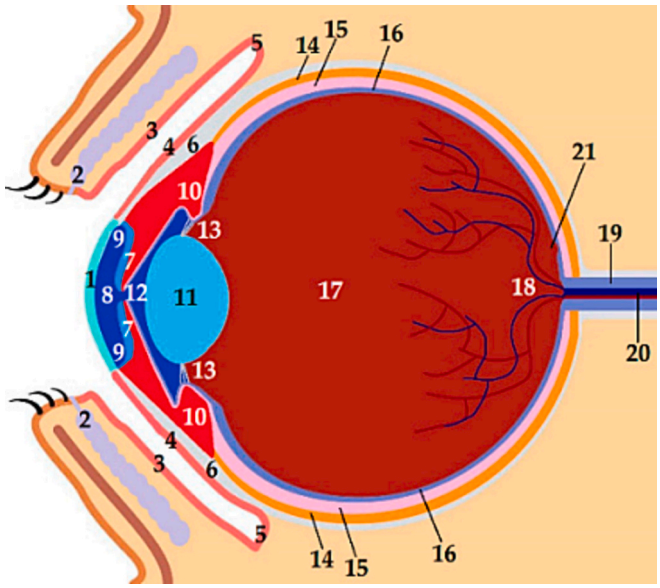

Fig. 1. Anatomy of the human eye: 1 - cornea; 2 - meibomian glands; 3 - palpebral conjunctiva; 4 - bulbar conjunctiva; 5 - conjunctival fornix; 6 - sclera; 7 - iris; 8 - anterior chamber; 9 - iridocorneal angle; 10 - ciliary body; 11 - lens; 12 - posterior chamber; 13 - suspensory ligament; 14 - choroid; 15 - retinal pigmented epithelium; 16 - retina; 17 - vitreous body; 18 - optic disc; 19 - optic nerve; 20 - central artery and vein of the retina; 21 – fovea. Reprinted from [1] under the terms and conditions of the Creative Commons Attribution (CC BY) license.

cornea, aqueous humour, iris, ciliary body and lens) may be effectively accomplished via topical, subconjunctival, or intracameral routes [5]. Both subconjunctival and intracameral routes are invasive and are associated with complications such as toxic anterior segment syndrome, cystoid macula edema, glaucoma, and endothelial cell loss [6]. The topical route is the most widely accepted route for administering therapeutics to the anterior part of the eye because of its user/patient friendliness - ease of administration and convenience [7]. Topically administered ocular drugs can penetrate the cornea through paracellular or transcellular pathways. The paracellular path entails the movement of drug particles via the intercellular space and tight junctions, while the transcellular pathway involves drug transport through the cells to the aqueous humor, but this transport has to be facilitated by either chemical manipulation of the drug structure (e.g., prodrug approach) or formulation approaches involving nanotechnology. From the aqueous humor, the drugs are distributed to other ocular tissues, where they exert their pharmacological action.

Although the topical route is non-invasive, handy and can be self-administered, there is a significant challenge to efficiently delivering drugs because of various anatomical and physiological barriers restricting the entry of therapeutic molecules into the ocular tissues [8]. Reflex blinking, tear turnover, and nasolacrimal drainage all work together to stop topically applied drugs from penetrating the eye [9]. In addition, the multilayer corneal structure is an important structural barrier to topically administered ocular drugs. Besides, the unproductive systemic absorption via the conjunctiva, choroid and uveal tract also limits drug access to the anterior segment. As a result, the amount of topically administered therapeutics reaching the aqueous humor is typically less than 5% [10].

Different approaches have been suggested to overcome these obstacles in ocular drug delivery. The development of novel drug delivery systems is one of the approaches adopted to enhance the absorption of topically applied drugs in the eye [11–13]. In the past few decades, research has been conducted on developing and applying new delivery systems to enhance the ocular retention time, and enhance mucoadhesion and permeation through the cornea [14,15]. Novel drug delivery systems based on nanotechnology such as micelles, nanosuspensions, nanoemulsions, nanoparticles, liposomes, dendrimers, niosomes, cubosomes and nanowafers have been investigated as effective options to traditional ocular systems in treating ASED [9,13,16,17]. They could overcome ocular barriers to deliver the drug to the target site. The biphasic composition of some nanotechnology-based ocular delivery systems (NODS) enhances the solubility of poorly soluble ocular drugs and improve their feasibility of being delivered as eye drops [18]. Due to their high surface area, NODS interact with the ocular surface to prolong ocular retention time. Moreover, their formulation components, such as chitosan, hyaluronic acid and cationic lipids, may increase the retention time on the ocular surface [11,19]. Besides, some surfactants used in the formulation of these systems enhance the trans-corneal permeation of drugs, increasing the bioavailability in intra-ocular tissues [20,21]. Additionally, NODS act as drug reservoirs and result in sustained drug delivery, minimized administration frequency and better patient compliance [22,23]. Besides, nanocarriers protect the entrapped active ingredients from enzymatic and metabolic degradation [24,25].

NODS have the potential for drug targeting and gene delivery to ocular tissues [26–29]. They can be functionalized with peptides and proteins and actively targeted to affected ocular tissues increasing the therapeutic efficacy and reducing off-target toxicity. Therefore, the use of nanocarriers in the therapy of ASED offers many advantages, including the ability to overcome ocular barriers, maximize drug contact time with ocular surface, facilitate transcorneal permeability, decrease drug degradation, achieve sustained/controlled release, drug targeting and gene delivery. There is a resultant reduction in the frequency of administration and adverse effects, as well as increased patient compliance and clinical outcomes. Several reviews have been published on application of nanotechnologies in ophthalmology in the last 5 years [9,30–32] focusing on various aspects of therapy and diagnostics of ocular conditions. One of these reviews [30] specifically looked at the use of nanotechnology for drug delivery to the anterior segment of the eye, focusing mostly on different types of nanomaterials. However, our review presents an overview of the most common anterior segment eye diseases, discusses anatomical and physiological barriers to topical drug delivery, describes different types of materials and nano-formulations, and looks at the challenges in translating these systems into clinical use. It also highlights the prospects of nanocarriers as a vehicle for the delivery of phytoactive compounds to the anterior segment of the eye.

2. Anterior segment eye diseases (ASED)

Diseases affecting the anterior segment of the eye include conjunctivitis, dry eye syndrome, keratitis, cataract, ocular hypertension (glaucoma), anterior uveitis, pterygium, corneal cystinosis and keratoconus. These conditions will be briefly discussed below.

2.1. *Conjunctivitis*

Conjunctivitis (pink eye) is an inflammation or swelling of the conjunctiva. It is one of the most common eye problems, although it is rarely severe and unlikely to damage vision if treated early. Conjunctivitis can be caused by allergens, infections or chemicals [33]. Allergic conjunctivitis mainly affects people already suffering from seasonal allergies. Contact lens users are predisposed to allergic conjunctivitis, especially if the lenses are not replaced frequently. Infectious conjunctivitis is caused mostly by streptococcal, staphylococcal bacteria and contagious viruses thriving in common cold. Ophthalmia neonatorum, infectious conjunctivitis that occurs in the first month of life, can be severe and capable of causing permanent visual impairment if not treated early [34]. Chlamydial conjunctivitis accounts for more than 40% of all cases of ophthalmia neonatorum and is transmitted during birth from mothers infected with *Chlamydia trachomatis* [35]. Chemical conjunctivitis may occur due to exposure to harmful chemicals in the environment. Therapy

for conjunctivitis depends on the cause and includes topical antihistamines, non-steroidal anti-inflammatory drugs, antibiotics, antibiotics and steroids [36].

2.2. Keratitis

Keratitis is an inflammation of the cornea and a potentially vision-threatening ocular emergency [37]. It is the primary cause of corneal opacity, the fifth leading cause of blindness and visual impairment globally [38]. Keratitis is a common ophthalmic condition characterized by acute ocular pain, redness of conjunctiva and eyelids, decreased vision, corneal ulceration, and stromal infiltrates. Infectious keratitis can be caused by bacteria, fungi, Acanthamoeba, and viruses [39]. Non-infectious keratitis can also occur due to injury to the cornea, prolonged use of contact lenses, or very dry eye.

Treatment of this condition depends on the type of keratitis and varies from artificial/antibiotic eye drops to corneal transplants. However, the insufficiency of donor corneal tissue limit transplant surgery [40]. Besides, there may be complications after corneal surgery ranging from inflammation to corneal transplant rejection requiring administration of immunosuppressants, antibiotics and anti-inflammatory drugs.

2.3. Dry eye disease (DED)

Dry eye disease, also known as keratoconjunctivitis sicca, is a damage to the ocular surface caused mainly by the lack of sufficient tears to lubricate the eye. It is characterized by tear film instability, hyperosmolarity, inflammation, and damage to the ocular surface [41]. Dry eye is a common eye disease with a prevalence of 5-50% globally [42]. Dry eye is a chronic disease; symptoms include ocular heat, pain, irritation, soreness, foreign body sensation and diminished visual acuity. Some of the most commonly used treatment options include artificial tears containing water-soluble polymers and punctual plugs.

2.4. Cataract

Cataract is the clouding of the ocular lens causing vision impairment. It is the major cause of blindness and the second major cause of visual impairment globally [4]. Although it can result from an injury that changes the lens, it develops with age. The proteinous component of the lens tends to clump together with increasing age. As a result, the lens becomes cloudy and reduces the amount of light getting to the retina. The treatment available for cataract is the lens replacement surgery. However, postoperative adverse effects such as endophthalmitis and suprachoroidal haemorrhage are common with lens replacement surgery and require drug therapy [43].

2.5. Glaucoma

Glaucoma is a set of conditions that can cause impairment and loss of vision through progressive destruction of the optic nerves. It is considered the second largest cause of vision loss globally [4]. The gradual degeneration of the nerve fibers at the back of the eye as a result of increased fluid buildup in the anterior portion of the eye is the characteristic feature of glaucoma. Ocular hypertension (an increase in intraocular pressure) results in fluid buildup. Open-angle glaucoma is a common and chronic type, while closed-angle glaucoma is usually the acute and painful type of glaucoma.

Blindness or vision loss from glaucoma can be avoided with early detection and treatment [44]. Treatment options range from topical eye drops to laser surgery or a combination of these methods. Reduction in intra-ocular pressure is the most effective way to treat glaucoma. Prostaglandins analogues, carbonic anhydrase inhibitors, miotic agents, alpha agonists and beta blockers are topically applied as eye drops to reduce intraocular pressure [45].

3. Ocular barriers

The anatomical structure and physiological properties of the eye obstruct the entry of drugs and other chemicals into the eye. The main barriers encountered by ocular drugs can be grouped into precorneal, corneal, and blood-ocular barriers. These barriers can be static, dynamic, or metabolic [46].

3.1. Pre-corneal barriers

The pre-corneal barriers are barriers encountered by topically administered drugs before it comes in contact with the cornea. They include barriers of the tear film, limited lacrimal volume and spillage, tear production, reflex blinking and nasolacrimal drainage. Tear film, which consists of an outermost oily, a middle aqueous, and an innermost mucin layers, is the first obstacle faced by topically administered ocular medications. The structure of the tear film is shown in Fig. 2. The outer and middle layers of the tear film act as barriers for lipophobic and lipophilic compounds, respectively. Mucins, large and highly glycosylated proteins, constitute the innermost layer of tear film. These negatively charged compounds interact electrostatically with cationic drugs or nanocarriers but repel anionic drugs and delivery systems [47].

Furthermore, the aqueous phase comprises proteins and enzymes that can bind and metabolize drugs, reducing the fraction of free drugs. Metabolism of ocular drugs can occur by the action of enzymes such as cytochrome P-450, esterases, and peptidases found in tear film [46]. Under normal circumstances, drug-protein binding and drug metabolism in the tear film are insignificant because of the low concentration of protein (6-11 mg/mL) [48]. However, this concentration is markedly increased in inflamed eyes.

The human eye can accomodate about 7-30 μL of fluid without spilling, whereas the typical eye drop dispensers deliver roughly 50 μL [49,50]. Consequently, a substantial amount of the medicine is lost due to the spillage of the excessive fluid. In addition to this limited ocular volume, the human tear turnover rate of 14.9% every minute minimizes drug contact time with the ocular surface, as the drug is totally washed out in the first few minutes [51].

Another vital route for eliminating administered drugs from the ocular cul-de-sac is nasolacrimal drainage. The ocular drugs are drained through the nasolacrimal duct into the nasal cavity where they are systemically absorbed as shown in Fig. 3.

3.2. Corneal barriers

Two possible paths available for topically administered medicinal compounds to reach the intraocular tissues are transcorneal and conjunctiva/sclera pathways. In the transcorneal pathway, drugs diffuse through the cornea to the aqueous humor where the drug is distributed to other tissues. The primary route of intraocular drug absorption is the cornea, which acts as the second physical barrier to topically

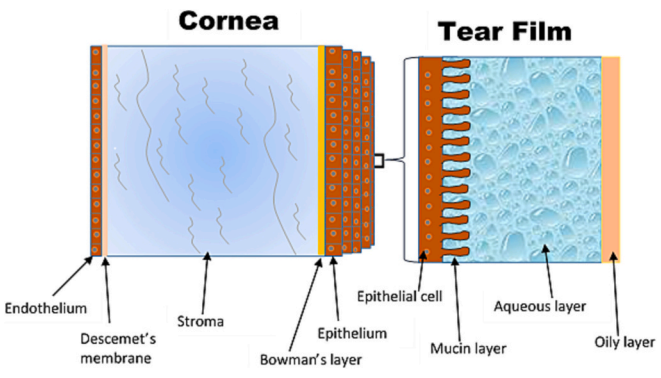

Fig. 2. Structure of the tear film and cornea

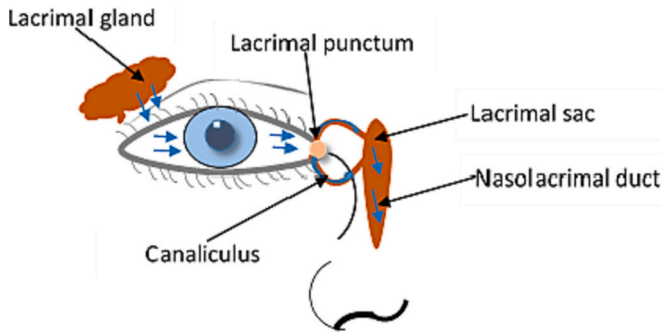

Fig. 3. Nasolacrimal drainage system

administered ocular drugs. It has a small surface area (less than 6% of the ocular surface) and is relatively impermeable due to its multilayered structure with combination of lipophilic and hydrophilic layers. The corneal epithelium, stroma and endothelium are the main structural barriers to ocular drug delivery [52]. The structure of the cornea showing the three structural barriers is shown in Fig 2.

The corneal epithelium is a five to seven-layered lipophilic structure and acts as a barrier to hydrophilic drugs [53]. At physiological pH, the corneal surface is negatively charged due to the presence of acidic groups such as sialic acid residues on the apical surface of the epithelium. Therefore, negatively charged drug particles may penetrate slower than positively charged ones.

The corneal epithelial cells establish tight junctions between cells with small paracellular pore sizes of 2.0 nm, thus forming a strong permeation barrier for hydrophilic drugs [54]. Generally, medicinal compounds with a molecular radius greater than 5.5 Å or a molecular weight higher than 500 Da cannot cross the corneal epithelium via the paracellular pathway [55–57]. The corneal stroma, which represents 90% of the cornea, is hydrophilic because of its high water content. Even though it permits the diffusion of molecules up to 500 kDa in size, penetration of lipophilic drugs is limited [58]. The corneal endothelium consists of a single cell layer with intercellular tight junctions limiting the diffusion of hydrophilic drugs. Similarly to the epithelium, hydrophilic compounds permeate more slowly than hydrophobic molecules. However, the endothelium permeability barrier is weaker because of the lower cell thickness. Besides, the porous cell network design of the endothelium enables the movement of macromolecules up to 70 kDa [59].

The precorneal and corneal impediments decrease the ocular bioavailability of topically administered drugs to below 5% [60]. Since the cornea has a complex multilayered and impermeable nature, only small molecules with optimal hydrophilic/lipophilic properties can efficiently penetrate these layers.

3.3. Conjunctival barrier

Compared to the cornea, the conjunctiva has a larger surface area (17 times higher), wider intercellular spacing, and higher permeability to drugs [53,61]. Nevertheless, the permeation of topical ocular drugs through the conjunctival/scleral route is considered non-productive. This is due to the presence of blood and lymphatic capillaries, which reduce ocular bioavailability by producing considerable drug outflow into the blood circulation [61].

3.4. Blood-ocular barrier

The blood-ocular barrier consists of the anterior blood-aqueous barrier and the posterior blood-retina barrier. The blood-aqueous barrier is the anterior eye segment barrier that prevents the permeation of drug molecules from the systemic bloodstream into the anterior portion of the eye. It is formed by the endothelium of the iris and ciliary muscle and the posterior iris and non-pigmented ciliary epithelium. The existence of tight intercellular junctions in the non-pigmented ciliary epithelium limits the passage of substances with large molecular weight or high hydrophilicity to the posterior chamber. The blood-retinal barrier is the posterior blood ocular barrier that restricts drug entry from the systemic circulation into the back of the eye. The blood-retinal barrier comprises the outer (also called the retinal pigmented epithelium, RPE, Fig. 4) and the inner blood-retinal barriers. Both barriers restrict molecule permeation between the blood and the retina depending on the molecules' size, charge, and lipophilicity [62,63]. In addition, tight junctions in RPE limit the paracellular transport of hydrophilic compounds. Hence, RPE limits the permeation of high molecular weight and hydrophilic molecules from the systemic circulation into the retina.

3.5. Efflux pump and melanin binding

In addition to the structural barriers, efflux pump and melanin binding of molecules are barriers to effective absorption of ocular drugs into intraocular tissues. Permeability glycoprotein (P-gp) and multidrug resistance protein, present in the apical surface of conjunctiva, cornea, iris, ciliary body and RPE, are the two major efflux proteins involved in drug efflux [65,66]. They promote the efflux of drug molecules from these cells, thereby reducing intracellular drug concentration.

Like drug-protein binding, drug-melanin binding significantly affects the pharmacokinetics of ocular drugs [67,68]. Melanin found in the ciliary body, iris, choroid and retinal pigmented epithelium bind reversibly to basic and lipophilic drugs reducing the concentration of free drug [67,69].

4. Pharmacokinetics in anterior ocular segment

Topically administered ocular drugs are distributed from the precorneal surface to the anterior segment of the eye mainly through the cornea and the conjunctiva/sclera pathways as shown in Fig. 5.

Drugs passively diffuse through the cornea to the aqueous humor by paracellular or the transcellular pathways. The paracellular pathway is the main route of passive drug ion movement and anatomically involves the intercellular space. It is limited by the presence of tight junctions. The movement of drug through this route is dependent on the lipophilicity, pKa and solubility of the drug. In transcellular pathways, the drug molecules permeate into the lipid cell membranes of the cornea influenced by the molecular size, charge and lipophilicity [70].

Drug penetration through conjunctiva/sclera pathway involves distribution of drug from the lacrimal fluid to the intraocular tissues through the conjunctiva and sclera. The conjunctiva is highly permeable to hydrophilic and large molecules which have poor penetration across the cornea [71]. However, the permeation of topical ocular drugs through the conjunctival/scleral route is considered non-productive. This is due to the presence of blood and lymphatic capillaries producing considerable drug outflow into the blood circulation, thereby reducing the ocular bioavailability of the drug [61].

In addition to cornea and conjunctiva routes, small quantity of drugs reach the anterior eye segment from the blood via blood–aqueous barrier. The drug distribution through this barrier depends on the molecular weight and lipophilicity of the drug, as well as the effects of ocular transporters, protein and melanin binding.

Once a drug crosses the cornea, sclera or blood aqueous barrier, it reaches the aqueous humor and anterior uvea (iris and ciliary body). Binding to melanin found in the anterior uvea can reduce the ocular bioavailability of drugs, as well as act as drug reservoir for the slow release. Half-lives of drugs in the anterior chamber are typically short, about an hour as drugs are eliminated from the aqueous humor either by the aqueous humor turnover to the trabecular meshwork and Schlemm's canal; or by the venous blood flow of the anterior uvea through the blood aqueous barrier [72].

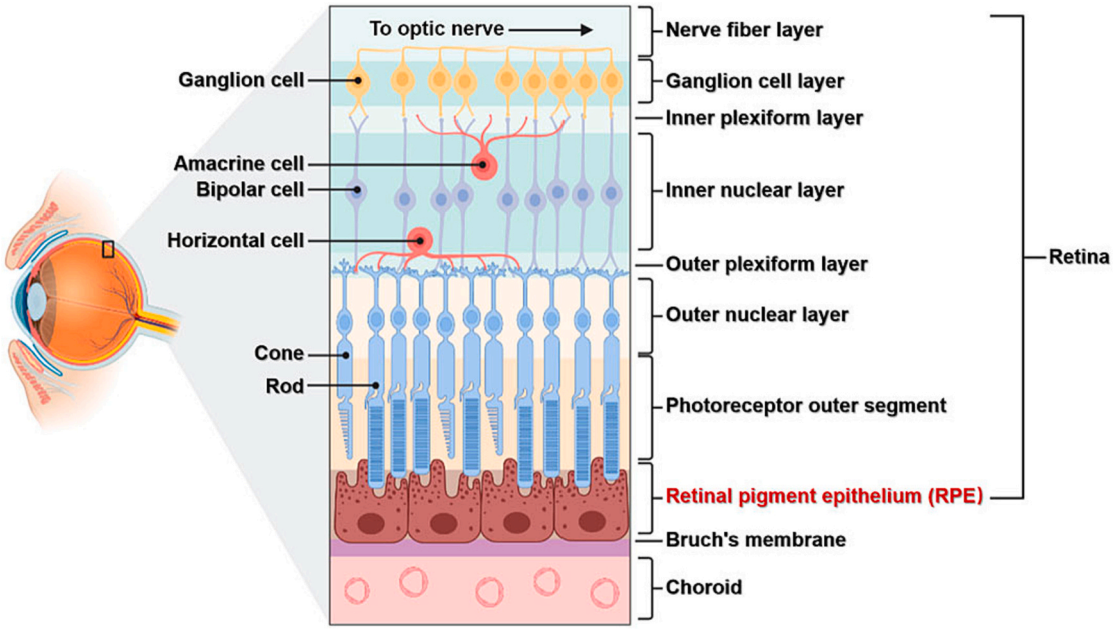

Fig. 4. Retinal pigmented epithelium. Reprinted from [64] with permission from Frontiers.

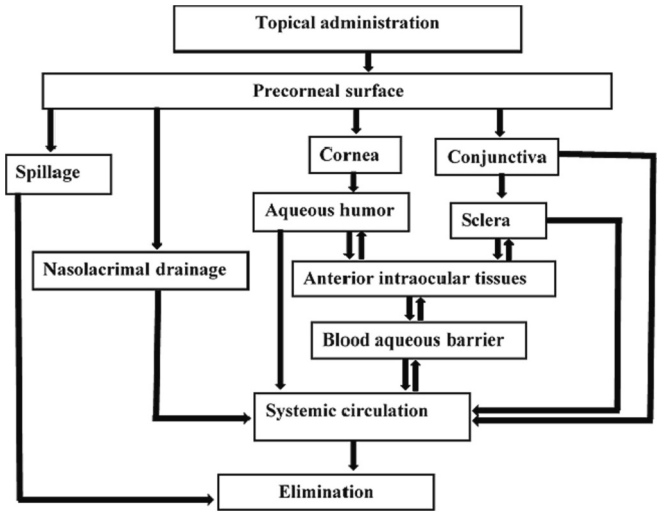

Fig. 5. Disposition of topically administered drug in the anterior segment of the eye

5. Nanotechnology-based delivery systems

Some of the nanocarriers that have been developed for ASED are micelles, nanosuspensions, nanoemulsions, nanoparticles, liposomes, niosomes, dendrimers, cubosomes and nanowafers. Nanotechnology delivery systems are expected to change the status quo in ocular drug delivery systems, especially for ASED. Numerous advantages can be attributed to nano ocular delivery systems including enhancement of bioavailability. Formulation of nano ocular delivery systems however involves rigorous development processes and careful choice of excipients/materials are required to ensure the desired efficacy and safety.

5.1. Formulation materials and methods for nanotechnology-based drug delivery systems

The major constituents of nanocarriers used as a vehicle for ocular delivery are the active pharmaceutical ingredients (drugs, phytochemicals, peptides and genes), polymers, lipids, and stabilizers. These formulation materials are outlined in Table 1.

5.2. Active pharmaceutical ingredients

The active pharmaceutical ingredients employed in NODS include drugs from different pharmacological classes such as anti-inflammatory, antimicrobials, immunosuppressing and antiglaucoma drugs [73–77]. NODS have also been utilized in targeting peptides and genes in ocular tissues for the prevention and treatment of cataract, DED, conjunctiva fibrosis and other ocular diseases [28,78–83]. In addition, phytochemicals with anti-inflammatory, antioxidant or antimicrobial activity such as naringenin, resveratrol, hesperetin, glycyrrhizin, curcumin, epigallocatechin gallate and myricetin, have been investigated for delivery to anterior segment of the eye using NODS [84–87].

5.3. Polymers

Both natural, semi-synthetic and synthetic polymers are utilized in the formulation of ocular nanocarriers. The natural polymers widely used are chitosan, hyaluronic acid, alginate, gelatin, gellan gum and albumin [88–91]. They offer the advantages of biocompatibility and biodegradability. Chitosan is a biocompatible positively charged polymer derived from chitin by deacetylation reaction. In addition to functioning as a mucoadhesive polymer, it enhances corneal drug permeation by reversibly relaxing intercellular tight junctions of the corneal epithelium [92,93]. Although its application is limited by low aqueous solubility at physiological pH, chitosan has been widely utilized in NODS to treat ASED in order to improve the mucoadhesive properties of the system [94–96]. Chitosan being hydrophilic has low encapsulation for hydrophobic drugs, hence the modification and grafting of chitosan with synthetic polymers is commonly explored. Chitosan derivatives with improved water solubility and ease of functionalization, such as galactosylated chitosan, N-trimethyl chitosan and glycol chitosan, are also used in ocular drug delivery [97–101].

Hyaluronic acid is a hydrophilic, biocompatible and biodegradable polysaccharide endogenous in some ocular tissues, including cornea and aqueous humor [102]. Hyaluronic acid binds to CD44 receptors on corneal epithelial cells thereby promoting ocular retention of nanoformulations [103]. It is used as a lubricating agent in eye drops for the

Table 1
Typical active ingredients and excipients used to formulate nanotechnology-based ocular delivery systems

Drug/Excipients	Examples
Active pharmaceutical ingredient	• Anti-inflammatory drugs - dicofenac, pranoprofen, flurbiprofen • Antibacterial - azithromycin, norfloxacin, moxifloxacin, sparfloxacin, ciprofloxacin, gemifloxacin, amikacin, lomefloxacin, vancomycin. • Antifungal - amphotericin B, natamycin, voriconazole • Antiviral - acyclovir, ganciclovir • Immunosuppressant - dexamethasone, cyclosporine A, tacrolimus, tramcinolone • Anti-glaucoma - timolol, carteolol, dorzolamide, acetazolamide, brinzolamide, brimonidine, latanoprost, brimatoprost, travaprost, pilocarpine • Proteins and peptides - lactoferrin, octreotide, catalase, protamine • Genes - transcription factor, plasma DNA, monoclonal antibody • Phytochemicals - naringenin, resveratrol, hesperetin, glycyrrhizin, curcumin, epigallocatechin gallate and myricetin
Polymers	• Natural - chitosan, hyaluronic acid, alginate, albumin, gelatin, gellan gum • Semi-synthetic - sodium carboxymethylcellulose, hydroxypropyl methylcellulose • Synthetic - poly (ethylene glycol), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), poly-lactic acid (PLA), poly(glycolic acid) (PGA), polyvinyl alcohol (PVA), poly(acrylic acid) (PAA), methacrylic acid-methyl acrylate copolymer (Eudragit®), poly (amidoamine)(PAMAM), carbosilane
Lipids	• Triglycerides - trilaurin, trimyristin, tripalmitin, and tristearin (Dynasan® 112, 114, 116, 118, respectively) • Partial Glyceride - glyceryl tribehenate (Compritol®), polyethylene glycol monosterate (Gelucire®), glyceryl palmitostearate (Precirol®) • Wax - cholesterol • Fatty acid - stearic acid • Amphiphilic lipids - glyceryl monooleate (Capmul®), phytantriol • Liquid lipids - oleic acid, castor oil, squalene, olive oil, coconut oil, palmitic oil, soybean oil, glyceryl tricarylate (Miglyol® 812) • Cationic lipids - 1,2-dioleoyl-3-Trimethylammonium-propane (DOTAP), 1,2-dioleoyl-Sn-glycero-3-phospho-choline (DOPC), cetyl trimethylammonium bromide, stearylamine. • Phospholipids - phosphatidylcholine (PC), phosphatidylglycerol, dipalmitoyl phosphatidylcholine, distearoylphosphatidylcholine (DSPC), dioleoyl phosphatidylcholine (DOPC), 1,2 dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE), 1,2-distearoyl-phosphatidyl ethanolamine-methyl-polyethylene glycol conjugate-2000 (DSPE-MPEG-2000), lecithin.
Surfactants	• Polysorbate (Tween®), sorbitan esters (Span®), poloxamers (Pluronic®, Lutrol®), tyloxapol, Vitamin E TPGS (D- α -tocopherol polyethylene glycol 1000 succinate), polyoxyl 40 hydrogenated castor oil (Cremophor RH-40), oleylamine, Solutol HS 15® (Kolliphor HS 15®), Transcutol® P • Co-surfactants – propylene glycol, glycerol, ethanol

symptomatic treatment of DED. Like chitosan, hyaluronic acid is widely used as a coating material for nanocarriers [78,90]. Another important natural polymer in NODS is alginate [83,104,105]. Alginate exhibits good mucoadhesive properties. For example, Kianersi and co-workers reported the preparation of alginate-based nanoparticles with encapsulated betamethasone sodium phosphate using three methods (electrospraying, emulsification and their combination) [105]. These nanoparticles were additionally coated with chitosan and gelatin and evaluated them for ocular delivery.

Semi-synthetic polymers, such as methylcellulose, carboxymethyl cellulose, sodium carboxyl methylcellulose and hydroxypropyl methylcellulose, are usually employed as viscosity enhancing and matrix-forming materials in nanotechnology-based delivery systems [75,106]. Also, several synthetic polymers have been employed in nanocarriers for treating ASED. They include poly(ethylene glycol) (PEG), poly (lactic-*co*-glycolic acid) (PLGA), poly-ε-caprolactone (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(vinyl alcohol) (PVA), poly (acrylic acid) (PAA) and polyamidoamine (PAMAM) [102]. PEG is commonly applied in NODS as a coating material for drug, gene and peptide delivery. It is a water-soluble polymer with stealth properties offering protection to the coated nanocarrier against opsonization and phagocytosis [107,108]. PLA is a hydrophobic polyester that has been used to deliver hydrophobic drugs. Its use in ophthalmology is limited by its poor degradability. To overcome this, lactic acid is usually copolymerized with glycolic acid to form PLGA, a more biodegradable copolymer [102].

Block and graft copolymers combining hydrophilic and hydrophobic polymers are widely utilized in nanocarriers such as polymeric micelles. The hydrophilic component is usually polyethylene glycol. 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000] (ammonium salt) (DSPE-PEG2000), and methoxy-poly (ethylene glycol)- poly(lactic acid) (MPEG-PLA) are examples of co-polymers employed in the formulation of micelles [109].

Polymeric dendrimers are emerging delivery systems for ocular delivery. PAMAM is the first commercialized and most commonly used dendrimer in drug delivery, offering a stable hydrophilic structure that can be easily functionalized for targeted drug delivery. Other dendrimers are poly(propylene imine), polyether-copolyester, PEGylated and peptide dendrimers [110].

5.4. Lipids

Lipids such as triglycerides, partial glycerides, fatty acids, steroids and waxes are employed to formulate lipid nanoparticles [111,112]. Partial glycerides are mixtures of mono-, di- and triglycerides. They offer the advantages of better drug loading and the prevention of drug expulsion resulting from lipid recrystallization [113].

Liquid lipids are also utilized in formulating nanocarriers, especially nanostructured lipid carriers. They are used together with solid lipids in nanostructured lipid carriers to overcome the problems of low drug loading and drug expulsion encountered with solid lipids. They include oleic acid, castor oil, soybean oil, medium chain triglycerides (such as Miglyol® and Labrafac®) [114–117].

Cationic lipids utilized in NODS include 1,2-dioleoyl-3-trimethylammoniumpropane (DOTAP), 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), cetyltrimethylammonium bromide (CTAB), and stearylamine. They are commonly employed in ocular gene delivery to promote the adhesion of the negatively charged gene material to the nanocarrier during formulation [28,83,118,119]. Cationic lipids also facilitate the adsorption of the nanocarriers on the negatively charged ocular surface [28].

Phospholipids such as phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine and their derivatives are employed in preparation of liposomes, lipid polymer nanoparticles, niosomes and nanoemulsions [28,75,90,120]. Their amphiphilic nature promotes the formation of lipid bilayers similar to the cell membrane, enhances drug encapsulation and stability.

5.5. Stabilizers/surfactants

Surfactants act as formulation stabilizers due to their amphiphilic nature. They are essential components of ocular nanotechnology-based systems as they affect the physicochemical and biocompatibility of the systems [121]. Due to their decreased toxicity, non-ionic surfactants such as sorbitan esters or polysorbates are favored in ocular nanocarriers. Nonetheless, benzalkonium chloride, a cationic surfactant, is

commonly used as a preservative in topical ophthalmic preparations. Polysorbate, sorbitan esters, poloxamers, cremophors, tyloxapol, kolliphor, Transcutol® P and vitamin E TPGS (D-α-tocopherol polyethylene glycol 1000 succinate) are common surfactants employed in ophthalmology [122].

6. Nanotechnology-based delivery systems for anterior ocular diseases

Nanotechnology-based ocular drug delivery systems employed in the treatment of diseases affecting the anterior segment of the eye are shown in Fig. 6.

6.1. Micelles

Micelles (Fig. 7) are colloidal drug delivery systems that form spontaneously in a solution when the concentration of the polymer/surfactant is above the critical micellar concentration (CMC) [123]. Amphiphilic surfactants or diblock polymers self-assemble in solutions when a particular concentration or temperature is attained to form micelles [124]. Their dimension ranges from 10-200 nm, and they can take different shapes such as spherical, cylindrical or star shapes. Normal micelles present as effective carriers for hydrophobic drugs in an aqueous solution, while reversed micelles can be employed in the delivery of hydrophilic drugs [125]. Micelles enhance the corneal permeability of topically applied drugs and are good candidates for drug targeting ocular tissues.

The main drawbacks of micelles are difficulty in drug loading, lack of scalability and toxicity effects caused by the use of surfactants, especially the ionic type [126]. Cyclosporin A is a hydrophobic and efficacious immunosuppressant drug employed in treating dry eye disease and for the avoidance of corneal transplant rejection. NODS of cyclosporine A have been extensively investigated to enhance its solubility and ocular bioavailability. Polymeric micelles consisting of a diblock polymer methoxypoly(ethylene glycol) - poly(lactide acid) were developed and loaded with cyclosporine A by thin film dispersion technique. The results showed that the micellar system enhanced the retention time on the precorneal surface up to 4.5 fold and reduced the drug's elimination when compared to cyclosporine emulsion [127]. The drug retention and reduced elimination demonstrate the potential of cyclosporine A micelles in increasing efficacy of the drug in treating DED.

Similarly, surfactant micelles incorporated into *in situ* gelling systems were formulated and studied for the delivery of cyclosporine A. Two non-ionic surfactants - d-α-tocopherol polyethylene glycol succinate and polyoxyl-40-hydrogenated castor oil were employed in formulating the micellar delivery systems. The micelles were then added to gellan gum dispersion to form a clear and easy-to-instill aqueous dispersion [128]. This dispersion transforms to gel once it comes in contact with lacrimal fluid. The combined strategy increased residence time on the ocular surface and demonstrated low toxicity to corneal cells. The ability to form a clear aqueous solution of a hydrophobic drug by micelles is advantageous in the formulation of eye drops.

Block copolymer of 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[amino (polyethylene glycol)-2000] (ammonium salt) (DSPE-PEG2000) was employed to encapsulate flurbiprofen for ocular delivery [109]. DSPE-PEG2000 is a biocompatible and biodegradable material that can be functionalized with various groups including peptides for drug targeting. The DSPE-PEG2000 micelles were functionalized with cyclic arginine-glycine-aspartic acid (cRGD) peptide to enhance mucoadhesive properties as the peptide binds with receptors on the ocular surface. In addition to improved ocular retention and corneal penetration of the drug, an enhancement in the anti-inflammatory

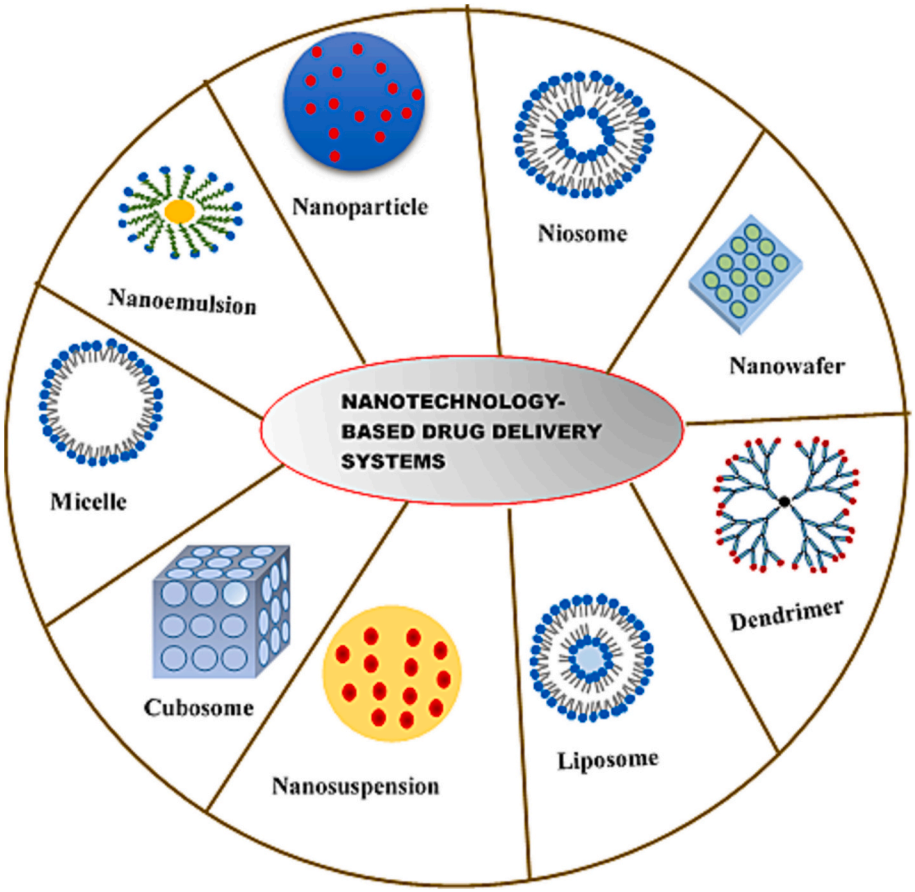

Fig. 6. Nanotechnology-based drug delivery systems for ocular application.

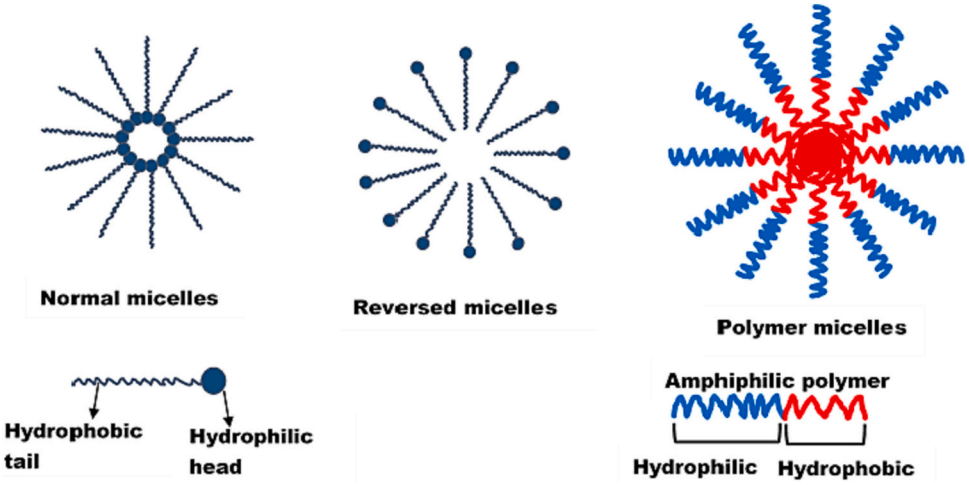

Fig. 7. Structure of normal, reversed and polymeric micelles.

activities of flurbiprofen was observed with the polymeric micelles of flurbiprofen. Thus, polymeric micellar systems have the potential for targeted ocular delivery and treatment of ocular inflammation.

6.2. Nanosuspensions

Nanosuspensions can be defined as colloidal dispersions of insoluble drug particles in a dispersion medium stabilized by an appropriate surfactant or polymer. Nanosuspensions are utilized in the formulation and delivery of aqueous dispersions of hydrophobic drugs to the intraocular tissues. They increase the solubility, retention time and sustain drug release, thereby enhancing the ocular bioavailability of poorly water-soluble drugs [129]. Natural, synthetic, or hybrid polymers are commonly used as stabilizers in the formulation of ophthalmic nanosuspensions. Physical instability (such as sedimentation) and toxicity resulting from the use of surfactants are the limitations of nanosuspensions in treating ASED [126].

The anti-inflammatory agent, flurbiprofen, was formulated as Eudragit RL 100-based nanosuspension by solvent displacement method [74]. The nanosuspension was found to be stable with a sustained drug release profile. Similarly, diclofenac-loaded cationic nanosuspension consisting of chitosan and methoxy poly(ethylene glycol)-poly(ε-caprolactone) diblock copolymer was investigated for treating ocular inflammation [88]. The polymeric nanosuspension showed superior bioavailability, as confirmed by a higher C_{max} in aqueous humor, and twice higher area under the curve than the commercial diclofenac eye drops in the albino rabbit model. The chitosan-coated nanosuspension showed improved corneal penetration and retention, as seen in the *in vivo* corneal penetration test. There was no ocular irritation. In addition, the nanosuspension was very stable in an aqueous humor solution after 24 hours.

Apart from anti-inflammatory agents, nanosuspensions have been used to deliver antimicrobial agents for treating bacterial and fungal infections of the anterior eye. A controlled release of moxifloxacin was observed from poly(lactic-*co*-glycolic acid) nanosuspension with 86% cumulative drug release in 24 h [130]. Furthermore, the nanosuspension showed a better permeation rate, and longer and superior control of bacterial conjunctivitis as against the marketed eye drop, thus reducing the frequency of administration.

A polymeric nanosuspension using Eudragit® RL 100 and Eudragit® RS 100 was employed to increase the ocular bioavailability of amikacin to effectively treat *Staphylococcus aureus* infections of the anterior eye [131]. The nanoparticles were formulated by a water-oil-water emulsification solvent evaporation method and downsized by high-pressure homogenization. From the *in vivo* pharmacokinetic study, it was demonstrated that the polymeric nanosuspension with amikacin was providing 2.12 times greater drug bioavailability than the commercially obtained amikacin eye drops. Nonetheless, the time to attain C_{max} was longer for the nanosuspension. The therapeutic efficacy of amikacin was also improved as the nanosuspension was shown to produce a symptomatic cure in 4 days.

Furthermore, combined moxifloxacin and pamoic acid nanosuspension formulated by ion pairing technique with mucus penetrating properties were studied to treat bacterial keratitis [73]. When compared with three times a day dosing of commercial moxifloxacin eye drops, once daily instillation of moxifloxacin-pamoate nanosuspension provided better prevention and treatment of *Staphylococcus aureus* infections. The drug was well distributed in the anterior ocular tissues including the aqueous humor as shown by the results of the pharmacokinetic study.

Similarly, Eudragit® RS 100-based nanosuspension of voriconazole was formulated by quasi-emulsion solvent evaporation technique to treat fungal keratitis [132]. N-methyl-2-pyrrolidone (Pharmasolve®) was added to the formulation as an ocular permeation enhancer. The suspension exhibited good ocular permeability and significantly inhibited the growth of *Candida albican.*

These promising results suggest that nanosuspensions can be used as an effective platform for delivering poorly water-soluble anti-inflammatory and antimicrobial drugs for treating ocular inflammation and infections. In addition, nanosuspensions have been used as the ocular delivery platform for immunosuppressants [133,134].

6.3. Microemulsions and nanoemulsions

Microemulsions are thermodynamically stable colloidal dispersions of oil-in-water or water-in-oil, stabilized by a surfactant [135]. Microemulsion is similar to nanoemulsion in terms of formulation components but they differ in stability. While microemulsion is thermodynamically stable, nanoemulsion is unstable thermodynamically [136]. There is increasing interest in using microemulsions and nanoemulsions for ocular drug delivery due to several benefits related to the small droplet size and high surface area. Such benefits include high solubilization of drug, non-irritant nature, improved corneal permeability, increased bioavailability, long shelf life, ease of formulation and ability to deliver hydrophilic and hydrophobic drugs [137]. Nonetheless, physical instability and cytotoxicity caused by the use of the large quantity of surfactant in nanoemulsions and microemulsions restricts their usage in ocular drug delivery [126].

Microemulsions are versatile as ocular drug delivery system and were investigated as an efficient ocular carrier for both hydrophilic and

hydrophobic drugs, riboflavin phosphate and triglyceride of docosahexaenoic acid (TG-DHA), respectively [138]. A relatively high quantity of water was used to reduce the cytotoxic effects resulting from the surfactant used. A clear and dilutable microemulsion of the hydrophobic TG-DHA was obtained. The topical administration of microemulsion-loaded TG-DHA relieved the symptoms of dry eye disease. On the other hand, riboflavin phosphate permeated the intact corneal tissue and enhanced the cornea's structural integrity on the administration of riboflavin phosphate microemulsion. The findings demonstrate the potential use of microemulsions in delivering both hydrophilic and hydrophobic drugs to the eye.

In order to overcome the challenge of multiple daily administrations of the conventional travoprost eye drops for the therapy of glaucoma, travoprost-loaded contact lenses were investigated as a viable option. Instead of the soaking method that is commonly used in loading drugs into contact lenses, stable travoprost microemulsion was used [139]. Compared to the contact lens prepared by the conventional soaking method, the drug loading of travoprost microemulsion-loaded contact lens was improved, and the *in vitro* release was prolonged from 42 to 84 h. The swelling and optical properties of the lens loaded with travoprost microemulsion were also improved. The contact lens demonstrated prolonged retention time on the ocular surface in comparison with travoprost eye drops [139]. Thus, microemulsion could enhance the drug loading and physical properties of drug-loaded contact lenses.

To improve the retention and bioavailability of cyclosporine A in treating ASED such as cornea allograft rejection and DED, mucoadhesive nanoemulsion of cyclosporine A was prepared and optimized using the pseudo-ternary phase diagram [76]. Examination by gamma scintigraphy revealed a slow clearance of the nanoemulsion from the cornea surface. Moreover, the concentrations of the drug were maintained within therapeutic levels in the cornea and conjunctiva for 24 h. The extended contact on the ocular surface and improved biodistribution of the chitosan-coated nanoemulsion of cyclosporine A indicates its potential in treating immunological-related anterior eye diseases.

6.4. Nanoparticles

Nanoparticles with sizes between 50 to 400 nm are widely utilized in delivery of therapeutics to the anterior eye as they can overcome physiological barriers and target drugs to specific ocular tissues [140]. They are usually prepared using biocompatible lipids and polymers or a combination of the two to form a hybrid system [94,120,141]. It is increasingly common to coat nanoparticles with mucoadhesive polymers such as chitosan, hyaluronic acid, or polyethylene glycol to prolong the time of residence of the nanocarrier on cornea and conjunctiva [94,142]. Nanoparticles offer several advantages such as high scalability potential, improved transcorneal penetration, sustained drug release, reduced irritation, targeted drug delivery, prevention of premature drug metabolism and non-specific uptake [142].

A novel eye drops consisting of glycol chitosan nanoparticles loaded with cerium oxide were developed for treating dry eye symptoms [100]. Signs such as tear film stabilization, and enhancement in the growth and integrity of conjunctival and corneal cells were observed after treatment with the nanoparticles. These signs are indicative of improvement in the symptoms of DED. Antioxidant biomarkers, such as superoxide dismutase, were enhanced, confirming the capacity of glycol chitosan nanoparticles loaded with cerium oxide to ameliorate the oxidative stress associated with DED.

Hybrid systems of nanoparticles and other nanocarriers can be employed in drug delivery to harness the benefits of both NODS. Both solid lipid nanoparticles and *in situ* gel of triamcinolone acetonide were prepared for topical delivery [143]. For the formulation of triamcinolone nanoparticles, glyceryl monostearate and Compritol® 888 ATO were used as the solid lipids, while Tween® 80 and Pluronic® F-68 were used as surface-active compounds to stabilize these carriers. Gellan gum was added to the optimized solid lipid nanoparticle to form the *in situ* gel. The results of *in vitro* transcorneal permeability study of triamcinolone acetonide nanoparticle and *in situ* gel presented 10.2- and 9.3-fold higher permeability, respectively than the suspension. However, the *in situ* gel showed an elevated amount of the drug in aqueous humor and cornea [143].

A recent study compared the ocular permeation and mucoadhesion of three different solid lipid nanoparticles- with different functional surfaces [94]. Compritol® 888 ATO, poly(2-ethyl-2-oxazoline) and Tween®80 were used to develop the nanoparticles. Poly(2-ethyl-2-oxazoline) was employed as a stealth material similarly to PEG for stabilisation of these nanoparticles. The *in vitro* release of ciprofloxacin from the three formulations after 24 h was similar and ranged from 71 – 75 %. At the same time, the *ex vivo* permeation and mucoadhesion were higher with the chitosan-coated lipid nanoparticles. Nevertheless, there was an improvement in ocular mucoadhesion of the three formulations compared to the control.

In order to reduce the frequency of administration of topical azithromycin and improve patient adherence, a novel single-dose nanoparticle/nanofibre system was developed as an effective alternative to the conventional dosage form in the treatment of ocular infections [144]. The azithromycin-loaded polymer nanoparticles were developed from a combination of poly(lactic-*co*-glycolic acid) and Pluronic F-127®and then added to electrospun poly(N-vinyl pyrrolidone) nanofibre to form the hybrid ocular insert. The multilayered nanoparticle/nanofibre system was biodegradable and mucoadhesive. A single dose of the hybrid system sustained the drug release for over 10 days. This controlled release system offers the benefits of reducing the frequency of drug administration, better patient compliance, reduced adverse drug reactions, and improved therapeutic efficacy [144].

Recently, tacrolimus-loaded polymeric nanoparticles for DED therapy were designed by ionotropic gelation method using natural polymer gellan gum [91]. Increased pre-corneal retention and sustained drug release were observed with the nanoparticles. The result of Hen's Egg Test – Chorioallantoic Membrane and Draize tests, as well as those of histopathological study, established that the formulation was non-toxic and safe for ocular use. Besides, the symptoms of DED were reduced on treatment with the tacrolimus nanoparticles in a rabbit model.

To increase the aqueous solubility and ocular bioavailability of a novel antibiotic agent (tedizolid) Kalam et al. [145] prepared tedizolid phosphate nanocrystals using the antisolvent precipitation technique. The addition of stearylamine and benzalkonium chloride to the formulation conferred a positive charge to the crystals. Compared to the pure drug, an increase in the solubility of the drug-loaded nanocrystal was observed. The reduction in the crystallinity of the nanocrystals, as seen in the DSC and XRD results, contributed to the improved solubility. The formulations demonstrated greater *in vitro* release at 12 h than the aqueous drug solution. In addition, the nanocrystals were stable at 4 ^{o}C, 25 ^{o}C and 37 ^{o}C for 180 days.

Recently, Hu et al. [146] prepared multifunctional betaxolol-loaded nanoparticles consisting of montmorillonite, hyaluronic acid, chitosan and Eudragit RS. The nanosystem increased the retention time of fluorescein on the ocular surface by approximately five folds compared to the drug solution. The IOP-lowering effect of the nanoformulation was better and stable over the 12 h period. The positive performance of this system was attributed to the interaction between the ocular surface and the positively charged nanosystem. The different constituents of the formulation worked synergistically to improve the pharmacokinetic profile of the formulation. Montmorillonite is a porous silicate with an excellent adsorbent property; hyaluronic acid binds with CD44 receptors on corneal epithelial cells, while cationic chitosan enables reversible disruption of tight junctions between corneal epithelial cells [93,103]. The cationic nature and hydrophilicity of Eudragit RS also contributed to the prolonged contact of the nanoparticles with the ocular surface. Apart from minor eye irritation, the multifunctional system presented excellent biocompatibility and reduced cytotoxicity compared to the pure drug.

Nanostructured lipid carriers (NLC) are widely employed as an alternative to solid lipid nanoparticles. The lipid phase of NLC consists of liquid lipid in addition to the solid lipid to form the less organized crystalline structure for more drug loading and less drug expulsion during storage. For the therapy of keratitis, amphotericin B encapsulated NLC was produced by emulsion evaporation-solidification at low temperature and modified with chitosan to enhance mucoadhesive properties of the system to ocular mucosa. The solid lipids used were Compritol® 888 ATO and lecithin, while soybean oil was used as the liquid lipid. The study demonstrated improved transcorneal penetration, sustained release profile and improved ocular bioavailability of amphotericin B from the chitosan-coated amphotericin B NLC when compared to the conventional eye drops and the uncoated NLC [115]. Similarly, chitosan-coated NLC formulated by ionic gelation technique was employed to deliver gemifloxacin to treat bacterial keratitis [148]. The study demonstrated increased amount of drug in the tear fluid and aqueous humour due to higher precorneal retention and increased corneal permeation. Furthermore, the antibacterial activity of gemifloxacin against *Staphylococcus aureus* and *Pseudomonas aeruginosa* was enhanced. Thus, symptoms of bacterial keratitis were ameliorated.

NLC could be exploited in active drug targeting by functionalizing the surface. The functionalization of dexamethasone-loaded NLC with (3-aminomethylphenyl)boronic acid-conjugated chondroitin sulfate (APBA-ChS) was investigated with the aim of the boronic acid group to interact with acidic moieties present in ocular mucins [149]. The non-toxic functionalized NLC demonstrated greater residence time and was able to ameliorate the symptoms of DED. It was concluded that the interaction of the NLC with the ocular surface prolonged the residence time and improved transcorneal penetration and ocular bioavailability of the drug.

In another recent study, a novel scalable NLC system loaded with dexamethasone was developed as eye drops for treating inflammatory symptoms associated with DED [116]. A combination of cholesterol and Labrafac® was used in formulating the NLC, and excellent tolerability of the system on corneal epithelial cells of humans was observed. The dexamethasone loaded NLC demonstrated high internalization capacity by the corneal cells. Furthermore, it down-regulated the levels of pro-inflammatory mediators such as TNF-α, MMP-9 and IL-6.

Lipid-polymer hybrid nanoparticles are novel type of nanocarriers representing a blend of polymeric and lipid particles. These consist of a polymeric core where the active pharmaceutical ingredient is incorporated. The core is surrounded by a phospholipid layer and an outer coating with a lipid-PEG shell [150]. The PEG shell offers steric stabilization by prolonging its circulation in the biological system [151]. Lipid-polymer hybrid nanoparticles combine the mechanical stability and biocompatibility of polymeric nanoparticles and liposomes [120]. The combination of the lipoidal and hydrophilic polymeric properties provides a system with a high loading capacity for various drugs. Advantages of lipid-polymer hybrid nanoparticles include stability, biocompatibility, high loading efficiency, improved retention of the entrapped drug, prolonged circulation time, controlled and sustained drug delivery profile [120,151].

Lipid-polymer hybrid nanoparticles containing hydrophilic moxifloxacin were prepared and investigated for their ability to deliver the drug to the eye [120]. A lipid mixture of 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine, cholesterol and egg phospholipid was employed, while chitosan was used as a polymeric ingredient. The nanoparticles were modified with hyaluronic acid ligand for active targeting. The findings from the study showed that the nanoparticles offered an improved retention time, greater penetration and enhanced ocular bioavailability. The *ex vivo* fluorescence imaging demonstrated higher drug concentrations in the cornea and conjunctiva.

In another study, vancomycin lipid-polymer nanoparticles were formulated to treat ocular bacterial infections using glyceryl tripalmitate as the lipid and Eudragit RS 100 as the polymer [152]. Polymers (chitosan and sodium alginate) and a lipid (oleic acid) were investigated as suitable co-excipients. The encapsulation of vancomycin in the lipid-polymer nanoparticles was improved on the incorporation of the co-excipients. The chitosan-modified nanoparticles showed the best sustained drug delivery. The *in vitro* activity of the formulation against *Staphylococcus aureus,* including the methicillin-resistant strain, was sustained for up to 5 days.

The findings from these studies denote the capacity of nanoparticles in treating infectious and inflammatory diseases of the anterior eye. Nevertheless, nanoparticles have some limitations that hinder their clinical translation for treating ocular diseases. These limitations include difficulties in achieving uniform dispersion of particles, inadequate drug loading, premature drug release during storage and toxic effects associated with the nature and concentration of surfactants used [126]. More research should be carried out to bring nanoparticles into clinical use.

6.5. Liposomes

Liposomes are phospholipid bilayered vesicular systems with a hydrophilic core. There are different classes of liposomes based on the size and the number of bilayers. These classes are small unilamellar, large unilamellar and multilamellar liposomes [153]. Their structure is similar to cell membranes, thus they are highly compatible with biological systems [124]. There is a strong interest in liposomes due to their biodegradability and biocompatibility. In addition, ocular therapeutics with high molecular weight and low solubility can be incorporated into liposomes for effective delivery [154]. Besides, the positively charged liposomal surface facilitates interaction with ocular mucosa prolonging the contact time and corneal permeation.

Liposomal formulations have been studied for the treatment of glaucoma, dry eye and fungal keratitis, and results showed a great potential for clinical translation of these vehicles for treating ocular diseases [155,156]. The challenges of liposomes for ASED include low drug loading capacity and leakage of encapsulated drug, difficulty to scale up, low stability and high production cost [126].

Based on the findings that azithromycin eye drops improve the quality, quantity and stability of tear film, a liposomal system of azithromycin was prepared and investigated for use in the treatment of DED [157,158]. To improve lipophilicity and loading of azithromycin in the liposomes, the drug was first added to cholesteryl hemisuccinate to form an ion pair [156]. A small quantity of medium chain triglyceride oil was also added to improve solubility and stability of the drug in the liposomes, thereby minimizing drug leakage. When compared to azithromycin-loaded liposomes without the ion pairing and oil, the average drug loading was reported to increase from 1.5% to 9.2%, while the entrapment efficiency increased from 74 % to 96%. The liposomal system was stable for three months, even at room temperature. In addition, the drug permeation through the cornea from the liposomes was two-fold greater than the azithromycin solution. Moreover, there was an alleviation of the symptoms of DED by the system.

Lactoferrin, a glycoprotein endogenous in ocular tissues, has been reported to possess many pharmacological activities, including antimicrobial, antifibrotic, anti-oxidative and anti-inflammatory activities [159]. Notwithstanding, its application in ocular delivery is restricted by poor aqueous stability and the high tendency for nasolacrimal drainage. Bovine lactoferrin liposomes coated with hyaluronic acid were investigated for managing DED and ocular inflammation [78]. The formulation method employed was the lipid film method and high-pressure homogenization. Lactoferrin liposomes were found to be non-irritant and stable for over 60 days. Furthermore, lactoferrin was released in a controlled and prolonged manner and was able to ameliorate symptoms of DED.

Moiseev et al [160] has recently reported the design of PEGylated and maleimide-decorated PEGylated liposomes for ocular drug delivery of ciprofloxacin. The *ex vivo* evaluation of their retention on bovine cornea and conjunctiva was evaluated using fluorescence flow-through method. It was established that maleimide-decorated liposomes

exhibited the best retention performance on the conjunctival tissue, which is likely related to the ability of maleimide groups of forming covalent bonds with thiols present in mucins (Fig. 8). However, all liposomal formulations exhibited relatively poor retention on the cornea, which is related to its poorer permeability and lower concentration of mucins present.

Liposomes have also been employed in ocular gene delivery. Myocardin-related transcription factor is a serum response factor that regulates some genes implicated in the pathogenesis of some anterior ocular disorders, including conjunctival fibrosis. Large unilamellar liposomes were designed to deliver myocardin-related transcription factor inhibitors for the treatment of conjunctival fibrosis [28]. The liposomes were formulated using two lipids - 1,2-di-O-octadecenyl-3-trimethylammonium propane and 1,2-dioleoyl-*sn*-glycero-3-phosphocholine. These lipids are positively charged and have been extensively used for gene transfection [161,162]. The researchers found that a large amount of the transcription factor inhibitor could be encapsulated in the proteoliposomes and slowly released over 14 days. The delivery system offers many advantages, including non-cytotoxicity and decreased conjunctival scarring. It also increased the mean bleb survival duration from 11 to 22 days. Furthermore, no local or systemic adverse reactions were recorded.

The use of cell-penetrating peptides (short amino acid sequences capable of penetrating cell membranes) is gaining interest in ocular drug delivery [163]. Flurbiprofen-loaded liposomes functionalized with a cell-penetrating peptide [Trans-activator of transcription (TAT) amino acid sequence] were designed and aimed to improve the transcorneal permeation of flurbiprofen [164]. The functionalized liposomes were found to increase the intracellular calcium ion level and cause the partial opening of the tight junctions. The enhanced permeation of the drug into ocular tissues reduced drug loss. The team reported down-regulation of pro-inflammatory mediators, including interferon-alpha, interleukin-6 and prostaglandin E, resulting in anti-inflammatory activity.

A novel hybrid formulation of liposomes and hydroxypropyl methylcellulose (HPMC) loaded with acetazolamide and dispersed in a solution of trehalose as an osmoprotectant, borates and erythritol was investigated in another study [75]. The efficacy of the liposome-polymer hybrid system in enhancing the ocular bioavailability and hypotensive action of acetazolamide, a poorly soluble antiglaucoma drug, was studied. The dispersion medium simulated the tonicity and pH of precorneal film to preserve its structure and function, while the hydroxypropyl methylcellulose enhanced the viscosity of the formulation. Interestingly, the hybrid system increased the ocular bioavailability of the drug by 30-fold when compared to an acetazolamide solution. The

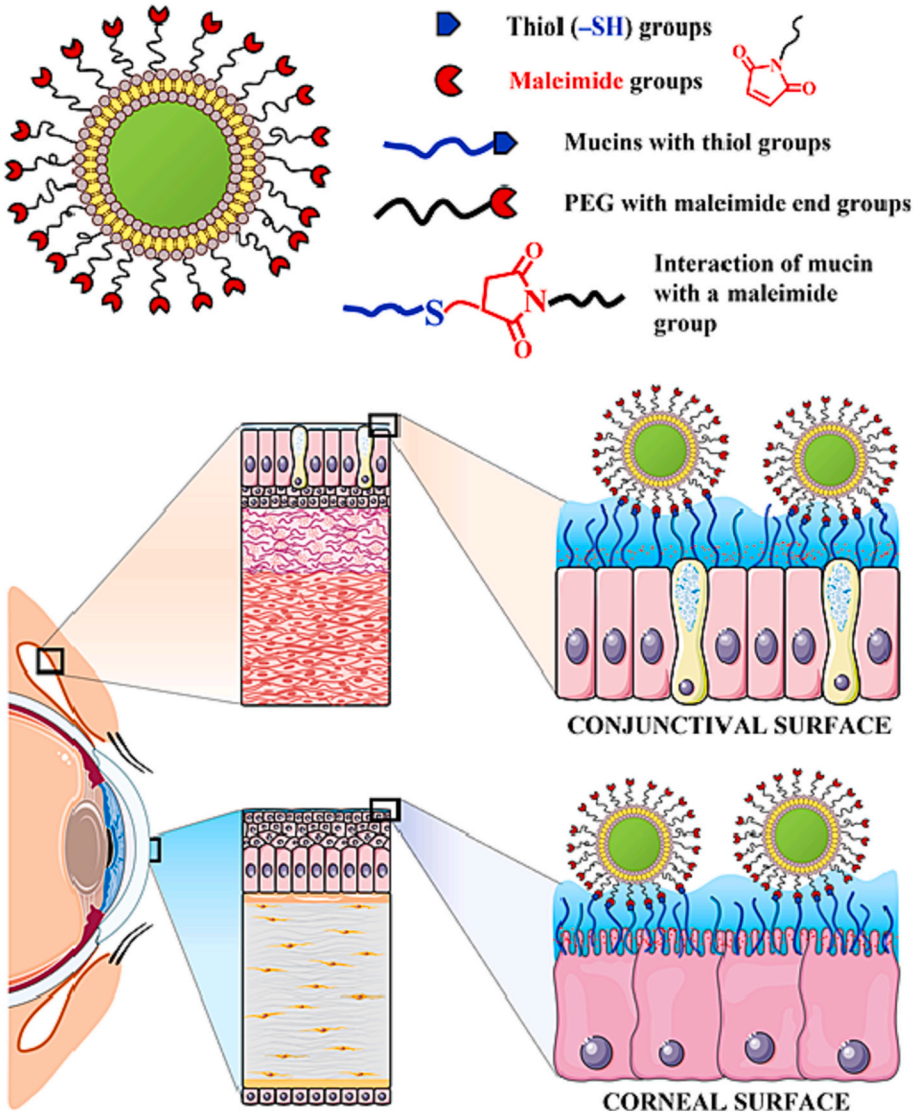

Fig. 8. Structure of liposomes functionalised with maleimide groups and their possible reaction with thiol groups present on the cornea and conjunctiva. Reprinted from [160] under the terms and conditions of the Creative Commons Attribution (CC BY) license.

system was well tolerated. Furthermore, the hypotensive effect of the drug was enhanced and sustained for several hours. The sustained drug release profile of the hybrid system could decrease the frequency of administration and improve patient adherence to therapy.

Transferosomes are lipid-based vesicular nano-carriers structurally similar to liposomes; however, they have more elastic, ultra-deformable and stress-responsive properties that facilitates better colloidal stability and penetration through biological membranes. These vehicles are composed of phospholipids, an edge activator (surfactant or bile acid), ethanol and water [165]. Typically, these vehicles are explored for drug delivery across the skin [165]. Recently, Uwaezuoke et al [166] reported the development of linoleic acid-based transferosomes with cyclosporine A for topical administration to the eye and used Span® 80 and Tween® 80 as edge activators. The formulation with Tween® 80 had a more favorable toxicological profile; however, *ex vivo* experiments on the corneal permeability demonstrated that there is no statistically significant difference ($p>0.05$) in the drug flux between Span ® 80 and Tween® 80 based transferosomes.

6.6. Dendrimers

A dendrimer is a polymeric nanotechnology-based delivery system having a branched star-shaped structure. These nanosystems have high drug encapsulation and conjugation ability and the ability to functionalize surface groups [167,168]. Active pharmaceutical ingredients can either be encapsulated in the core or conjugated to the surface of the dendrimer [123,169,170]. Different generations of dendrimers (G1, G2, G3, G4, and G5) depend on the carboxylic and hydroxyl functional groups attached to polyamidoamine dendrimer (PAMAM, Figure 9). Their small dimensions, ability to be functionalized, drug targeting and ease of preparation are some of the advantages of dendrimers. Also, dendrimers are great platforms for ocular drug delivery with improved aqueous solubility, high encapsulation rate, and monodispersity. Nevertheless, there are some drawbacks to the use of dendrimers in ophthalmology.

A fast dissolving dendrimer/nanofibers system consisting of polyamidoamine dendrimers electrospun with polyethylene oxide and brimonidine tartrate was developed for glaucoma therapy [172]. *In vitro* and *in vivo* safety studies revealed that the dendrimer/nanofibers exhibited no cytotoxicity at therapeutic levels in the cultured cells. No ocular irritation was observed and the dendrimer accumulated in the anterior chamber of the eye. When a single dose of dendrimer/nanofiber system was administered, similar intraocular pressure lowering effect was observed compared to brimonidine solution. However, dendrimer/nanofiber system proved to be more efficacious over 3-weeks with a daily dose regimen.

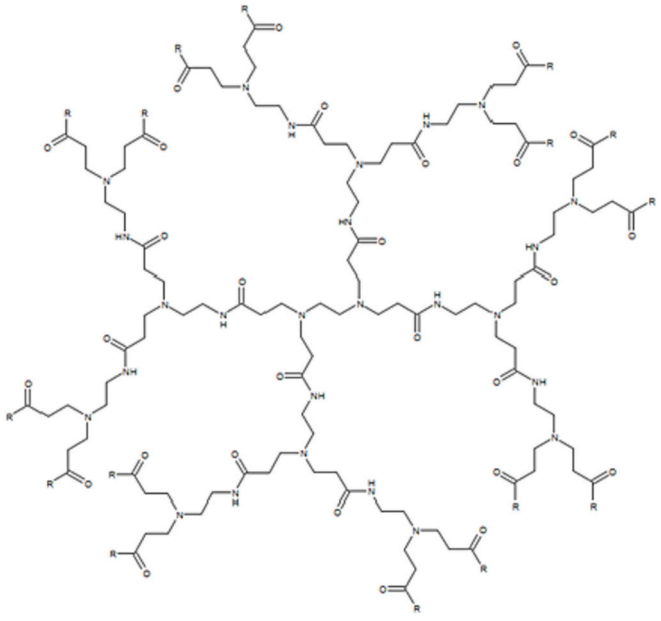

Fig. 9. Structure of PAMAM dendrimers. The increase in generation number (G0, G1, G2, etc.) results in an incremental increase in size, molecular weight, and number of amine or carboxylate or hydroxyl surface groups. G1.5: R = OH; G2: R = -NH-$(CH_2)_2$-NH_2; G2(OH): R = -NH-$(CH_2)_2$-OH. Reprinted from [171] with permission from Wiley & Sons

In another study, a polymeric dendrimer containing timolol analogue was designed for the treatment of ocular hypertension [173]. First, a complex of timolol analogue and polyethylene glycol was formed and was then coupled to third generation polyamidoamine dendrimer to obtain the drug-loaded polymeric dendrimer. Up to 8% of the drug permeated the corneal tissue in 4 h and intraocular pressure lowered by 30% compared to the untreated eye. No ocular irritation or local toxicity was found after daily administration of the timolol dendrimer for one week.

In a recent study, three different nanocarriers were developed into one hybrid system to harness the benefits of the individual nanocarriers in improving the bioavailability of the topically administered glaucoma drugs [174]. The dendrimer-hydrogel-particle system was used as a vehicle to deliver brimonidine tartrate and timolol maleate. The nano-sized hybrid system was biodegradable and biocompatible. Interestingly, drug permeation through the cornea was reported to be 17-fold greater from the hybrid system than in the drug solution. Furthermore, a remarkable lowering of intraocular pressure was observed both on single dosing and 7-day daily dosing. The hybrid system offered many advantages, including precise dosing, sustained drug release and delivery of multiple drugs.

Apart from polyamidoamine dendrimers, carbosilane dendrimers have been investigated in ocular delivery. The therapeutic efficacy of cationic carbosilane dendrimers of generation 3 as eye drop excipients for acetazolamide, a poorly water-soluble hypotensive drug, was investigated [175]. The dendrimer was found to interact strongly with transmembrane mucins exhibiting a bioadhesive effect. The carbosilane dendrimer-based eye drop loaded with acetazolamide was safe at low concentrations and enhanced the intraocular pressure lowering effect.

In summary, using dendrimers for ocular drug delivery has provided practical approaches to resolving delivery issues of drugs based on solubility, distribution and targeting due to the relative ease of manipulating the physicochemical characteristics of dendrimers, making them effective carriers for ophthalmic applications. Nevertheless, clinical translation of this system is hindered by multiple formulation procedures, difficulty in large-scale production, cytotoxicity and low drug loading [126]. More research should be carried out in this regard.

6.7. Niosomes

Niosomes are stable vesicular delivery systems composed of bilayers of amphiphilic nonionic surfactants [176]. They are biocompatible and exhibit low toxicity due to the use of nonionic surfactants. Hence, they have great potential as excellent carrier systems for ocular drug delivery. Besides, niosomes have been employed in targeted delivery, sustained drug release, and enhanced drug bioavailability [176]. Low drug loading, leakage of encapsulated drug, physical instability and high production cost are some of the factors limiting the use of niosomes in drug delivery [126].

Niosomes modified with hyaluronic acid were studied for their ability to enhance the transcorneal permeability and ocular bioavailability of tacrolimus [90]. Tacrolimus is an immunosuppressant drug used after corneal transplantation surgery to reduce the risk of graft rejection. It is a relatively high molecular weight drug (822.5 D) that is highly hydrophobic and difficult to permeate through the cornea. These properties make the formulation and topical delivery of tacrolimus challenging. The hyaluronic acid-coated niosomes utilize the benefits of

niosomes and hyaluronic acid to enhance the permeability and therapeutic efficacy of tacrolimus. The plasmon resonance study confirmed the adhesion of the hyaluronic acid-coated tacrolimus-loaded niosomes on ocular mucins resulting in prolonged contact time and enhancement of transcorneal drug permeability. In addition, the drug concentration in aqueous humor was increased by 2.3 fold when compared to tacrolimus suspension [90].

Similarly, chitosan-coated niosomes loaded with azithromycin were investigated as the potential drug delivery system to increase the retention time, corneal permeability and ocular bioavailability of the antibacterial drug [177]. They employed thin film hydration technique to formulate the chitosan-coated azithromycin niosomes. The niosomes improved the corneal permeability of the drug up to 2.6-fold compared to commercial azithromycin eye drops. In addition, the niosomes were non-irritant to ocular tissues.

There are many other recent studies on the application of niosomes in ocular drug delivery, and the findings show the great potential of niosomal formulations in treating ocular disorders [178–181].

6.8. Cubosomes

Cubosomes (Fig. 10) are liquid crystalline cubic phase nanoparticles formed by self-assembling of amphiphilic lipids in water [13,182]. They have particle diameters between 100 and 300 nm. Cubosomes are prepared either by the self-assembly of amphiphilic lipids in excess aqueous solution or by high-energy emulsification of lipids and water with an appropriate stabilizer [183,184]. The amphiphilic lipids usually employed in the preparation of cubosomes are glyceryl monooleate (monoolein) and phytantriol while Pluronics are used as stabilizers [185]. Cubosomes are efficient delivery vehicles for hydrophobic drugs. However, they exhibit low efficiency in entrapping hydrophilic drugs [126].

A biodegradable *in situ* gel based on ciprofloxacin cubosomes was prepared and aimed to enhance corneal permeability as well as the therapeutic efficacy of topically administered ciprofloxacin in the treatment of corneal ulcer and bacterial keratitis [89]. The cubosomal system was optimized based on the amount of ciprofloxacin, phytantriol, lutrol and pH of the hydration solution. The optimized formulation demonstrated enhanced antibacterial activity, which was 2.5 times greater than the commercial eye drops. Once daily dosing of ciprofloxacin cubosome/*in situ* gel-based eye drops were able to maintain the drug concentration in the aqueous humour above the minimum inhibitory concentration. The researchers concluded that the cubosomes increased the antibacterial activity of ciprofloxacin by prolonging the residence time on the ocular surface and enhancing the transcorneal permeability. In another study, natamycin cubosomal nanoparticles were investigated as fungal keratitis therapy [187]. The probe sonication method was employed to get the nanosized cubosomal dispersion. The researchers reported an enhancement in corneal permeation and sustained release of natamycin from the cubosomes. The antimicrobial assay demonstrated an enhanced antifungal activity against *Candida albicans* and *Aspergillus fumigatus* compared to natamycin suspension. In addition, natamycin cubosomes were not irritating to ocular tissues.

6.9. Nanowafers

Nanowafers (Figure 11) are nano-sized transparent membranes or discs loaded with drugs which can be easily applied to the ocular surface using a fingertip [123]. They are composed of biodegradable and biocompatible polymers that are easily degraded and eliminated over time. Nanowafers serve as drug reservoirs controlling drug release and increasing the retention time of the therapeutic agent on the ocular surface, thereby facilitating drug absorption into anterior ocular tissues. In addition, nanowafers act as protective membranes for damaged corneal surfaces typical seen in dry eye disease [188,189].

In a study, a biodegradable carboxymethyl cellulose nanowafer loaded with dexamethasone was designed to treat dry eye [106]. The polymeric nanowafer consisted of 500 nm^2 reservoirs containing the incorporated drug, which is released slowly. In the *in vivo* efficacy study using an experimental mouse dry eye model, it was found that a once alternate day administration for 5 days with the dexamethasone nanowafer was efficacious in restoring the corneal integrity and the health of the ocular surface. This reported efficacy is comparable to twice daily dosing of dexamethasone eye drops. Besides, reduced levels of pro-inflammatory mediators such as TNF-α, IFN-γ, CXCL-10, CCL-5 and MMP-3 were also found on treatment with dexamethasone nanowafer. This indicates an enhancement in anti-inflammatory properties of dexamethasone.

To overcome the issues of multiple daily dosing (6-12 times daily) and the side effects associated with cysteamine in the therapy of corneal cystinosis (a rare metabolic disease), a design of biodegradable cysteamine nanowafer was made [189]. The cysteamine nanowafer can be easily translated into clinical use. The findings of the study demonstrated enhanced stability at room temperature for months, increased

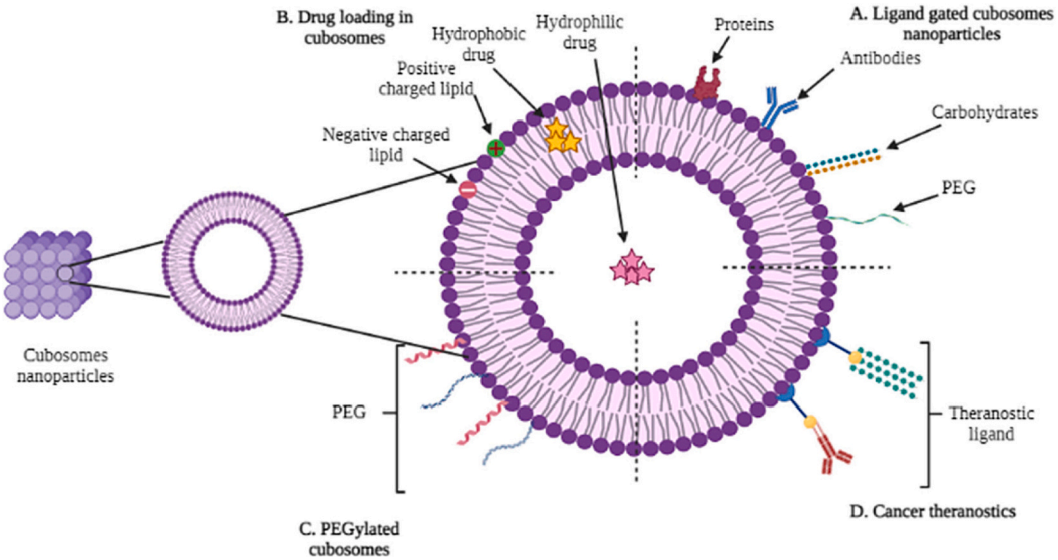

Fig. 10. Cubosomes with internal and cubic structures as potential carriers for drug delivery. Reprinted from [186] under the terms and conditions of the Creative Commons Attribution (CC BY) license.

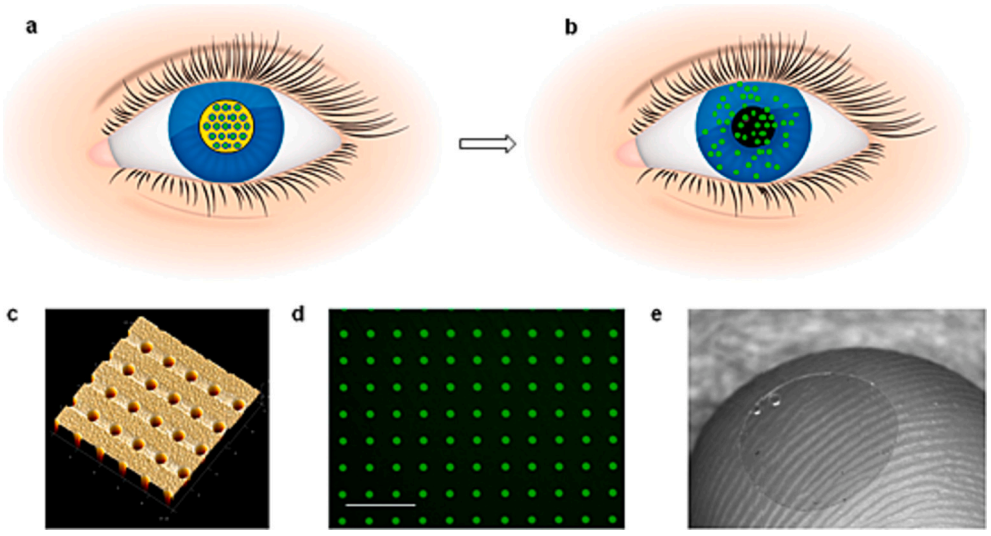

Fig. 11. Nanowafers for ocular drug delivery. (a) Schematic of the nanowafer administered on the cornea. (b) Diffusion of drug molecules into the corneal tissue. (c) AFM image of a nanowafer demonstrating an array of 500 nm diameter nanoreservoirs. (d) Fluorescence micrograph of a nanowafer filled with doxycycline (scale bar 5 μm). (e) Nanowafer on a fingertip. Reprinted from [190] under the terms and conditions of the American Chemical Society Author Choice License.

therapeutic efficacy at a low concentration and on once-daily dosing, and a better safety profile.

Dorado et al [191] designed poly(vinyl alcohol)-based nanowafers containing a synthetic peptide PnPP-1, derived from a toxin present in the spider *Phoneutria nigrivente* venom. This peptide was found to exhibit hypotensive effects in rat eyes and considered as a novel drug candidate to treat glaucoma. *In vivo* experiments performed in rats established that PnPP-1 administered as eye drops resulted in significant reduction of intraocular pressure; however, this effect lasted only for a few hours. When PnPP-1 was administered in nanowafers the reduction in intraocular pressure was less intense, but the hypotensive effect was observed for a longer period of time.

Some recent developments on NODS for treating diseases of the anterior eye segments are summarized in Table 2.

7. Ocular-specific characterization of nanotechnology-based drug delivery systems

Optimizing different formulation and process parameters, as well as the characterization of the physicochemical and biological properties of nanocarriers, is of utmost importance in developing effective delivery systems. In ocular drug delivery, it is necessary to characterize the particle size and distribution, surface charge, encapsulation efficiency, drug loading, drug release and uptake, stability, and the safety/toxicity of the nanocarrier. Also, the delivery system must comply with other ocular-specific requirements such as sterility, osmolality, pH, surface tension and viscosity.

7.1. Particle size

Particle size and polydispersity index (PDI) are key properties of nanocarriers and major determinants of the physical stability. These parameters are commonly analyzed by photon correlation spectroscopy through dynamic light scattering [76,94,115]. This method is quick, sensitive and easy to use.

Optimizing the size and distribution of particles in liquid-based formulations intended for ocular use is important. Generally, formulations intended for ocular delivery should not contain particles with size greater than 10 μm [192]. Smaller nanosized and monodispersed particles are generally preferred as they offer better stability and biodistribution profile. They increase the stability of the nanoformulation during storage by preventing creaming, coalescence, Ostwald ripening, flocculation, and sedimentation [193,194]. Also, particles of smaller size ranges penetrate the inner mucin layer of the tear film faster than larger particles [195]. Moreover, they cause less irritation and are easily taken up by corneal epithelial cells [196,197]. Nanoparticles with small particle size demonstrated higher absorption into the aqueous humor than large particles; however, they were cleared faster from the tear fluid [198]. The fast clearance was attributed to higher dissolution of the small particles in the tear fluid. The particle size of nanoformulations can be influenced by the type and concentrations of excipients and formulation methods [199,200].

7.2. Zeta potential

Zeta potential is another essential characteristic of nanoformulations. It is one of the most studied parameters because of its impact on the stability and the interaction of nanocarriers with biological systems. High zeta potential values ($> \pm 30$ mV) can stabilize nanoformulations via electrostatic repulsion. However, positively charged particles are better for enhancing the electrostatic interaction with the negatively charged ocular surface [19,83]. It is worth noting that particles with zeta potential value ≤ 30 mV may also be stabilized sterically [194].

7.3. Surface morphology

The surface morphology of nanoparticles influences their biodistribution, cellular uptake and toxicity [201]. Nanoparticles can present as different shapes including spheres, cubes and rods. Spherically shaped nanoparticles are more favourable in improving drug performance [202,203].

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are widely utilized in studying the structure of nanoparticles [89,115,128,204]. SEM shows the surface structure and morphology of the particles while TEM shows the internal structure, shape and size of particles.

7.4. Lipid crystallinity

Crystallinity and thermal behaviour of lipid nanoformulations can be studied using differential scanning calorimetry [94,205]. Powder X-ray diffractometry (PXRD) is another technique extensively used to analyze the crystal structure of nanocarriers [94]. The crystallinity of lipid

Table 2
Recent developments in nanotechnology-based delivery systems for anterior segment eye diseases

Nanocarrier	Drug	Major excipients	Formulation method	Targeted disease	Reference
Micelles	Cyclosporine-A	D-α-tocopherol, poly(ethylene glycol) succinate (vit E-TPGS) and polyoxyl 40 hydrogenated castor oil (RH-40)	Self-Assembling	Dry eye disease	[128]
	Flurbiprofen	DSPE-PEG 2000, cRGD	Solvent evaporation method	Ocular inflammation	[109]
Nanosuspensions	Cyclosporine A	mPEG-PLA	Solvent evaporation	Dry eye disease	[127]
	Diclofenac	Chitosan and methoxy poly(ethylene glycol)-poly (ε-caprolactone) (mPEG-PCL)	Co -incorporation	Ocular inflammations	[88]
	Flurbiprofen	Eudragit® RL 100, Poly(vinyl alcohol).	Solvent displacement	Ocular inflammations	[74]
	Moxifloxacin, Pamoic acid	Pluronic® F127	Wet bead milling	Ocular infections. Bacterial keratitis	[73]
Micro/ Nanoemulsions	Voriconazole	Eudragit RS 100 Pharmasolve®	Quasi-emulsion solvent evaporation	Fungal keratitis	[132]
	Travoprost	Tween® 80 and isopropyl alcohol	Aqueous titration (Emulsification)	Glaucoma	[139]
	Riboflavin phosphate, Docosahexaenoic acid in triglyceride form (TG-DHA)	Tween® 80, Cremophor® EL, glycerol	Aqueous titration (Emulsification)	Keratoconus and Dry eye syndrome	[138]
	Cyclosporine A	Chitosan, Transcutol® P, oleic acid, Tween® 20	Aqueous titration (Emulsification)	Cornea transplant rejection, dry eye disease	[76]
Nanoparticles	Tacrolimus	Gellan gum, aluminum chloride	Ionotropic gelation	Dry eye disease	[91]
	Cerium oxide	Glycol chitosan	-	dry eye disease	[100]
	Triamcinolone acetonide	Glyceryl monostearate, Compritol® 888 ATO, Tween® 80 and Pluronic® F-68, gellan gum	Hot homogenization and ultrasonication method	Ocular inflammations	[143]
	Ciprofloxacin	Compritol® 888 ATO, Tween® 80, chitosan, poly (2-ethyl-2-oxazoline).	Melt-emulsion sonication and low-temperature solidification methods	Ocular infections	[94]
	Azithromycin	Poly(lactic-*co*-glycolic acid), Pluronic® F-127, poly (vinyl alcohol), Poly(vinyl pyrrolidone)	Nanoprecipitation	Ocular bacterial infection	[144]
Nanostructured Lipid Carriers	Dexamethasone	Cholesterol, Labrafac®, Tween® 80	Solvent diffusion	Dry eye	[116]
	Dexamethasone	Phenylboronic acid, (3-aminomethylphenyl) boronic acid (APBA) chondroitin sulfate, Precliol® ATO 5, Compritol® 888 ATO, Miglyol® 812 N, Kolliphor® HS15, and CTAB, Cremphor® EL	Melt-emulsification	Dry eye syndrome	[149]
	Amphotericin B	Compritol® 888 ATO, lecithin, soybean oil, Poloxamer® 188, chitosan	Emulsion evaporation-solidification at low temperature	Fungal keratitis	[115]
Lipid Polymer Hybrid	Gemifloxacin	Chitosan	Ionic gelation method	Eye infections	[148]
	Moxifloxacin	Chitosan, hyaluronic acid, cholesterol, egg phospholipid, 1,2 dipalmitoyl-sn-glycero-3-phosphoethanolamine.	Ionic gelation and film hydration methods	Ocular bacterial infections	[120]
	Vancomycin	Glyceryl tripalmitate, Eudragit RS100, Solutol HS15, chitosan, oleic acid, sodium alginate.	Hot high pressure homogenisation and ultrasonication	Ocular bacterial infecttions	[152]
Liposomes	Azithromycin	Cholesteryl hemisuccinate, medium chain triglyceride oil, lecithin, DSPE-PEG 2000, α-tocopherol	Thin film dispersion and homogenization method.	Dry eye disease	[156]
	Lactoferrin	Cholesterol, soybean phospholipid (Lipoid S75), Polysorbate® 80, sodium hyaluronate	Lipid film method and high pressure homogenization	Dry eye Ocular inflammation	[78]
	Acetazolamide	Phosphatidylcholine (Phospholipon 90G®), cholesterol, vitamin E, trehalose, erythritol, borates, HPMC	Solvent evaporation	Glaucoma	[75]
	MRTF/SRF inhibitor CCG-222740	1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTAP) and 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC).	Thin film hydration technique	Conjunctival fibrosis Glaucoma	[28]
Niosomes	Tacrolimus	Poloxamer® 188, Soybean phosphatidylcholine, cholesterol, hyaluronic acid	Reconstitution	Corneal allograft rejection	[90]
	Azithromycin	Chitosan, Tween® 60, Span® 60	Modified thin-film hydration strategy	Bacterial Conjunctivitis	[177]
Dendrimers	Brimonidine tartrate and Timolol maleate	Poly(ethylene glycol) diacrylate (PEG-DA), Span® 80, Tween® 80	Inverse emulsion method and highly efficient Aza-Michael addition reaction	Glaucoma	[174]
	Brimonidine tartrate	Polyamidoamine (PAMAM), methoxy poly(ethylene glycol), poly(ethylene oxide)	Electrospinning	Glaucoma	172[172]
	Acetazolamide	Carbosilane	Chemical synthesis	Glaucoma	[175]
Cubosomes	Ciprofloxacin	Phytantriol, poloxamer (Lutrol® F1), chitosan, β-glycerophosphate 127	Top-down approach, sonication and high-pressure homogenization	Conjunctivitis and corneal ulcers	[89]
Nanowafers	Natamycin	Monoolein, Span® 80, Poloxamer® 407	Probe sonication technique	Fungal keratitis	[187]
	Cysteamine	Poly(vinyl alcohol)	Hydrogel template	Corneal cystinosis	[189]
	Dexamethasone	Sodium carboxymethyl cellulose	Modified Hydrogel template	Dry eye disease	[106]

nanoparticles could affect their stability, drug loading and release [205,206]. The use of highly crystalline lipids in nanoformulations leads to instability issues such as drug expulsion during storage. Therefore, a combination of lipids is used to achieve a less crystalline structure with better stability and drug loading capacity [77,207].

7.5. Entrapment efficiency and drug loading

A high drug payload is desired for nanocarriers to avoid drug waste during formulation. The entrapment efficiency of nanoformulation is usually determined by first separating the unentrapped drug from the entrapped drug by centrifugation at 10,000 - 20,000 rpm for 10-30 min. The drug content is then assayed using HPLC or spectrophotometrically [116,208,209].

Drug release is sustained in nanocarriers with high entrapment efficiency. The drug is also protected from degradation and premature metabolism. Additionally, the ratio of the concentration of drug to excipients is higher, enabling the production of high-dosed formulation [210]. Moreover, the use of a high dose per unit volume formulation aids in avoidance of huge change in the fluid dynamics of the eye associated with instilling large volume of ocular formulation. Thus, high drug loading improves biocompatibility. The primary determinant of drug loading is drug solubility.

7.6. Drug release/Permeability studies

The regulation of drug release in the ocular system is vital to maintain therapeutic drug concentration and to avoid toxicological effects. The development and optimization of nanocarriers are focused on achieving controlled and sustained drug release [207]. *In vitro* drug release and *ex vivo* permeation studies of nanoformulations are commonly carried out using Franz diffusion cells. A dialysis membrane (molecular weight cut-off of 12-14 kDa), whole bovine eye, excised cornea (rabbit, porcine or bovine) or human cornea construct is employed as the barrier membrane, while a phosphate buffer solution (pH 7.4), glutathione bicarbonate Ringer's solution, simulated or artificial tear fluid is used as the release medium [55,75,77,207,209]. The temperature of the setup is maintained at 37 °C under continuous stirring to simulate the biological environment. The cumulative amount permeated per unit area is obtained by analyzing the concentration of drug that permeated through the barrier membrane into the receptor compartment of the release apparatus. Other permeability parameters such as apparent permeability coefficient and steady-state flux (Js) are also determined [75,94,209].

In vivo release studies are usually carried out using rabbits due to the close similarity of the rabbit eye to the human eye in terms of structure and composition of tears [89]. The nanoformulation is applied to one eye, while the other eye is treated with normal saline and serves as a control. The aqueous humour is withdrawn and analyzed for drug content [89,115,147]. Other pharmacokinetic parameters such as the maximum drug concentration (C_{max}), time to attain the C_{max} (t_{max}) and area under the concentration-time curve (AUC_{0-t}) are computed [144].

7.7. Ocular retention/Mucoadhesion

Ocular retention or mucoadhesiveness is an essential attribute of an effective topical ocular delivery system as it contributes largely to the ocular bioavailability of drugs. Surface plasmon resonance spectroscopy, fluorescence imaging and gamma scintigraphy are methods employed by researchers for the *in vivo* evaluation of the ocular retention of topically applied nanoformulations [76,94,175,211–214].

7.8. Stability study

Stability issues such as Ostwald ripening, flocculation, creaming, sedimentation and coalescence are significant concerns in developing nanocarriers. Lipid modification due to a change in lipid crystallinity in lipid nanoformulations can result in physical instability [205,215]. These instability problems can be monitored by analyzing alterations in particle size, zeta potential and entrapment efficiency during storage [215].

7.9. Toxicity study

During the development of a novel drug delivery system, the evaluation of its biocompatibility and safety profile is of paramount importance. The primary safety concerns in nanoformulations result from the use of surfactants and cationic lipids in the formulation [216]. Some cationic lipids extensively used in nanoformulations can destroy corneal epithelial cells on prolonged use [19,217].

Different tests, including Draize's test, HEM-CAM test, Schimer's test, bovine opacity and permeability test, cell viability study and histopathological studies, have been utilized to investigate the safety of nanoformulations for ocular delivery [78,91,128,211,218–220]. Signs of ocular toxicity and intolerance may appear as inflammation, redness, ocular hyperthermia, irritation, corneal opacity and conjunctival chemosis. A rise in the ocular surface's temperature indicates an inflammatory process, which can be investigated using an infra-red camera [221]. In the HEM-CAM test, ocular toxicity is seen as irritation, coagulation, and haemorrhage in a chorio-allantoic membrane of a fertilized chicken egg after applying nanoformulations [78]. A cell viability study involves incubating human corneal epithelial cells with the test formulation for some hours, after which the number of viable cells is determined. This method has been extensively used to investigate the cytotoxicity of nanoformulations designed for ocular use [21,78,116,144]. Other specifications for ocular formulation such as sterility, pH, viscosity, osmolality and surface tension should be optimized.

8. Nanotechnology-based drug delivery systems for anterior eye diseases under clinical trials

The research efforts of pharmaceutical and drug delivery scientists have yielded ocular nano formulations under various stages of clinical trials. Nanotech drug delivery systems for anterior eye diseases under clinical trial are outlined in Table 3. NCT03001466 [222] is a Phase II clinical study of a urea-loaded nanoparticulate system applied as an eye drop, proposed to treat cataracts [222]. Urea efficacy enhancement was accomplished using polymeric nanoparticles comprised of Pluronic® F-127 copolymer. Urea-loaded nanoparticles were compared with a placebo made up of balanced salt solution eye drop. Each group of patients receiving either urea nanoparticles or balanced salt solution received one drop of eye drop five times a day for 8 weeks, and the difference in the score of visual acuity in 6 months was measured.

Another clinical trial (NCT02420834) conducted at Aston

Table 3
Nanomedicines currently undergoing clinical trials for the therapy of anterior ocular diseases

Drug / Product	Formulation	Disease	Phase	Identifier
Urea	Nanoparticle	cataract	II	NCT03001466
Phospholipid	liposome	Dry eye disease	NA	NCT02420834
Omega-3 Fatty acids (Remogen® Omega)	Microemulsion	Dry eye	NA	NCT02908282
Dexamethasone (OCS-01)	Nanoparticle	Inflammation, corneal pain, postoperative	II	NCT04130802
Cyclosporine OTX-101	Nanomicelle	Dry eye disease	III	NCT02845674
Latanoprost (POLAT-001)	Liposome	Glaucoma	II	NCT02466399

University, United Kingdom, involved the treatment of dry eye with various artificial tears, including a phospholipid liposomal spray [223]. These artificial tears, as well as the liposomal spray, were administered to patients for one month when required following a short wash-out period. Symptoms were reviewed after four months using a short questionnaire (Ocular Surface Disease Index). Other measured outcomes included non-invasive break-up time, tear meniscus height, lid parallel conjunctival folds, Ocular Surface Staining and Phenol Red Test.

A more recent Phase III clinical trial (NCT02845674) involving dry eye treatment using 0.09% cyclosporine micellar solution was completed in November 2021 [224]. The 258 participants in the study comprised of both sexes aged 18 years and older. NCT02908282 is yet another clinical trial of a microemulsion containing omega-3-fatty acids for treating dry eye [225]. While Systane® is a propylene glycol-based nanoemulsion in Phase IV clinical trial for the treatment of dry eye disease. Systane® is proposed to replenish deficiencies in both the lipid and aqueous layers of the tear film. An ongoing clinical trial on Systane®, which is currently recruiting participants, aims to demonstrate reduced corneal staining with Systane® hydration lubricant eye drops in persons with DED undergoing lens replacement surgery [226]. Participants will receive Systane Hydration lubricant eye drops 4 times daily 2 weeks before surgery and 4 weeks after the surgery, with the standard post-operative care. The control group will not be treated with Systane Hydration lubricant eye drop but will be subject to investigator-defined post-operative standard of care.

A clinical Phase II trial comparing POLAT-001 to latanoprost ophthalmic solution in subjects suffering from ocular hypertension and open-angle glaucoma was recorded on ClinicalTrials.gov (NCT02466399) [227]. In this clinical trial, 80 participants were recruited. The efficacy and safety of subconjunctival liposomal latanoprost (POLAT-001) were compared to latanoprost ophthalmic solution, and the outcome measured was the difference in the intraocular pressure after 3 months of treatment.

Recent advances and successes of some nanomedicines for ocular diseases have led to increased interest in designing more nanoformulations. However, efforts should be intensified to hasten the entry of these nanomedicines into the market at affordable rates.

9. Approval status of nanotechnology-based delivery systems for anterior ocular diseases

The development of nanotechnology for the treatment of diseases affecting the anterior eye seems to be promising as the number of marketed products is increasing (see Table 4) Nanocarriers that are commercially available for the treatment of anterior ocular diseases are nanosuspensions (Besivance®, Tobradex ST®, Inveltys®, Eysuvis®), nanoemulsions (Restasis®, Durezol®, Xelpros®, Ikervis®, Verkazia®, Cyclokat®), liposomes (Lacrisek®, Artelac Rebalance®) and micelles (Cequa®) [228]. Restasis® (cyclosporine A), Cequa® (cyclosporine A), Lacrisek® (vitamin A palmitate and vitamin E), Eysuvis® (loteprednol etabonate) and Artelac Rebalance® (vitamin B12) are used for the treatment of dry eye syndrome, while Durezol® (difluprednate), Tobradex ST® (tobramycin and dexamethasone), BromSite® (bromfenac) and Inveltys® (loteprednol etabonate) are indicated for ocular inflammation [126,228,229] Besivance® (besifloxacin), Verkazia® (cyclosporine) and Ikervis® (cyclosporine A) are used for the treatment of vernal keratoconjunctivitis and allergic conjunctivitis/keratitis, respectively [228,230]. The only nanomedicine approved for the treatment of glaucoma or ocular hypertension is Latanoprost microemulsion (Xelpros®) [228].

Different technologies have aided in the development of ocular nanoformulations. Durasite technology, a topical polymer-based sustained delivery technology that helps solubilize drugs in aqueous solutions, was used to develop Bromsite® [231]. Eysuvis®, approved in 2020, was also based on mucus penetrating particle (MPP) technology. This platform allows for optimal penetration of drugs through the mucin layer of the tear film, thereby minimizing drug loss by nasolacrimal drainage [232].

Though the approval of nanocarriers over the past two decades has been slow, there is hope for more nanocarriers including ocular nanomedicines to be launched into the market in the near future.

10. Prospects of phytochemical-based nanocarriers in diseases of the anterior segment of the eye

Many anterior segment eye diseases involve inflammatory responses and oxidative stress and are commonly treated with corticosteroids and non-steroidal anti-inflammatory agents. However, prolonged use may lead to adverse reactions such as cataracts and increased intraocular pressure [233–235]. Plants and other natural sources of medicinal compounds are considered safer and more effective alternatives to synthetic compounds. Hence, there is an increasing interest in phytochemicals with known anti-inflammatory and anti-oxidative properties for the therapy of inflammatory ocular diseases [85,87,236]. These phytochemicals could serve as lead compounds for the development of new medicines. Bioactive compounds from plants have contributed to developing new drugs for many years. The drawbacks to the clinical translation of these phytochemicals for topical ocular drug delivery are poor solubility, low stability, low permeability and low ocular bioavailability. To overcome these limitations, nanocarriers based delivery systems are employed as vehicles for these phytochemicals. Some phytochemicals studied in the nanotechnology-based therapy of anterior eye diseases are naringenin, resveratrol, hesperetin, glycyrrhizin, curcumin, epigallocatechin gallate and myricetin.

In order to increase the solubility of a poorly soluble naringenin, it was first complexed with sulfobutylether-β-cyclodextrin before coating with chitosan to form nanoparticles via the ionic gelation method [236]. The naringenin-loaded nanoparticles demonstrated longer contact time on the ocular surface and a moderate sustained release compared to the naringenin suspension. Similarly, naringenin was complexed with poly (N-vinyl pyrrolidone) to formulate a nanocomplex ophthalmic solution [237]. The nanocomplex solution was reported to be stable for three

Table 4
Some FDA-approved nanocarriers for anterior eye segment diseases.

Product	Nanocarrier	Drug	Indications	Approval date
Restasis®	Nanoemulsion	Cyclosporine A	Dry eye	2002
Durezol®	Nanoemulsion	Difluprednate	Postoperative ocular inflammation	2008
Besivance®	Nanosuspension	Besifloxacin	Ocular bacterial infection	2009
Tobradex ST®	Nanosuspension	Tobramycin Dexamethasone	Ocular inflammation and bacterial infection	2009
BromSite®	Solution	Bromfenac	Postoperative inflammation and pain	2016
Cequa®	Nanomicelle	Cyclosporine A	Dry eye	2018
Xelpros®	Microemulsion	Latanoprost	Glaucoma or ocular hypertension.	2018
Inveltys®	Nanosuspension	Loteprednol etabonate	Postoperative ocular inflammation and pain	2018
Eysuvis®	Nanosuspension	Loteprednol etabonate	Dry eye	2020
Verkazia®	Nanoemulsion	Cyclosporine	Vernal keratoconjunctivitis	2021

months and well tolerated. *In vivo* and *in vitro* studies showed that the naringenin nanocomplex enhanced intraocular permeability, antioxidant and anti-inflammatory activities of naringenin. Recently, naringenin micelle solution solubilized with dipotassium glycyrrhizinate was prepared and investigated for the therapy of dry eye disease [84]. The micellar solution was stable for three months. In addition, it demonstrated good ocular tolerability with slit lamp test and histopathological study on rabbit eye. The *in vivo* study in mice revealed an enhanced ocular penetration of naringenin. Moreover, it reduced the symptoms of DED as in the BAC-induced DED mouse model compared to naringenin solution or hyaluronic acid sodium salt commercial eye drop. Administration of naringenin nanoformulation led to increased tear volume, reversal of corneal damages and amelioration of the histopathological symptoms of DED. These positive effects were attributed to the inhibition of inflammatory mediators and modulation of HMGB1 signaling [84].

In another similar study employing dipotassium glycyrrhizinate aided solubilization of phytochemical, hesperetin was utilized as the bioactive compound and investigated for treating bacterial keratitis [238]. In addition to the tolerability of the hesperetin-loaded micellar solution, the ocular permeation, and bioavailability, antioxidant and antibacterial effects of hesperetin were improved remarkably. Compared with hesperetin suspension, the symptoms of bacterial keratitis were alleviated. Furthermore, nanoformulation of dipotassium glycyrrhizinate and palmatine demonstrated a marked corneal wound healing effect on both diabetic and healthy mice model, which was attributed to inhibition of HMGB1 signaling [86].

Resveratrol is one of the phytochemicals that has shown promising results in the treatment of anterior eye diseases. It exhibits many pharmacological actions, including anti-inflammatory, antiallergic, antioxidant, and antimicrobial properties. Resveratrol-loaded Soluplus® micelles showed no irritation and cytotoxic effects; rather, this formulation aided cell proliferation. The aqueous stability of resveratrol was enhanced by the Soluplus® micelles when compared to the free resveratrol solution. Besides, the corneal permeation and cellular uptake of resveratrol were enhanced. Resveratrol micelles decreased the release of inflammatory cytokines and led to the expression of antioxidant factors. These effects were attributed to its wound healing effects on the cornea. Resveratrol-loaded niosomes consisting of cholesterol, Span® 60 and Poloxamer® 407 were prepared by ethanol injection technique [239]. The coating with chitosan improved the mucoadhesiveness of the formulation and led to the prolonged release of resveratrol. The ophthalmic niosomal formulation was stable for 6 months at 4 ^{o}C, and a histopathological study confirmed the tolerability of the niosomal formulation. The expression level of pro-inflammatory cytokines (TNFα and IL-6) was reduced by half when treated with niosomal solution for three days.

Epigallocatechin gallate is the most well-known representative of green tea's catechins family. It has been reported to possess anti-inflammatory activity through its inhibitory action on the MAPK signaling pathway. Therapy with hyaluronic acid-modified epigallocatechin gallate-gelatin nanoparticles did not affect the integrity of the corneal tissues. Besides, improvement in tear production and fluorescein staining with the nanoparticles indicate amelioration in the symptoms of DED [240].

Nanoformulation of myricetin was developed as a strategy to improve the solubility, stability and therapeutic efficacy of the myricetin. Polymeric micelles based on polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer were used to deliver myricetin to ocular tissues [241]. The micelle-based solution increased the aqueous solubility as well as the stability of myricetin. The cellular uptake, as well as corneal permeability, were greatly enhanced. Furthermore, myricetin micelles demonstrated enhanced anti-inflammatory and antioxidant properties on the ocular tissues.

Curcumin is a polyphenol phytochemical obtained mainly from *Curcuma longa* (turmeric). Besides possessing anti-inflammatory, antiallergic, and anti-oxidative activity, curcumin can induce apoptosis [87]. Induction of apoptosis is necessary for managing some anterior eye segment diseases such as pterygium. Curcumin-loaded silver nanoparticles prepared via a modified Bettini's method were investigated for its efficacy in the therapy of pterygium. The nanoparticle formulation aimed to deliver both silver and curcumin to the eye and present as a non-invasive option in the management of pterygium.

The use of nanocarriers as vehicles for delivering phytochemicals to the eye holds a great prospect in the near future. More research is needed to improve the safety and stability of these systems to harness the benefits of this platform.

11. Challenges in clinical translation of nano-based drug delivery systems for eye diseases.

The complex and numerous physiological barriers in the eye make drug delivery very challenging, hence the development of various novel delivery systems. Despite the numerous studies on these new delivery systems for the treatment of diverse ocular diseases, only very few have been successfully marketed as nano-based drug delivery systems [242]. The slow translation of NODS may be a result of the fact that these nano-based systems are more complex than the conventional delivery systems, and as such, the process of approval may be longer, more rigorous and more expensive [242,243]. Also, another major reason for the limited clinical transition of these nanosystems is the inability of animal models to completely simulate the physiological features as seen in human [244]. Rodents, especially mice, rats and rabbits have been extensively employed in many preclinical studies because they are easily managed and relatively affordable. However, the differences in ocular anatomy and physiology have been reported to cause significant variations in the pharmacokinetic characteristics of these formulations [244]. For instance, rodents have smaller eyes than humans and larger lens:cornea ratio.

Additionally, rabbits have lower blinking rates, higher mucus production and are more prone to ocular irritation [245]. Also, the immunological composition of the human retina is quite different from those of the rodents used in most preclinical studies. All of these make it very challenging to predict the efficacy of the clinical studies using animal-based preclinical tests [123].

Scaling up the nano-based delivery systems from laboratory to large industrial scale has also been reported to be a hindrance to the clinical translation of many of these products [126]. For instance, scaling up nano-based delivery systems like nanoparticles formulated via low-energy approaches like phase inversion temperature, phase inversion composition as well as emulsion inversion point methods have been reported to cause diverse alterations in properties, especially in the physicochemical properties of the nanoparticles [126]. As a result, several high-energy methods were designed in a bid to tackle the shortcomings of these low-energy processes. However, the use of high-energy methods such as ultrasonication and hot homogenization for the formulation of nanoparticles has been reported to bring about recoalescence, which in turn makes the entire system thermodynamically unstable [126]. In addition, studies suggest that various methods of preparing these nano-based systems usually involve complex multi-step procedures. These procedures are also not adequately consistent, with very poor reproducibility. Hence, the production of nano-based systems is very challenging as it causes problems such as batch-to-batch variations and stability of dispersions which in turn makes the process of quality control very difficult [243,246]. Slight variations in certain process parameters have been reported to bring about significant changes to the particle size as well as percentage yield. These parameters have been known to influence encapsulation efficiency largely, rate of drug release and, ultimately, the efficacy of the system as the pharmacokinetic and pharmacological properties of the active ingredients can be affected [246]. New materials are constantly being discovered and applied in the development of nano-based delivery systems. This makes

the evaluation and proper characterization of the systems very challenging and, as such, could limit the clinical translation of these systems [242]. The particle size of nano-based systems confers on their properties entirely different from similar materials in the macro size range. Thus, the inability to appropriately determine the safety profiles of these systems over the years constitutes a huge limitation to the clinical approval of these formulations [126,242]. These systems must be biocompatible and nontoxic on the ocular system; thus, safety assessment is paramount. It is also vital to ensure that they are easily metabolized and should not accumulate in the eye [243]. However, the complex nature of the nanosystems and the insufficient evidence to fully support their biosafety and nontoxicity have also limited their smooth transition from the preclinical stage to clinical trials.

Despite the limitations for the successful clinical translation of nanotech-based drug carriers for ophthalmology, there is a positive outlook for the approval of many nanotechnology products in the near future.

12. Conclusions and future perspectives

Effective treatment of ASED remains a formidable challenge due to the barriers present in the anterior ocular segment. Considering the WHO report on the prevalence of preventable anterior segment diseases, investment into research for new drug formulations should be encouraged as there is a very huge market relevant to the number of people affected. No individual would want to lose their sight and issues concerning eyesight are treated seriously. Although numerous advances in the development of nanotechnology-based strategies have been made to overcome the limitations associated with ocular topical therapy, there is still a need for the design of novel formulations with decreased dosing and frequency of administration, improved eye penetration, enhanced drug release, action, eye contact and reduced adverse effects. Since a major focus of nano-based drug delivery systems is currently on the development of nanoparticles for topical administration and subconjunctival administration for implants, diversification may be essential and beneficial. Future research should also consider the engineering of nano formulations for drug delivery to the anterior eye segment that are safer, can deliver both small molecules and biologics (including genes/peptides), are less toxic, highly stable, and effectively delivers the drug with better pharmacokinetic and pharmacodynamic characteristics. Formulation direction should also be towards co-encapsulating ocular active drugs and enzyme inhibitors that would inhibit ocular specific enzymes and promote ocular absorption and bioavailability. The formulation of nanoparticles that can release drugs in different eye tissues and are suitable for biodegradation and patient comfort should be considered. A typical example is that ways to avoid possible obscurement of vision by the carrier should be properly investigated and avoided. An ideal nano formulation following a single application should maintain effective drug levels and possess high bioavailability. To release and maintain effective drug levels and duration, the loading capacity of nanocarriers is of utmost importance. Nanocarriers should be designed in such a way to be able to be loaded with enough drugs to last for days or months to avoid frequent administration. The characteristics of nanoformulations should be manipulated to enable depot formation and slow drug release. More extensive research should be performed on viscosity and permeation enhancers in promoting ocular bioavailability. To achieve this, there must be collaborations between formulation scientists and clinicians to identify and address specific needs hindering the translation of these systems into clinical use. New technologies such as mucus penetrating particles, hydrogel template method and particle replication in non-wetting template that will enhance the overall performance of ocular drugs should be fully harnessed. Although some of these nanoformulations are currently under clinical trials and others in the market, it is necessary for future research to monitor all the perspectives on the use of nanoformulations since the regulations required for the approval of ophthalmic preparations are enormous. Some of these perspectives that demand urgent attention include a wider understanding of the uptake and distribution mechanisms of the various nanoformulations. Stability issues such as particle growth also need to be addressed.

Data availability

No data was used for the research described in the article.

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