Nano-Based DDS for Anterior Segment Diseases

Subjects: Ophthalmology

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The eye is a delicate and complex organ protected by anatomical barriers that limit the bioavailability and residence time of topically administered drugs. Polymeric nano-based drug delivery systems (DDS) have been developed to address this challenge and improve therapeutic outcomes. Biodegradable polymers are often used in these DDS to minimize adverse effects and control the release of different loaded drugs.

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1. DDS for Ocular Surface Disease

Ocular surface disease refers to damage of the surface layers of the eye, namely the cornea and conjunctiva. Dry eye disease (DED), or keratoconjunctivitis sicca, is the most common type of ocular surface disease. It is a complex condition characterized by insufficient or poor-quality tears, leading to discomfort, visual disturbances, and ocular surface damage. Various factors contribute to its development, including aging, medical conditions, medications, environmental factors, lifestyle habits, and hormonal changes. The severity of DED determines the pharmacologic therapy needed, ranging from mild cases, such as artificial tears, to severe cases requiring topical corticosteroids, immunosuppressants, or autologous tear therapies. However, these treatments have their limitations and side effects. For instance, artificial tears need frequent application and compliance, topical steroids can cause adverse effects, and autologous tear therapy is expensive and time-consuming. Moreover, DED affects ocular drug delivery, reducing topical medication efficacy and increasing systemic absorption risk. Thus, other therapeutic strategies have been developed to manage DED and enhance drug delivery.

Nanoemulsions encapsulating cyclosporine A such as CyclokatTM and RestasisTM have been approved for treating dry eye disease due to their highly solubilized state and improved stability. However, the high molecular weight of cyclosporine A and its higher affinity with the oil phase of the nanoemulsion have hampered drug delivery to ocular tissue. CequaTM, a nanomicelle solution containing cyclosporine A, has been shown to improve ocular surface integrity and increase tear production after 84 days of treatment. KPI-121, a mucin-penetrating particle (MPP) for the delivery of loteprednol etabonate, has also been approved by the FDA for the treatment of dry eye disease. The nanosuspension, developed by a milling procedure containing loteprednol etabonate and Pluronic F127 polymer, has a low molecular weight, evades entrapment by mucin, and has a reduced clearance rate

compared to conventional eye drops. In clinical trials, KPI-121 has shown minimal toxicity and has successfully reduced signs and symptoms of dry eye disease. The F127 polymers used in KPI-121 form nanomicelle structures that can form hexagonal morphologies at higher temperatures, improving the stability of the system.

Recent clinical trials have investigated several novel biodegradable nano-sized DDS that aim to improve drug delivery for dry eye disease by reducing the need for frequent administration and increasing bioavailability. Mun et al. (2019) synthesized cholesterol-hyaluronate nanomicelles crosslinked with ethylene glycol dimethacrylate and hydroxyethyl methacrylate, resulting in contact lenses that demonstrated a prolonged therapeutic effect in a dry eye disease rabbit model. Other formulations of cyclosporine A based on mPEG-PLA copolymers have also been developed, demonstrating increased stability and prolonged shelf life through lyophilization.

Rebamipide is a promising drug for treating tear deficiency and corneal epithelial damage. It has been shown to increase mucin and lipid layers in the tear film while reducing ocular surface dryness. To improve drug delivery and increase compliance, researchers are developing novel drug delivery systems that can evade nasolacrimal clearance. Copolymeric nanoparticles made from 2-hydroxypropyl-β-cyclodextrin and methylcellulose have demonstrated sustained release and improved delivery to the goblet cells and meibomian glands. Additionally, hydrogenated soybean phospholipids and high-purity cholesterol multilamellar nanoliposomes have shown equivalent therapeutic effects to the commercially available formulation, while reducing the frequency of administration and adverse effects by improving drug retention and concentration at the cornea and aqueous humor.

Wang et al. recently synthesized rapamycin nanospheres based on 3-hydroxybutyrate-co-3-hydroxyvalerate copolymers that can effectively penetrate the tear film barrier. These nanospheres have shown potential advantages for Sjögren-associated dry eye disease, such as increasing tear meniscal height, decreasing tear break-up time, and improving Schirmer’s test scores. However, further research is needed to determine their long-term safety and efficacy [1].

Luo et al. have developed a thermo-responsive in situ gel for the treatment of dry eye disease. This gel is synthesized by functionalizing poly(N-isopropylacrylamide) with mucoadhesive gelatin and helix pomatia. In a rabbit model, a single application of the gel increased the bioavailability of the drug epigallocatechin gallate beyond the therapeutic level for 14 days [2].

Mucolytic agents are drugs that reduce mucus viscosity and inhibit inflammation. These agents typically have a thiol group, which breaks disulfide bonds in mucoprotein complexes, or are enzymes like papain or bromelain that cleave cross-links of mucus glycoproteins. Modification of nanocarriers with mucolytic agents can enable controlled drug release, enhanced permeation, and improved mucoadhesion. However, while mucolytic enzyme-loaded nanoparticles have been developed for penetrating intestinal mucous layers, research on ocular delivery is currently limited [3].

N-acetylcysteine (NAC) is a mucolytic agent that has been used to treat various anterior segment diseases, including cataracts, DED, and filamentous keratitis. However, intracorneal injection of NAC is associated with rapid mucolytic activity and adverse side effects, such as edema, sloughing, and corneal haze. To address this issue, thiolated polymers can be used to achieve a controlled, sustained release of NAC. Chitosan is an attractive option for forming highly mucoadhesive copolymers for ocular drug delivery systems. By optimizing the concentration of NAC on the surface of chitosan, the thiol groups of NAC can form covalent bonds with mucosal glycoproteins. Nepp et al. found sustained improvement in patients with dry eye disease with chitosan-NAC eye drops (LacrimeraTM). Thiolated polymers have the advantage of significantly improving adhesion to the ocular mucus layer, and therefore improving contact time with the drug, by binding with positively charged glucosamine as well as negatively charged carboxylic acids in mucosal proteins. This approach was used by Sheng et al. to synthesize nanomicelles for the delivery of flurbiprofen to reduce inflammation in DED. The nanomicelles successfully increased the bioavailability of flurbiprofen in an in vivo rabbit eye model. However, a practical barrier with mucoadhesive nanocarriers is that in vivo studies in rabbit models may not bring clinically translatable results given that rabbit eyes have superior bioadhesion and higher mucus production compared to human eyes [4].

Several novel drug-delivery systems have been developed to treat dry eye disease. The most widely used topical medications in North America are nanoemulsions encapsulating cyclosporine A (RestasisTM) and its nanomicelle form (CequaTM). These DDS offer promising results by increasing drug bioavailability, reducing the need for frequent administration, and translating clinically into improved symptom management, greater compliance, and fewer side effects.

In addition to DED, Meibomian gland dysfunction (MGD) is another common ocular surface disease that impairs meibomian gland function, leading to decreased meibum secretion and blockages. This can cause changes in the tear film composition, specifically the lipid layer, resulting in increased tear evaporation, hyperosmolarity, inflammation, and ocular surface damage. Treatment for MGD currently involves heat therapy, massage, and lid margin hygiene, but artificial tears and topical steroids may have limited effectiveness due to low patient compliance.

Chronic inflammation and oxidative stress are critical factors in the development and progression of MGD [5]. While preservative-free fluorometholone eyedrops can be used for drug administration, multiple installations are required, and they can cause adverse effects if used without DDS [6]. To address this issue, Choi et al. developed polyhydroxyethyl methacrylate-based contact lenses embedded with cerium oxide nanoparticles for scavenging reactive oxygen species. These contact lenses improved the viability of human conjunctival and meibomian gland epithelial cells, even in media with high H2O2 concentrations, and showed protective effects in a mouse model when 3% H2O2 eyedrops were administered [7].

In Phase 3 clinical trials, nanoemulsions encapsulating cyclosporine A (nano-cyclosporine; Cyporin NTM, Taejoon, Korea) have shown promise as a treatment for MGD. These nanoemulsions are considered more stable and transparent than normal emulsions. Results of the trial indicate that the group receiving cyclosporine nanoemulsions experienced significant improvement in dry eye disease secondary to MGD compared to the

control group. After one month of treatment, the cyclosporine nanoemulsion group had better corneal staining and increased lipid layer thickness compared to those receiving the conventional cyclosporine formulation [8].

2. DDS for Conjunctivitis

Conjunctivitis is inflammation of the conjunctiva, the clear outer membrane covering the sclera and inner surface of the eyelids. It can result from viral or bacterial infections, allergens, irritants, or a combination thereof. Treatment depends on the cause and severity and may include artificial tears, topical antibiotics, corticosteroids, and immunosuppressants.

3. Nano-based DDS in clinical Studies

In phase III clinical trials, cyclosporine A nanoemulsions are being investigated as a potential treatment option. These cationic emulsions interact with negatively charged ocular surfaces, leading to increased residence time. The formulation has shown promise in improving signs and symptoms of severe vernal keratoconjunctivitis and good biocompatibility, with the exception of instillation site pain [9].

4. Nano-based DDS in preclinical Studies

A biodegradable DDS based on solid lipid nanoparticles has been developed to improve the stability of tacrolimus, a topical immunosuppressant used to treat ocular inflammation, including vernal keratoconjunctivitis. Solid lipid nanoparticles, made of natural fats or oils, can encapsulate lipophilic molecules, improving drug solubility. The nano-based DDS demonstrated thermo-responsive gelation at 32 degrees and showed promising therapeutic effects in vivo compared to conventional eye drops for conjunctivitis treatment [10].

Several novel DDS are being investigated for the treatment of bacterial conjunctivitis to prolong the release of topical antibiotics. Chitosan and PVA nanofibers have been designed to encapsulate ofloxacin, and the linking of the nanofibers by glutaraldehyde vapor has been found to reduce burst release and increase bioavailability. Co-delivery of multiple guest compounds is another important strategy, with hydrogels made from chitosan and poloxamer 407 being invented for the co-delivery of neomycin and betamethasone. These hydrogels have been found to increase the bioavailability of drug guest molecules and reduce the frequency of dosing required for conjunctivitis eye drops [11][12].

5. DDS for Keratoconus

Keratoconus is a progressive eye condition that causes the cornea to become thin and cone-shaped, leading to vision distortion, nearsightedness, and irregular astigmatism. Early treatment options, such as rigid contact lenses or corneal crosslinking (CXL), can help slow the disease's progression. CXL involves creating new chemical bonds within the cornea's collagen fibers by performing epithelial debridement with a blade, applying riboflavin drops, and

exposing the cornea to ultraviolet light. However, traditional CXL has a limitation in that the cornea must be of a certain thickness to avoid postoperative corneal ectasia. Advanced drug-delivery systems have the potential to eliminate the need for mechanical epithelial debridement, reducing the risk of complications and making the procedure safer, especially in patients with thin corneal thickness. Nano-sized DDS can penetrate the cornea and directly target the photosensitizing agent to the cornea's deeper layers.

To improve the effectiveness of riboflavin delivery in corneal crosslinking for keratoconus treatment, nanocarriers have been studied for their ability to penetrate the tear film and corneal epithelium and reach the corneal stroma. Among these, nanostructured lipid carriers (NLCs) have shown improved stability and loading capacity compared to solid lipid nanoparticles. NLCs loaded with riboflavin have demonstrated sustained release and enhanced penetration compared to conventional eye drops and solid lipid nanoparticle formulations. Additionally, a thermoresponsive gel consisting of poloxamer 407 and hydroxypropyl methylcellulose has been developed for co-delivery of dexamethasone and riboflavin, exhibiting therapeutic potential in increasing corneal thickness and fibroblast cells associated with keratoconus [13][14].

To enhance the therapeutic efficacy of peptides for keratoconus treatment, appropriate drug delivery systems (DDS) are required. The rate of diffusion and residence time of peptides in the cornea are major barriers to their effectiveness. One solution is the use of copolymeric nanoparticles synthesized from chitosan-tripolyphosphate and chitosan-Sulfobutyletherβ-cyclodextrin for the delivery of lactoferrin, a peptide that can promote corneal healing. These nanoparticles display superior mucoadhesive properties, enabling them to achieve an ocular retention time of more than 240 minutes [15].

6. DDS for Keratitis

Keratitis is a condition that causes inflammation of the cornea, and it can be caused by a range of factors, from infections to autoimmune diseases. In severe cases, keratitis can lead to corneal melting, perforation, or scarring, which can result in severe vision loss. Therefore, prompt and proper treatment is essential. Treatment options for keratitis depend on the underlying cause and can include topical corticosteroids, antibiotics, and immunomodulatory agents.

To treat keratitis, topical delivery of drugs is commonly used. A gel formulation synthesized from sodium hydroxide, mannitol, and benzalkonium chloride has been approved as a polymeric drug delivery system for ganciclovir. This gel formulation solubilizes ganciclovir better than hydrophobic emulsions and increases the drug’s contact time within the eye. However, it needs to be applied five times a day. To improve the ocular retention and bioavailability of ganciclovir and reduce the need for frequent administration, non-mucoadhesive nanocarriers have been studied.

7. Nano-based DDS in preclinical Studies

Jain et al. developed an in situ gel from hydroxypropyl methylcellulose and sodium alginate to increase the precorneal residence time of levofloxacin, a broad-spectrum antibiotic used to treat infectious keratitis. The

hydrogels spontaneously self-assemble at corneal pH and displayed higher permeation compared to QuixinTM eye drops, with minimal in vivo toxicity [16].

Recently developed microneedles made from poly(vinylpyrrolidone) and polyvinyl alcohol offer an improved solution for the ocular delivery of amphotericin B, a polyene antibiotic. The microneedles do not contain deoxycholate, which eliminates the painful side effects associated with current options. In comparison to liposomal amphotericin B formulations, microneedles were more effective in targeting Candida species. Another important DDS has been synthesized using hydroxypropyl methylcellulose with PEG and Poly(vinylpyrrolidone) for the delivery of moxifloxacin. The in situ gel formation prolonged the adhesion of the drug to the cornea and enabled better drug permeation compared to current commercial forms. Additionally, carboxymethyl-alphacyclodextrin conjugated with chitosan has been shown to increase the biocompatibility and aqueous stability of econazole, an antifungal medication, resulting in a 29-fold increase in relative ocular bioavailability compared to conventional eye drop controls [17][18][19].

8. DDS for Cataracts

Cataract surgery involves the replacement of the diseased lens with a synthetic intraocular lens, and while it is commonly performed with a high success rate, it can carry risks and complications, including corneal edema, cystoid macular edema, endophthalmitis, and retinal detachment. The FDA has approved topical NSAIDs for the prevention of postoperative cystoid macular edema. Although the use of pharmacological compounds as an alternative to cataract surgery is still under development, various strategies aim to combat lens opacification by enhancing the bioavailability of antioxidants in the lens. This is because oxidative stress caused by reactive oxygen species and free radicals is a significant factor in the onset of cataracts.

Silver moieties have been used to synthesize nanoparticles, which can enhance the topical delivery of drugs, including antioxidants, for the treatment of cataracts [20][21]. Although silver nanoparticles have a high surface-area-to-volume ratio and are easy to manufacture, they have been linked to increased reactive oxygen species in the target tissue [22]. Mesoporous silica nanoparticles loaded with CeCl3 have also been developed to potentially reduce reactive oxygen species around the lens, but the formulations were designed for systemic injections, and the non-biodegradable nature of silica would result in the persistence of toxic metabolites in the blood [23][24]. As a result, biodegradable polymers are emerging as DDS applications for the treatment of cataracts, as they have a predictable release profile and increased biocompatibility.

Liu et al. recently developed a PLGA-based nanoformulation by combining curcumin and cerium oxide nanoparticles. This formulation exhibited effective antioxidant and anti-glycation potential to protect lens epithelial cells. Notably, it showed lower in vivo toxicity and increased cerium nanoparticle bioavailability in the rat eye compared to subcutaneous injections. Similarly, low molecular weight chitosan-coated mPEG-PLGA nanoparticles were used to deliver baicalin, another antioxidant. The nanoparticles had a small size and resulted in increased cellular uptake compared to the solution group. Additionally, in vivo tests demonstrated the nanoparticles' ability to

improve precorneal residence time and significantly enhance the activities of catalase, superoxide dismutase, and glutathione peroxidase, which neutralize reactive oxygen species [25][26][27].

Chitosan-NAC nanoparticles have been developed as a biodegradable nanocarrier for drug delivery to the anterior segment, using hydroxypropyl β-CD to encapsulate and deliver quercetin for cataract treatment. This approach, developed by Lan et al., has shown enhanced permeability of quercetin and deeper delivery into the corneal epithelium.

Biodegradable gels offer an attractive DDS for cataracts due to their prolonged contact with the target membrane, resulting in higher permeation of the drug at the site of administration while maintaining its bioactive form. Bodoki et al. used biodegradable nanoparticles composed of zein and PLGA to deliver the antioxidant Lutein for preventing cataract progression. In vivo experiments demonstrated a significant reduction in cataract severity in rats treated topically with lutein-loaded NPs compared to the positive control [28].

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