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Recent progress of nanomedicine in managing dry eye disease

Zeen Lv [a,1], Su Li [a,1], Guixiang Zeng [b], Ke Yao [a,*], Haijie Han [a,**]

[a] Eye Center, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Zhejiang Provincial Key Laboratory of Ophthalmology, Zhejiang Provincial Clinical Research Center for Eye Diseases, Zhejiang Provincial Engineering Institute on Eye Diseases, Hangzhou, 310009, China
[b] Department of Pediatrics, No. 903 Hospital of PLA Joint Logistic Support Force, Hangzhou, 310013, China

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ABSTRACT

Background: Dry eye disease (DED) is a commonly reported ocular complaint that has garnered significant attention in recent research. The global occurrence of DED ranges from 5% to 50%, impacting a substantial proportion of individuals worldwide with increasing frequency. Although topical administration remains the mainstream drug delivery method for ocular diseases, it suffers from drawbacks such as low bioavailability, rapid drug metabolism, and frequent administration requirements. Fortunately, the advancements in nanomedicine offer effective solutions to address the aforementioned issues and provide significant assistance in the treatment of DED.

Main text: DED is considered a multifactorial disease of the ocular surface and tear film, in which the integrity of tear film function and structure plays a crucial role in maintaining the homeostasis of the ocular surface. The conventional treatment for DED involves the utilization of artificial tear products, cyclosporin, corticosteroids, mucin secretagogues, and nonsteroidal anti-inflammatory drugs. Furthermore, nanomedicine is presently a significant field of study, with numerous clinical trials underway for various nanotherapeutics including nanoemulsions, nanosuspensions, liposomes, and micelles. Notably, some of these innovative nanoformulations have already received FDA approval as novel remedies for DED, and the advancement of nanomedicine is poised to offer enhanced prospects to solve the shortcomings of existing treatments for DED partially.

Conclusions: This article provides an overview of the latest advancements in nanomedicine for DED treatment, while the field of DED treatment is expected to witness a remarkable breakthrough shortly with the development of nanomedicine, bringing promising prospects for patients worldwide suffering conditions.

1. Introduction

DED is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities have aetiological roles.[1] DED can greatly affect visual functionality (e.g., hemeralopia, halos, double vision, flash of light, photophobia, and the like) causing ptosis, filamentary keratitis, and swelling in the area of the lacrimal gland, leading to ocular discomfort (e.g., dryness, redness, foreign body sensation, burning sensation, nociceptive pain, neuropathic pain, eye fatigue and the like) and the disease may result in visual loss as it advances.[2–5]

DED is a highly prevalent ocular surface disease that affects a substantial number of individuals, and it affects 5%–50% of individuals worldwide according to statistics.[6] The presence of risk factors such as drug usage, eye surgery, unsuitable environmental conditions, and the use of contact lenses contributes to the increasing prevalence of DED.[7] Given its significant patient population, the investment required to treat DED is very important. Various therapeutic approaches are available for managing this condition including warm compress meibomian glands treatment, nasal tear nerve stimulation, contact lenses, surgical interventions, topical medications, etc. Among these options, topical medication stands out as the most crucial one.[8] However, the topical administration of DED is associated with several limitations, including patient compliance, increased intraocular pressure, and side effects.[9] In

* Corresponding author.
** Corresponding author.
E-mail addresses: 22318228@zju.edu.cn (Z. Lv), ls5774217@163.com (S. Li), zeng_gui_xiang@126.com (G. Zeng), xlren@zju.edu.cn (K. Yao), hanhj90@zju.edu.cn (H. Han).
[1] These authors contributed equally.

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addition, due to tear dilution and drainage of the tear ducts, the concentration of topical medications is extremely low, resulting in a short duration of action of the eye drops. As a result, the frequency of topically administered treatments for DED is high.[10] Nowadays, the recent advancements in nanomedicine have the potential to address the challenges associated with the topical administration of DED effectively and nanomedicine has played a pivotal role in the domains of ophthalmology, oncology, autoimmune diseases, and other disciplines by offering novel insights into disease diagnosis, prevention, and treatment.

In brief, the objective of this article is to present the recent advancements and utilization of nanomedicine in the treatment of DED. Firstly, we will introduce the pathogenesis of DED, and then the existing therapeutic approaches for DED. Lastly, we will discuss the categorization and roles of nanocarriers in the treatment of DED.

2. Pathogenesis of DED

Clinically, DED is characterized by loss of tear volume, the more rapid breakup of the tear film, and increased evaporation of tears from the ocular surface, so the destruction of both function and structure of the tear film appears to play a pivotal role in the pathogenesis of DED.[11] The tear film is a barrier between the ocular surface epithelium and the external environment. It serves several important functions, such as smoothing and regulating the corneal epithelium, inhibiting bacterial growth with antibacterial ingredients like lysozyme, and providing oxygen and nutrients to the cornea. The tear film is typically categorized into three components (from outside to inside): the lipid layer, the aqueous layer, and the mucin layer (Fig. 1). The lipid layer is secreted mainly by the meibomian glands and has the function of preventing tear evaporation, with a thickness of 15 nm – 160 nm.[12] The intermediate aqueous layer is primarily secreted by the main and accessory lacrimal glands. It contains a variety of enzymes, proteins, and essential nutrients that play a crucial role in maintaining lubrication and safeguarding the ocular surface against pathogens, thereby promoting ocular health. Moreover, decreased tear volume can lead to tear hyperosmolarity, which is considered an important factor contributing to ocular surface diseases such as DED.[13] The innermost mucin layer is secreted by goblet cells in the conjunctival epithelium, the acinar cells of the lacrimal glands, and corneal cells.[14] The mucin layer is composed of various types of mucins and serves multiple functions, including hydrodynamic lubrication, anchoring the aqueous tear film, maintaining tear film stability, eliminating pollutants, and preserving the integrity of epithelium.[15] In addition, the lacrimal functional unit (LFU) plays a dominant role in maintaining the integrity of tear film structure and function, which is an umbrella term for all the tissues accountable for tear generation, transportation, and elimination. It consists of main and accessory lacrimal glands, meibomian glands, conjunctival goblet cells, surface epithelium, eyelids, lacrimal drainage system, the glandular and mucosal immune system as well as its dominant nerve.[16] Dysfunction in any of the components of the LFU can result in alterations to tear volume, concentration, osmolarity, and stability,[17–19] which in turn may induce DED. In recent decades, research on the pathophysiology of DED has witnessed significant advancements and continues to evolve. Tear film instability, tear hyperosmolarity, apoptosis, and inflammation are the main pathophysiological factors contributing to the development of DED. These etiologies are intricately interconnected cyclically, rendering DED an autonomous self-perpetuating condition that gradually dissociates from its initial cause. Tear film stability plays a crucial role in reducing evaporation and ensuring continuous tear coverage of the ocular surface during intervals between blinks.[20] Specifically, the rapid breakdown of the tear film following blinks (tear film instability) leads to localized epithelial surface dryness and hyperosmolarity. Consequently, this triggers apoptosis of corneal and conjunctival epithelial cells. Conjunctival epithelial cells harbor a diverse repertoire of resident immune cells, encompassing natural killer cells, dendritic cells, macrophages, γδ T cells, $CD4^+$ T cells, $CD8^+$ T cells et al. These immune cells may have a significant impact on the immunological homeostasis of the ocular surface.[21] The hyperosmolarity exerts a potent proinflammatory effect, leading to the upregulation of proinflammatory cytokines (such as IL-1β and TNF-α) and C-X-C chemokine IL-8 via the activation of c-Jun N-terminal kinase (JNK) and extracellular-regulated kinase (ERK) mitogen-activated protein kinase (MAPK) signaling pathways.[22] The proinflammatory milieu

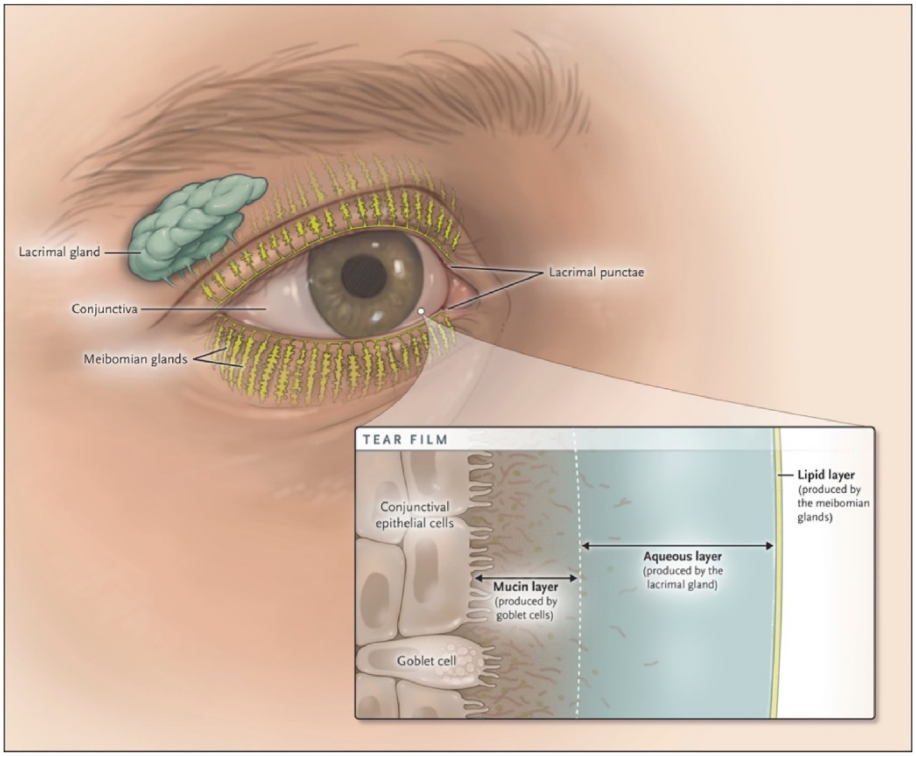

Fig. 1. Schematic diagram of the tear film and the structures.[96]

facilitates the activation and maturation of antigen-presenting cells (APCs) including conventional dendritic cells, monocytes, and macrophages, ultimately initiating a more specific adaptive immune response.[23] These matured APCs migrate to regional lymph nodes via newly formed lymphatic vessels (facilitated by vascular endothelial-derived growth factor (VEGF)-C and VEGF-D)[24,25] and trigger the generation of antigen-specific T cells (including T_H1, T_H2, T_H17, and T regulatory (T_{reg}) lymphocytes and the like.), which then migrate to and reactivate at the ocular surface upon exposure to ocular stressors. Upon migration towards the ocular surface, T_H1 and T_H17 cells elicit the secretion of interferon (IFN)-γ and IL-17, respectively.[26,27] These cytokines subsequently stimulate conjunctival and corneal epithelial cells to release proinflammatory mediators such as cytokines, chemokines, and matrix metalloproteinases (MMPs).[23] This reactivation leads to an acute proinflammatory innate response accompanied by a loss of immune regulation, thus initiating a vicious cycle of pathological

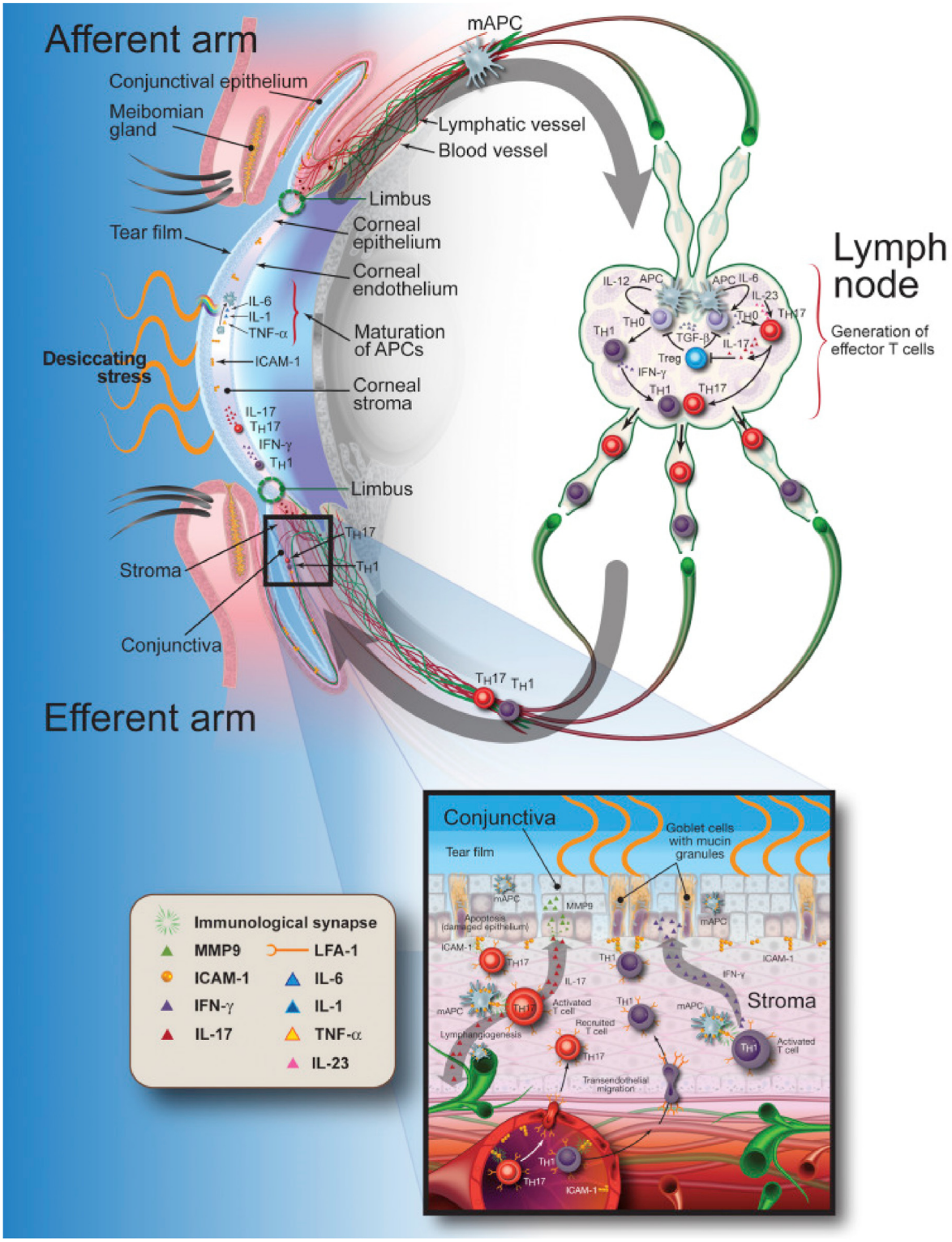

Fig. 2. Schematic diagram of the immunoinflammatory pathway of DED.[23]

immune responses.[28] Both the initial innate immune response and subsequent adaptive immune response mentioned above are observed as the shared mechanism in the development of DED.[29,30] These inflammatory disorders can disrupt goblet cells and compromise ocular surface defense systems. Ultimately, it perpetuates further damage to the tear film integrity while perpetuating the vicious cycle[31] (Fig. 2).

3. Clinical treatment of DED

Due to the high prevalence of DED, the treatment has always been a prominent subject. The primary objective in managing DED is to return the tear film and ocular surface to their natural state of balance.[1] Nevertheless, most commercially available medications for DED, such as artificial tear products, mucin secretagogues, corticosteroids, antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs), primarily focus on alleviating its symptoms rather than providing a complete remedy. The two approved drugs for DED, cyclosporine, and lifitegrast, specifically target T cells that play a crucial role in the pathophysiological process of chronic DED, which effectively addresses the underlying causes of DED from a pathogenic perspective.[21] In the following sections, we will provide a brief overview of some available medications for managing DED.

The current first-line treatment for DED involves the use of artificial tear products, which act as lubricants to enhance the viscosity of the tear film and maintain ocular surface moisture by preventing moisture loss, consequently alleviating patients' discomfort. Artificial tear products consist of a variety of ingredients including viscosity-enhancing agents, electrolytes, osmoprotectants, oily agents, antioxidants, and preservatives.[32] However, frequent administration inevitably leads to suboptimal patient adherence. Meanwhile, due to its limited effect, the use of artificial tears is often accompanied by various other medications to manage DED more effectively.[33]

The most common mucin secretagogues on the market are diquafosol and rebamipide. The P2Y2 receptor is widely distributed in the eyelid, bulbar conjunctival epithelium, corneal epithelium, and meibomian gland. It plays an important role in the regulation of tear secretion and mucin secretion.[34] As a P2Y2 receptor agonist, diquafosol can stimulate tear and mucin secretion, making it an effective means to enhance tear film stability in individuals with DED.[35] In addition, Zhang et al. demonstrated that 3% diquafosol was effective in improving the ocular surface condition of patients after cataract surgery.[36] As for rebamipide, it was originally developed to treat gastric ulcers, but subsequent research has indicated that the topical application of rebamipide can effectively augment goblet cell count and stimulate the production of mucin-like proteins in both the lacrimal ducts and bulbar conjunctiva of human subjects.[37]

Corticosteroids are a class of drugs with strong immunosuppressive and anti-inflammatory properties, mainly conducted by activation of glucocorticoid receptors, suppressing vasodilation, mitigation of vascular permeability, and control over cell adhesion.[38] The efficacy of methylprednisolone, the first topical corticosteroid demonstrated to be effective in treating DED, has been proven to enhance both clinical manifestations and subjective symptoms of the disease.[39,40] Loteprednol Etabonate is widely recognized as a highly sought-after option for addressing DED conditions among the various topical corticosteroids available, and it has obtained FDA approval for short-term therapeutic use.[41] The use of corticosteroids for a short duration is recommended due to the potential risk of glaucoma, cataracts, and other infections associated with long-term usage.

Cyclosporine A (CsA) is an immunomodulatory agent widely used in anti-inflammatory treatment, and its primary mechanism of action involves suppressing the synthesis of cytokines that play a crucial role in regulating the activation of T cells (CsA has potent immunosuppressive properties and it can block the transcription of cytokine genes in activated T cells).[42,43] In the field of ophthalmology, CsA was initially employed as a topical treatment to prevent rejection of corneal transplants during the 1980s. Subsequently, it found utility in managing different inflammatory conditions affecting the surface of the eye.[44] In addition to its anti-inflammatory effects, CsA was found to inhibit the apoptotic pathway mediated by mitochondria.[43] Two CsA formulations, namely Restasis® (CsA 0.05%) and Cequa® (CsA 0.09%), received the FDA approval for the treatment of DED respectively in 2002 and 2018.[45] However, these CsA formulations are often associated with ocular adverse effects including conjunctival hyperemia, ocular burning, instillation site pain, stinging, and epiphora as well as very low solubility in water. Indeed, Brignole et al. have demonstrated that the application of a 0.01% CsA emulsion can effectively modulate various aspects of the immune response in patients with DED. This is achieved by reducing the expression levels of human leukocyte class II antigen (HLA-DR) in the conjunctiva, as well as suppressing the expression of IL-17A and IFN-γ in animal models subjected to desiccating stress.[46]

Lifitegrast is a novel small molecule integrin antagonist that effectively suppresses the T cell-induced inflammation cycle by blocking the binding of intercellular adhesion molecule 1 (ICAM-1) to lymphocyte function-associated antigen 1 (LFA-1), thereby reducing overall inflammatory reactions.[23] Holland et al. conducted a phase III, randomized, double-masked, placebo-controlled trial (OPUS-3) to demonstrate that lifitegrast markedly improved symptoms of eye dryness, and the main evaluation index is the eye dryness score.[47] Xiidra® is a 5% ophthalmic solution of lifitegrast, which has received the approval of the FDA. A sufficient number of clinical trials have demonstrated the efficacy of Xiidra® in improving both symptoms (i.e., change from baseline to day 84 in eye dryness visual analog scale score) and signs (i.e., change from baseline to day 84 in inferior corneal fluorescein staining score) associated with DED.[48]

4. Nanomedicine for DED treatment

The eye's anatomical position facilitates the application of medication through topical administration, thereby reducing the likelihood of adverse effects linked to systemic absorption.[49] Furthermore, the bioavailability of topically administered medications is often restricted (<5%) due to various physical and biochemical obstacles, such as the precorneal, limited capacity within the cul-de-sac for drug absorption, drainage system for tears, reflex tearing response and aqueous outflow dynamics within the eye.[50] The cornea is an amphipathic tissue, with the epithelial cell layer being hydrophobic and the stromal layer being hydrophilic, which also leads to limited bioavailability of topical administration.[51] Furthermore, certain challenges persist in the topic administration of DED, including excessive frequency of drug application, limited ocular surface residence time for drugs, and suboptimal drug concentration.

Over the past three decades, nanotechnology has rapidly advanced, offering promising new strategies for the treatment of DED. Nanoparticles can deliver both lipophilic and hydrophilic drugs, hence, effectively solving low drug bioavailability. The classification of nanoparticles can be broadly categorized into three main groups: polymeric nanoparticles (e.g., polymersome, dendrimer, etc.), inorganic nanoparticles (e.g., silica nanoparticles, gold nanoparticles, cerium oxide nanoparticles, etc.) and lipid-based nanoparticles (e.g., liposome, emulsion, nanostructured lipid carriers, etc.)[52] (Fig. 3). The subsequent sections will concentrate on the nanoparticle-mediated drug delivery systems (DDS) including dendrimers, nanoemulsions, micelles, nanosuspensions, liposomes, nanostructured lipid carriers (NLCs) and inorganic nanoparticles whose merits containing excellent bioavailability, targeted delivery, lower dosage, less administration frequency, lower side effects, better patient compliance than commercially available drugs[53] and their capacity to tailor and optimize the unique physicochemical properties of nanoscale materials and structures through the manipulation of nanoparticle size and morphology to meet diverse requirements.[54,55] On the other hand, the effectiveness and safety of certain products have been validated, and a range of nanomedicine for treating DED have obtained approval from regulatory bodies such as the

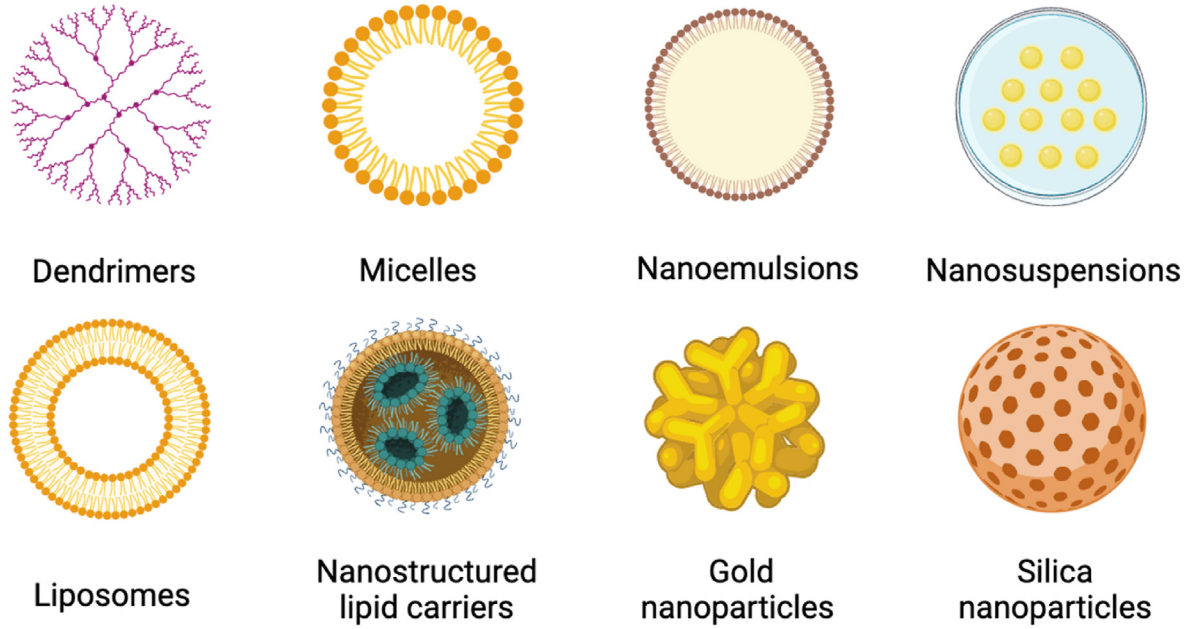

Fig. 3. Illustration of nanoparticles for topical administration in ophthalmology.

FDA and European Medicines Agency (EMA) for commercialization. A brief overview of the commercial products is presented in Table 1. This section provides an overview of studies investigating diverse nanotechnology systems for therapeutic drug delivery systems that are suitable for the treatment of DED.

4.1. Dendrimers

The dendrimer is a unique polymer compound composed of a central core, an inner repetitive unit, and an outer terminal group. It is characterized by its hyperbranched structure. The utilization of dendrimer offers numerous benefits, including its high solubility in water, simple modification of its surface, and the presence of an internal cavity for drug incorporation.[56] The core determines the 3D structure and dimensions of the dendrimer, while the surface groups govern its physicochemical characteristics. Peripheral groups on dendritic polymers can be further tailored to meet specific requirements for targeted drug delivery to desired organs, tissues, cells, and subcellular locations.[57] As versatile carriers for drug delivery, polyamidoamine (PAMAM) dendrimers hold great promise due to their highly branched structure and the ability to conjugate drugs with multivalent surface groups.[58] For example, PAMAM-based divalent water-soluble dendrimers, containing two sulfonamide units, exhibit a remarkable affinity towards MMP9, which plays a vital role in the progress of inflammation of the DED.[33] Lin et al. conducted experimental studies based on a rabbit model of autoimmune lacrimal gland inflammation and demonstrated that the dendrimer-dexamethasone conjugate exhibited an enhanced anti-inflammatory effect when used for the treatment of DED. The mechanism was that the conjugate preferentially localized to infiltrating cells and significantly reduced infiltration after subconjunctival injection.[33,59]

Table 1
Representative commercially available nanomedicines for the treatment of DED.

Product	Nanoformulations	Drug	Manufacture
Restasis®	Nanoemulsions	Cyclosporine-A (0.05%)	Allergan, Inc.
Clacier®	Nanoemulsions	Cyclosporine-A (0.05%)	Huons Co.Ltd.
Ikervis®	Nanoemulsions	Cyclosporine-A (0.1%)	Santen Ltd.
Cationorm®	Nanoemulsions	Cyclosporine-A (0.1%)	Santen Ltd.
Soothe XP	Nanoemulsions	Artificial tear products	Bausch & Lomb Inc.
Lacrinmune®	Nanoemulsions	Cyclosporine-A (0.05%)	Bausch & Lomb Inc.
Cequa®	Micelles	Cyclosporine-A (0.09%)	Sun Pharma Canada Inc.

4.2. Nanoemulsions

Nanoemulsions belong to a homogeneous disperse system, consisting of water, oil, surfactant, and cosurfactant particles ranging in size from 1 to 100 nm. It offers benefits such as stability under varying conditions, straightforward preparation methods, precise drug administration capabilities, and enhanced drug absorption rates. Nanoemulsions can be divided into three types: oil-in-water nanoemulsions (O/W), water-in-oil nanoemulsions (W/O), and bicontinuonal nanoemulsions (B.C). Daull et al. demonstrated that the suitability of oil-in-water nanoemulsions as a carrier for drugs with lipophilic properties.[60] The current formulations of nanoemulsion for the treatment of DED available in the market include Restasis® (Allergan), Lacrinmune® (Bausch & Lomb), and Ikervis® (Santen).[61] The lipophilic drug CsA is utilized for the treatment of DED, and its nanoemulsion formulation, Restasis®, has been approved by the FDA for managing DED. This drug Lacrinmune®, the nanoemulsion drug approved in Argentina for the treatment of DED, is similar in composition to Restasis® but with the addition of sodium hyaluronate to increase viscosity and thus prolong the retention time on the ocular surface. The EMA has approved Ikervis®, an oil-in-water emulsion of CsA with a concentration of 0.1% (1 mg/mL). Moreover, Ikervis® has good ocular surface persistence properties because it contains cetalkonium chloride, a cationic agent that has the property of increasing the residence time of drugs on the ocular surface.[62] The application of an eye drop based on 0.6% Povidone-Iodine nanoemulsion has demonstrated efficacy in alleviating DED symptoms encompassing burning sensation, eye dryness, foreign body sensation, and tearing. Furthermore, it exhibits the potential for rebalancing bacterial overgrowth commonly observed in patients with DED.[63] Kim et al. used Clacier® (a novel 0.05% CsA nanoemulsion formulation) and Restasis® to treat two groups of moderate to severe DED patients, respectively, and verified the therapeutic effect of Clacier®

on DED by comparing the therapeutic effect of the two groups. The main observation index was the change in corneal fluorescein staining score compared with baseline after 12 weeks of treatment. The results showed that both groups could significantly reduce the degree of corneal surface damage, and the Clacier®-treated patients were more ameliorated in terms of tear film stability and conjunctival surface damage.[64]

4.3. Micelles

Micelles are colloidal structures, characterized by their amphiphilic nature. The versatile applications of micelles as drug carriers stem from their capacity to encapsulate lipophilic drugs within their hydrophobic core, while simultaneously interacting with polar molecules on the surface of the micelle.[65,66] Micelle technology is extensively utilized in ocular drug administration due to its minute particle size, convenient preparation process, and remarkable capacity for drug encapsulation.[67] The utilization of polymeric micelles as an innovative and promising approach for drug delivery exhibits potent potential in addressing the treatment of DED. Moreover, Tommaso et al. demonstrated that the MPEG-hexPLA micelle formulation possesses patient-centric attributes such as transparency, ocular tolerance, and biocompatibility. Consequently, it can be conveniently administered topically without compromising patient adherence.[68] The stability of lyophilized micelles loaded with CsA was observed for a minimum duration of 3 months in the in vitro experiments, and the release pattern indicated a sustained release mechanism for CsA. Yu et al. demonstrated that the micellar formulations exhibited an enhanced retention effect in terms of ocular distribution in vivo, with a 4.5-fold increase compared to the emulsion containing 0.05% CsA.[69,70] The novel aqueous solution of micellar CsA, known as Cequa®, has the potential to deliver therapeutic concentrations of CsA while minimizing patient discomfort. Mandal et al. conducted an experiment based on adult female New Zealand white rabbits to demonstrate that Cequa® exhibits superior bioavailability and longer residence time on the ocular surface compared to Restasis®.[17] Guo et al. demonstrated that the 0.5 mg/mL CsA-loaded Soluplus® micelles ophthalmic drops have better performance in the field of corneal residence time compared with the commercial CsA oil-based 10 mg/mL ophthalmic solution and the CsA micelles have low cytotoxicity.[71] Mitra et al. developed a novel aqueous, transparent 0.1% CsA micellar formulation comprising a polymer blend of polyoxyethylene hydrogenated castor oil 40 (HCO-40) and octoxynol 40 (Oc-40).[72] The 0.1% CsA micelle preparation showed improved drug entrapment (>95%), and loading efficiencies (8.8%) and there are considerable drug concentrations on ocular surface tissues such as cornea and conjunctiva, so it has the significant potential to treat DED.[72]

4.4. Nanosuspensions

The nanosuspension is a colloidal dispersion and nano-controlled release system,[73,74] which is a technique utilized to enhance the dissolution and bioavailability of drugs with poorly water-soluble. The utilization of nanosuspension has been extensive in the management of DED owing to its capacity to prolong the retention time of hydrophobic medications within ocular surface tissues and enhance drug bioavailability. The application of nanosuspension is frequently employed for the encapsulation of corticosteroids (prednisone, dexamethasone, hydrocortisone, and the like) thereby enabling a reduction in steroid dosage and mitigating potential side effects of corticosteroids such as glaucoma and cataracts.[73] The superiority of nanosuspensions in terms of drug concentration in targeted tissues over the previously described nanoemulsions is widely acknowledged. The assessment of the biological tolerability and the corneal drug concentration through periodic eye examinations over 180 min and quantification using a defined grading system revealed that the in-situ nanosuspension (INS) elicited minimal to no irritations and the experiment shows that the concentration of CsA in the cornea of the nanosuspension group was (1683 ± 430) ng CsA/g cornea, surpassing that of Restasis® (350 ng CsA/g cornea) and cationic emulsion (750 ng CsA/g cornea).[75]

4.5. Liposomes

Liposomes are a type of vesicular drug delivery system characterized by their positively charged surface and composed of phospholipid bilayers, with vesicles ranging in size from 20 nm to 10 μm in diameter. Liposomes primarily consist of glycerophospholipids, which are lipids with both hydrophilic and hydrophobic properties. These lipids are composed of a phosphate group and two fatty acid chains (which can be saturated or unsaturated) attached to a glycerol molecule.[76] Thanks to its unique composition of a phospholipid bilayer, this substance can accommodate both hydrophobic and hydrophilic drugs.[77] Moreover, the presence of their positively charged nature facilitates their engagement in electrostatic interactions with the negatively charged moieties present in mucin, thereby augmenting the efficacy of drug transportation. The commercially available liposomal spray (Tears Again®) is an option for the treatment of DED. The main constituents of liposome spray, namely phospholipids, and phosphatidylcholine, can bind to the tear film in the stable form of liposomes. This binding increases the thickness of the lipid layer in the tear film, thereby enhancing its stability and alleviating symptoms experienced by patients with DED.[78,79] Trimix® eye drops are liposomal formulations for the treatment of DED, consisting of viscosity-enhancing hyaluronic acid, trehalose, stearyl amine, and phospholipids. Vigo et al. set detailed enrollment criteria to screen patients, and those who met the criteria were treated with Trimix® for two months. The experimental findings demonstrated significant improvements in both objective signs and subjective symptoms among a cohort of patients with mild to moderate DED following treatment with a two-month Trimix® formulation.[80] Therefore, liposomes have the potential to mitigate symptoms of DED in individuals and improve the integrity and durability of the tear film. However, in the practical application of liposomes, there still exist certain challenges that need to be addressed, such as the complexity of multi-batch preparation and the liposomes' inadequate stability observed during the preparation process.[81]

4.6. Nanostructured lipid carriers (NLC)

The NLC is affiliated with lipid-based nanoparticles and the development of NLC was primarily driven by the need to address the deficiencies of solid lipid nanoparticles. Meanwhile, NLC possesses the advantages of solid lipid nanoparticles, including sustained drug release capabilities, biodegradability, low toxicity potential, drug protection against harsh environments, and prevention of organic solvents during manufacturing.[82] The solid lipid structure primarily governs the release behavior of the carrier. Additionally, the particle size of cationic NLCs also plays a crucial role in influencing the rate of drug release. A smaller particle size enhances the specific surface area for release, thereby expediting drug liberation. Tan et al. developed mucoadhesive NLCs loaded with dexamethasone, which possess the ability to adhere to mucin on the ocular surface, thereby enhancing precorneal retention time and causing minimal irritation.[83] The results of animal experiments conducted on New Zealand albino rabbits demonstrated that chondroitin sulfate and L-cysteine modified cationic NLC (CS-Cys-cNLC) loaded with dexamethasone exhibited a slower rate of tear concentration decrease, a higher peak concentration, and a longer retention time compared to TobraDex preparation.[84] Under desiccative stress conditions, the methylene blue absorption value of the NLC group (0.04 ± 0.01) was found to be lower than that of the commercial artificial tears group (0.07 ± 0.02), and comparable to that of the negative control group (0.04 ± 0.01). This result demonstrates that NLC eye drops are effective in protecting ocular surface cells under desiccative stress.[85]

4.7. Inorganic nanoparticles

The composition of silica nanoparticles consists primarily of silicon dioxide. The silica nanoparticles possess dimensions ranging from 30 to 300 nm, exhibit a significant specific surface area, and demonstrate excellent chemical stability.[70] There are two forms of silica nanoparticles, non-mesoporous silica nanoparticles (NSiNPs) and mesoporous silica nanoparticles (MSiNPs). MSiNPs present several advantages, including good biocompatibility and biodegradability, high loading capacity, and easily modifiable surface.[86] Park et al. demonstrated that silica nanoparticles have minimal cytotoxic effects on human corneal epithelial cells.[87] As an excellent drug delivery nanoparticle, silica nanoparticles have been effectively utilized in the treatment of some ocular diseases such as retinoblastoma, retinal neovascularization, primary open-angle glaucoma, and other ocular diseases by incorporating various pharmaceutical agents, and it is believed that silica nanoparticles have great potential for the treatment of DED.[88]

Gold nanoparticles exhibit stable chemical properties, facilely modifiable surfaces, and biocompatibility. The biocompatibility and cytotoxicity of gold nanoparticles can be significantly influenced by their shape and size.[70,89] Li et al. developed a gold nanoparticle loaded with amfenac, which effectively inhibits the inflammation induced by cyclooxygenase enzymes and the oxidative stress induced by reactive oxygen species (ROS), both of which are the primary causes of DED. By comparing the fluorescein vital staining score of the CsA group and the amfenac-loaded gold nanoparticles group (the former score was approximately 5 times higher than the latter), it can be proved that the amfenac-loaded gold nanoparticles can effectively maintain the integrity of the corneal epithelium.[90] In addition, Wechsler et al. have successfully developed anionic hydrogel-coated gold nanoshells, which exhibit the capability to enhance protein recognition through the formation of dynamic covalent imine bonds with solvent-accessible lysine residues present on specific tear proteins. As a result, these innovative nanoshells hold great potential for clinical translation in establishing diagnostic methods for DED.[91]

Ceria (cerium oxide) nanoparticles, composed of cerium atoms coordinated by oxygen atoms, have low toxicity and strong antioxidant capacity.[92,93] The findings of previous studies have demonstrated that ceria nanoparticles possess the capability to restore both the quantity and morphology of conjunctival goblet cells in animal models with DED, thereby indicating the potential therapeutic application of ceria nanoparticles for treating this condition.[94] The experiment based on corneal and conjunctival cells demonstrated that glycol chitosan CeNPs (GCCNP) effectively mitigated reactive oxygen species (ROS) production and upregulated superoxide dismutase (SOD) expression thereby exhibiting remarkable antioxidant properties. Furthermore, GCCNP treatment significantly enhanced tear secretion in mice, suggesting its potential as a viable therapeutic approach for DED.[10] The research conducted by Zou et al. has successfully developed a novel nanozyme consisting of cerium oxide, in combination with branched poly(ethylene imine)-*graft*-poly(-ethylene glycol) (referred to as CNP@bPEI-g-PEG). The novel nanoenzyme emulates the functionality of SOD and catalase, effectively eliminating intracellular ROS, thereby exerting a reparative effect on the ocular surface.[95]

5. Conclusions

DED has significantly impacted the quality of life and resulted in substantial economic burdens on society. The past few years have witnessed a significant upsurge in research about various facets of DED, leading to an enhanced comprehension of the diagnosis, pathogenesis, and treatment modalities associated with this condition. Particularly in terms of treatment, a plethora of novel methods and medications have been developed to manage DED. The current advancements in nanoparticle-based drug development offer a partial solution to the constraints of existing DED medications. A wide range of nanomedicines have been approved for the treatment of DED, with numerous novel agents undergoing clinical trials of various stages. It seems only a matter of time before the potential of these agents to treat DED is realized. Despite the immense potential of nanomedicine in ophthalmology, the successful clinical translation and commercialization of this field remains an urgent challenge to be addressed. In addition, further research on the application of nanoformulations in ophthalmology is warranted in future investigations of biocompatibility, scale-up, drug release, and pharmacokinetics. In conclusion, the inherent properties of nanomedicine, combined with extensive research, will contribute to the advancement of its diverse applications in treatments for DED.

Study approval

Not applicable.

Author contributions

The authors confirm contribution to the paper as follows: Conception and design of study: HH, KY; Drafting the manuscript: ZL, SL and GZ; All authors reviewed the results and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

APCs	Antigen-presenting cells
CsA	Cyclosporine A
DDS	Drug delivery systems
DED	Dry eye disease
FDA	Food and Drug Administration
GCCNP	Glycol chitosan CeNPs
ICAM-1	Intercellular adhesion molecule 1
INS	In-situ nanosuspension
LFA-1	Lymphocyte function-associated antigen 1
LFU	Lacrimal functional unit
MMPs	Matrix metalloproteinases

MSiNPs	Mesoporous silica nanoparticles
NLC	Nanostructured lipid carrier
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSiNPs	Non-mesoporous silica nanoparticles
PAMAM	Polyamidoamine
ROS	Reactive oxygen species
SOD	Superoxide dismutase

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