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Novel drug delivery systems for the management of dry eye

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ABSTRACT

Dry eye disease (DED) is a frequently observed eye complaint, which has recently attracted considerable research interest. Conventional therapy for DED involves the use of artificial tear products, cyclosporin, corticosteroids, mucin secretagogues, antibiotics and nonsteroidal anti-inflammatory drugs. In addition, ocular drug delivery systems based on nanotechnology are currently the focus of significant research effort and several nanotherapeutics, such as nanoemulsions, nanosuspensions, microemulsions, liposomes and nanomicelles, are in clinical trials and some have FDA approval as novel treatments for DED. Thus, there has been remarkable progress in the design of nanotechnology-based approaches to overcome the limitations of ophthalmic formulations for the management of anterior eye diseases. This review presents research results on diagnostic methods for DED, current treatment options, and promising pharmaceuticals as future therapeutics, as well as new ocular drug delivery systems.

Contents

Abbreviations: AF/Au_Poly-CH NPs, amphenac-loaded poly(catechin) capped-gold nanoparticles; CNE, cationic nanoemulsions; CsA, cyclosporin A; Cys-PEG-SA, thiolated polyethylene glycol monostearate; DDS, drug delivery systems; DED, dry eye disease; EGF, epidermal growth factor; FDA, Food and Drug Administration; ICAM-1, intercellular adhesion molecule-1; IgA, immunoglobulin A; IL, interleukin; LFA-1, lymphocyte function-associated antigen-1; MGD, myibomian gland dysfunction; MMP-9, matrix metalloproteinase-9; MPEG-hexPLA, a methoxy poly(ethylene glycol)-hexylsubstituted poly (lactides); mPEG-PLA, methoxy poly(ethylene glycol)-poly(lactide) polymer; MPPs, mucus-Permeable Particles; NF-κB, nuclear factor-kappa B; NLCs, nanostructured lipid carriers; NOD, non-obese diabetic; NP, nanoparticle; NSAIDs, nonsteroidal anti-inflammatory drugs; PEG-DSPE, polyethylene glycol-distearoyl phosphatidylethanolamine; PLGA, Poly(lactic acid-*co*-glycolide); PS, phosphosulindac; PVAc-PVCap-PEG, graft copolymer containing polyvinyl acetate, polyvinyl caprolactam, and polyethylene glycol; SLNs, solid lipid nanoparticles; TBUT, tear film break-up time; TFI, tear function index; TG-DHA, triglyceride of docosahexaenoic acid; TNF-α, tumor necrosis factor-α.

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1. Introduction

Tear fluid is classified into three major fluid layers: lipid, aqueous and mucin (Fig. 1). The outer lipid-layer, which has a thickness of 0.1 μm, is responsible for preventing evaporation of the tear fluid as well as its overflow. The middle aqueous-layer, which has a thickness of 7–8 μm, comprises the bulk of the tear film. By contrast, the inner mucin-layer is 0.2 μm thick. Dry eye disease (DED) is caused by various genetic and/or environmental factors that may involve excessive tear evaporation or tear deficiency and is known as dry eye syndrome, keratoconjunctivitis, hypofunctional tear syndrome, ocular surface disease, scarring syndrome and scarring keratitis [1–3]. Thus, the putative pathogenetic mechanisms of DED include inflammation of the lacrimal gland and hyperosmolarity of the tear film.

The prevalence of DED varies widely among epidemiological studies depending on how the disease is defined and diagnosed, and which population is surveyed. Therefore, it is difficult to keep a tally of the number of patients in the world diagnosed with DED. On the other hand, the number markedly increases with age and is estimated to make up 7.4% to 33.4% of the worldwide population in the 1998–2003 studies [4]. DED particularly affects those over 50 years of age, and onset more frequent in females than males [5,6]. Established causes of DED include abnormal lipid production, mucus in the tear film, and too much tear evaporation or decreased secretion [7–9]. DED can be classified into evaporative DED and tear deficient DED (Fig. 2). Tear evaporative DED is brought on by increased tear evaporation, whereas tear deficient DED is caused by decreased amounts of tear secretion. For evaporative DED, the eyes become dry due to greater tear evaporation. Factors, such as reduced blinking due to excessive screen time, use of contact lenses, preservatives used in topical ocular therapies, dry weather, heating, deficiency in vitamin A and air pollution can interfere with the tear film, leading to corneal ulcers, infection, and in severe cases, blindness [10–12]. Abnormal lipid production due to blepharitis or meibomian gland dysfunction is known to be the main cause of these evaporative forms of DED, and an inadequate lipid-layer induces evaporative loss of tear fluid [13,14]. In addition, tear deficient DED is also found in individuals suffering from autoimmune diseases, such as Sjögren's syndrome, in the elderly, and in postmenopausal women [15–17]. Dysfunction of the tear fluid functional unit induces activation of inflammatory cells, such as T lymphocytes, due to lack of anti-inflammatory components in the eye and uncontrolled irritation of the eye. As a result, T cells liberate cytokines, which cause inflammation of the ocular glands and the ocular surface, leading to lytic symptoms and abnormal tear drops [18,19]. DED decreases the quality of life and reduces functional vision, leading to difficulty in typing and reading.

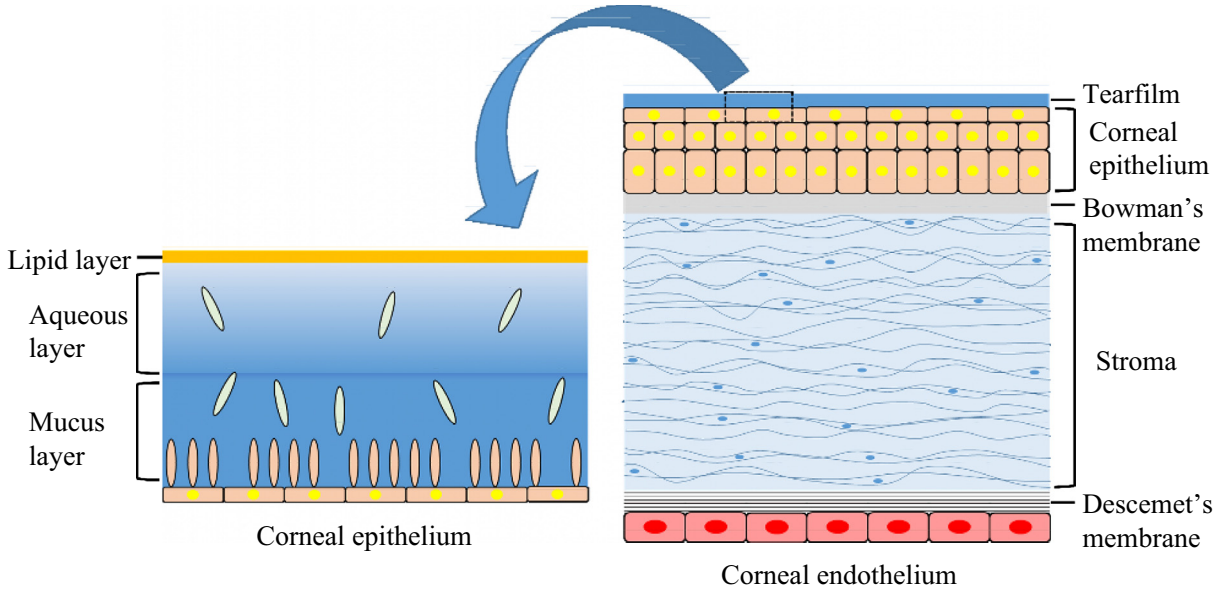

Fig. 1. Schematic diagram of the ocular surface.

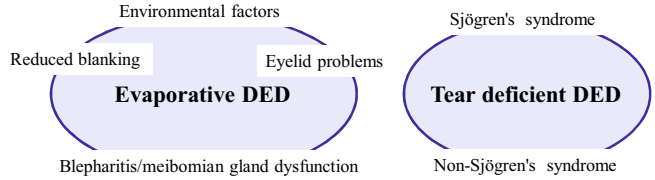

Fig. 2. Factors involved in the development of evaporative DED and tear deficient DED.

Moreover, DED causes eye pain, redness, blurred vision, foreign body sensation, excessive tearing, variable vision, and burning/itching of the eyes [20,21]. DED is classified into three stages (Grade 1–3) according to diagnostic results shown in Fig. 3 [1,22]. This review describes the management of DED, in addition to the latest drug delivery systems (DDS) that may be used to treat the disorder.

2. Diagnosis of DED

Diagnostic tests for DED include tear fluid protein immunoassay, impression cytology, tear film break-up time (TBUT), Schirmer test, epithelial staining, tear fluid osmolarity test, and Tear Function Index (TFI). Tear fluid contains proteins, such as immunoglobulin A (IgA), lipocalin, aquaporin 5, epidermal growth factor (EGF), tear fluid lactoferrin, and tear fluid lysozyme. These proteins can be quantified by ELISA in a so-called tear fluid protein immunoassay. Impression cytology is a measurement method in which biopsies of the conjunctiva and outer lacrimal gland are taken and observed using a microscope to obtain information on the etiology of the disease, such as progressive ocular surface changes (e.g., keratinization or a significant decrease in goblet cell count) [23,24]. This method is highly sensitive and robust, although it requires expert microscopic evaluation and the application of appropriate stains. The Schirmer test can also be used to quantitatively measure the amount of tear secretion over a specified period of time [25]. This procedure is carried out by using a local anesthetic and positioning a slim strip of filter paper over the inferior vessels [26,27]. TBUT is a quantitative test to measure the stability of tear fluid [28], evaluated by the time it takes for the tear fluid to break down after blinking. The normal value of TBUT is 20 to 30 s, but<10 s indicates a pathological state of DED development. Epithelial staining can assist in assessing corneal damage, tear characteristics, and the degree of dryness. Fluorescein, lissamine green, or rose bengal are typically used for this type of assessment [29]. The normal osmolarity of the eye is approximately 310 mOsm/L, but this increases with the progression of DED. Therefore, measurement of tear osmolarity provides qualitative information on tear production [27,28]. Previous multicenter studies suggest that tear osmolarity testing is the best way to diagnose and evaluate DED (Lemp *et al.* [30]). A more sensitive and specific test that measures tear dynamics to diagnose DED is a quantitative tear measurement test known as TFI. In addition, meibomian gland dysfunction (MGD) can be identified by meiboscopy, meibography, and meibometry [31]. Typically, two or more tests are performed to accurately diagnose DED.

3. Management of DED

There are many treatment options for DED (Fig. 4). The goals of treatment are to restore the ocular surface and normalize tear fluid production, improve patient comfort, and alleviate DED symptoms [28]. Treatment can range from artificial tear products, anti-inflammatory medications, cyclosporin A (CsA), mucin secretagogues, corticosteroids, dietary supplements (omega-3 fatty acids), vitamin A, autologous serum eye drops, tetracycline, tacrolimus, macrolides, punctal plugs, and surgery. Moreover, education, environmental or dietary modifications are also effective. Table 1 and Table 2 list the representative commercially available products (Table 1) and representative DED drugs currently in clinical trials (Table 2) for the treatment of DED. The following are the conventional treatment options used for DED [32].

DED severity levels

	Grade 1	Grade 2	Grade 3
Discomfort	None or episodic mild fatigue	Annoying and/or activity limiting episodic	Annoying, chronic and/or constant limiting activity
Corneal/ Tear sign	None to mild	Mild debris, meniscus	Filamentary keratitis, mucus, clumping tear debris
Lid/Meibomian glands	Meibomian gland disease (MGD) variably present	MGD variably present	Frequent
Corneal staining	None to mild	Variable	Moderate central
Conjunctival staining	None to mild	Variable	Moderate to markedty
Schirmer score	Variable	≦10 mm/5 min	≦5 mm/5 min
TBUT: tear film break-up time	Variable	≦10 sec	≦5 sec

Fig. 3. Three stages (Grade 1–3) of clinical severity.

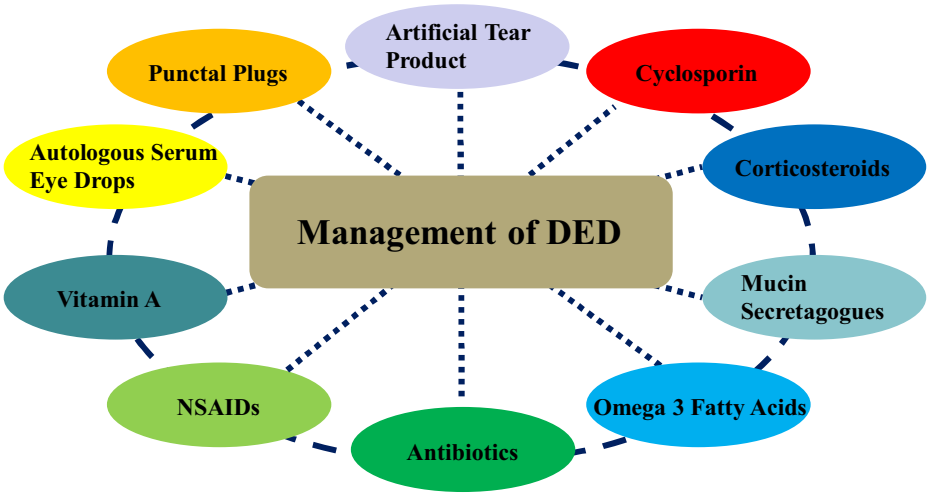

Fig. 4. Schematic diagram of treatment options for DED.

Table 1
Representative commercially ophthalmic formulations for treatment of DED.

Drug	Brand name	Manufacture
No drug	Lacrisek® Ofta mono	BIOSOOFT
No drug	Modusik-A Ofteno®	SOPHIA
No drug	Tears Again®	OCuSOFT Inc.
Artificial tear products	Systane Ultra lubricant	Alcon Inc.
Artificial tear products	Tears Naturale Forte Lubricant Eye Drops	Alcon Inc.
Artificial tear products	Tears Naturale P.M. eye ointment	Alcon Inc.
Artificial tear products	Refresh Celluvisc	Allergan India Pvt. Ltd.
Artificial tear products	Refresh contacts	Allergan India Pvt. Ltd.
Artificial tear products	Refresh Endura (for long-term relief)	Allergan India Pvt. Ltd.
Artificial tear products	Refresh Liquigel	Allergan India Pvt. Ltd.
Artificial tear products	Refresh Tears Drops	Allergan India Pvt. Ltd.
Artificial tear products	Tear Plus lubricant drops	Allergan India Pvt. Ltd.
Artificial tear products	Advanced eye relief environmental lubricant	Bausch & Lomb Inc.
Artificial tear products	Advanced eye relief lubricant ointment	Bausch & Lomb Inc.
Artificial tear products	Soothe XP	Bausch & Lomb Inc.
Artificial tear products	GenTeal drops and gel	Novartis Ltd.
Artificial tear products	Hypo Tears Plus eye drops	Novartis Ltd.
Bromfenac (0.1%)	Bronuc ophthalmic solution 0.1%	Takeda Pharmaceutical Co. Ltd.
Cationic O/W emulsion technology	Retaine	Ocusoft, Inc.
Cationic O/W emulsion technology	MGD	Ocusoft, Inc.
Cyclosporine-A (0.05%)	Systane Balance	Alcon Inc.
Cyclosporine-A (0.05%)	Optive Plus®	Allergan, Inc.
Cyclosporine-A (0.05%)	Refresh Dry Eye Therapy	Allergan, Inc.
Cyclosporine-A (0.05%)	Refresh Endura®	Allergan, Inc.
Cyclosporine-A (0.05%)	Restasis®	Allergan, Inc.
Cyclosporine-A (0.05%)	Lacrinmune®	Bausch & Lomb Inc.
Cyclosporine-A (0.05%)	Liposic® Ophthalmic Liquid Gel	Bausch & Lomb Inc.
Cyclosporine-A (0.05%)	*T*-sporin®	Hanlim Pharm. Co., Ltd
Cyclosporine-A (0.05%)	Emustil®	Moorfields Pharmaceuticals
Cyclosporine-A (0.05%)	Cyporin-N®	Taejoon Pharmaceutical Co., Ltd
Cyclosporine-A (0.09%)	Cequa®	Sun Pharma Canada Inc.
Cyclosporine-A (0.05%)	Cyclomune	Sun Pharma Ind. Ltd.
Cyclosporine-A (0.1%)	Cationorm®	Santen Ltd
Cyclosporine-A (0.1%)	Ikervis®	Santen Ltd
Cyclosporine-A (0.1%)	Papilock mini®	Santen Ltd
Diclofenac sodium ophthalmic solution (0.1%)	Voltaren	Novartis Ltd.
Diquafosol sodium (3%)	Diquas ophthalmic solution 3%	Santen Pharmaceutical Co. Ltd.
Ketorolac tromethamine (0.4%)	Acular LS	Allergan India Pvt. Ltd.
Lifitegrast	Xiidra	Novartis Ltd.
Loteprednol etabonate (0.5%)	Lotemax	Bausch & Lomb Inc.
Ofloxacin and dexamethasone	ZO-D eye drops	FDC Ltd.
Omega 3 fatty acids	Thera tears nutrition	Advanced Vision Research
Omega-3 fatty acids	Remogen® Omega	TRB Chemedica Ltd.
2 osmolytes L-carnitine	Refresh Optive	Allergan, Inc.
Pranoprofen (0.1%)	Pranopulin	Senju Pharmaceutical Ltd.
Rebamipide (2%)	Mucosta ophthalmic suspension UD2%	Otsuka Pharmaceuticals Co. Ltd.
Sodium hyaluronate	Hyalein ophthalmic solution	Santen Pharmaceutical Co. Ltd.
Tobramycin USP	Toba	Allergan India Pvt. Ltd.
Tobramycin and dexamethasone	Toba DM	Allergan India Pvt. Ltd.
Tobramycin and fluorometholone	Toba F	Allergan India Pvt. Ltd.

Table 2
Representative DED drugs in clinical trials.

Functions	Drug	Stage	Reference
A mucin-like glycoprotein	Lacritin	Phase II	[33]
A mucin-like glycoprotein	Lubricin	Phase II	[34]
Anti-inflammatory and/or immunosuppressive	Loteprednol etabonate 0.25% suspension	FDA-approved	[35]
Anti-inflammatory and/or immunosuppressive	OCS-02	Phase II	[36]
Anti-inflammatory and/or immunosuppressive	A higher concentration of Cyclosporine	Phase III	[37]
Anti-inflammatory and/or immunosuppressive	Tacrolimus (0.03%) eye drops	Phase Ⅳ	[38]
Anti-inflammatory and/or immunosuppressive	Rapamycin (sirolimus)	Phase I	[39]
Anti-inflammatory and/or immunosuppressive	EBI-005	Phase III	[40]
Anti-inflammatory and/or immunosuppressive	Resolvin E1 analogues	Phase II	[41]
Biological components	Albumin 5%	Phase II	[42]
Biological components	Estradiol	Phase II	[43]
Biological components	*N*-acetylcysteine	Phase II	[44]
Biological components	Thymosin b4	Phase II	[45]
Biological components	Amniotic membrane extract eye drops	Phase I / II	[46]
Biological components	Mesenchymal stem cells	Phase I / II	[47]
Mucin secretagogues	Tavilermide (MIM-D3, 1% or 5%)	Phase II	[48]
Mucin secretagogues	Ecabet sodium	Phase III	[49]
Mucin secretagogues	Mycophenolate mofetil	Phase II	[50]
Mucin secretagogues	15(s)-HETE or Icomucret	Phase III/ II	[51]
Other's products	Visomitin (SkQ1)	phase II / III	[52]
Other's products	Tivanisiran (SYL1001)	phase III	[53]

3.1. Artificial tear products

Artificial tear products are ocular lubricating eye drops used as the first line of treatment for irritation and dryness associated with tear deficient DED. The artificial tears have both active and inactive ingredients, and the demulcents and emollients are main active ingredients. The demulcent is usually a water-soluble polymer that helps to protect and lubricate the mucous membranes of the eye, and the emollient is a fat or oil found in both tears and ointments, and many artificial tears use flaxseed oil, castor oil or mineral oil. In the treatment of DED, the lubricating tear ointments are also used. Due to decreased vision after application, lubricating tear ointments are generally used just before sleep. Although mild cases require four applications per day, severe cases need more frequent dosing (usually 10–12 times per day). Increasing the viscosity of the artificial tear product prolongs its residence time in the eye but may cause temporary blurring [54]. Components, such as sodium hyaluronate, chondroitin sulfate, polyvinyl derivatives and cellulose influence adhesion to the ocular surface, residence time and viscosity [55]. Many ophthalmic products also contain preservatives to prolong shelf life and reduce the likelihood of bacterial contamination. Artificial tear products are prescribed based on the severity of the disorder, sensitivity to preservatives, risk of contamination and cost. Management of DED often involves artificial tear products combined with other treatments, such as cyclosporin, corticosteroids, mucin secretagogues and antibiotics.

3.2. Cyclosporin

Topical administration of the immunomodulator cyclosporin A (CsA) is used as a treatment for DED caused by inadequate tear secretion [56,57]. Indeed, several studies show the topical application of CsA can provide beneficial effects for patients with DED [58]. CsA inhibits the activation of T lymphocytes and enhancement of goblet cells, while also reducing the amount of inflammatory cytokines in the conjunctival epithelium [3,59]. Moreover, CsA prevents the mitochondria-mediated apoptosis pathway [60]. Thus, the CsA is widely used, but negative results have also been reported. The CsA ophthalmic solution 0.05% (Restasis®) is used treatment for chronic DED in the USA, although, 0.05% CsA eye drops/emulsions reduced cytokines and inflammatory cells on ocular surfaces, and also led to the severe burning sensation which was the major limiting factor for its use in patients of DED [61]. Thus, it is required cautions design of CsA eye drops/emulsions. Since the approval of Restasis® in 2002 several original CsA-based products for ocular diseases have been developed. Topical formulations of CsA used in different parts of the world include the following: 0.005% Lacrinmune® emulsion (Argentina), 0.05% Cyclorin® (Bangladesh), 0.05% Cyporin® solution (Myanmar and Bangladesh), 0.05% TJ Cyporin® (Korea), 0.1% Ikervis® cathionic emulsion (Europe), 0.1% Papilock mini ophthalmic solution (Japan) and 0.1% Modusic-A Ofteno® Solution (South America). All of these commercial products are regional [62].

3.3. Corticosteroids

Corticosteroids applied directly to a part of the body, for example fluorometholone, methylprednisolone, prednisolone, dexamethasone, and loteprednol etabonate, are effective in treating inflammatory conditions of the ocular surface. Corticosteroids provide induction of lymphocyte apoptosis, downregulation of interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) by inhibition of the NF-κB (nuclear factor-kappa B) signaling cascade, and suppression of inflammatory factor production. Loteprednol has been granted Food and Drug Administration (FDA) approval to treat short-term DED [35,63]. These corticosteroids also have FDA approval for the treatment of inflammatory conditions associated with keratoconjunctivitis, which is inflammation of the cornea and conjunctiva [3,64,65]. However, short-term treatment with topical corticosteroids is recommended because prolonged use can lead to cataracts, glaucoma, and ocular infections.

3.4. Mucin secretagogues

Diquafosol directly promotes tear secretion from epithelial cells and mucin secretion from goblet cells in the conjunctiva via interaction with $P2Y_2$ receptors. However, it has been reported that diquafosol does not act directly on the lacrimal gland and fails to elicit protein secretion from isolated glands [66]. Nonetheless, diquafosol both stimulates mucin secretion from goblet cells in the conjunctiva and increases expression of genes encoding membrane-bound mucin in epithelial cells of the cornea [67]. Diquas ophthalmic solution (3% diquafosol ophthalmic solution), which was developed by Santen Pharmaceutical Co. Ltd., was launched in Japan at the end of 2010 as a new treatment for DED with a novel mechanism of action for stimulating tear and mucin secretion [68]. Indeed, Diquas ophthalmic solution is now the established treatment for DED in Japan.

Rebamipide has long been used as a therapeutic agent for gastric ulcers, and its mucoprotective properties are also beneficial for the treatment of DED [69–72]. Previous studies have shown that topical application of rebamipide increases the number of goblet cells and promotes secretion of mucin-like proteins in the human bulbar conjunctiva and tear ducts [73,74]. Moreover, rebamipide improves both vital stain and tear fluid degradation time. Mucosta ophthalmic solution UD 2% (2% rebamipide ophthalmic solution), developed by Otsuka Pharmaceutical, Co., Ltd., was given regulatory approval in 2011. In clinical trials, patients with DED were treated with four daily infusions of Mucosta ophthalmic solu-

tion UD 2%. These trials have demonstrated that Mucosta ophthalmic solution UD 2% is effective in improving the symptoms of DED [69,70,75]. The effect of two formulations are similar, and Diquas ophthalmic solution, which promotes tear and mucin secretion onto the ocular surface, and Mucosta ophthalmic suspension UD2%, which stimulates mucin secretion, facilitate the selective treatment of the lacrimal layer. On the other hand, the major difference is that Diquas ophthalmic solution is a solution type, while Mucosta ophthalmic suspension UD2% is a suspension type, and some patients complain of temporary visual disturbances after Mucosta ophthalmic suspension UD2%, possibly because of the suspension type.

3.5. Omega 3 fatty acids

Eicosanoids, which are derived from 20-carbon containing polyunsaturated fatty acids, act as local hormones [76] to reduce inflammation and alter the composition of myoblast lipids. Therefore, the oral administration of omega 3 fatty acids has been beneficial for DED patients [3,77]. Indeed, several commercial products, such as Bio Tears and Thera Tears, have demonstrated the value of some fatty acids in the treatment of DED. Research indicates the topical application of α-linolenic acid may be a novel therapy for treating inflammatory changes and clinical signs in keratoconjunctivitis. Specifically, the topical administration of α-linolenic acid significantly reduces inflammatory changes and signs of DED at both the molecular and cellular levels [78].

3.6. Antibiotics

Antibiotics, for example bacitracin and erythromycin, are prescribed to treat meibomian gland dysfunction [79]. In addition, an ophthalmic formulation of tetracycline has been designed for the treatment of chronic DED. Tetracycline and its variants, minocycline and doxycycline, are broad-spectrum antibiotics with anti-inflammatory activities that are frequently used as ocular surface anti-inflammatory agents. Several studies have demonstrated tetracycline can diminish the activity of collagenase and phospholipase A2, as well as matrix metalloproteinase-9 (MMP-9) in ocular surface tissues, and downregulate production of IL-1β and TNF-α [80]. In addition, when the derivative doxycycline is applied topically to a DED model, it exhibits a sedative effect and acts as a barrier to the corneal epithelium [80]. In the clinical, the frequency and interval of the eye drops are adjusted according to the condition of the patient.

3.7. Nonsteroidal anti-Inflammatory drugs (NSAIDs)

NSAIDs eye drops are used to reduce inflammation associated with DED. This drug is prescribed primarily for its anti-inflammatory rather than antibacterial action [3,81]. The NSAIDs reduce ocular surface inflammation by inhibiting cyclooxygenase activity, inhibiting prostaglandin synthesis, and lowering granulocyte and monocyte migration and phagocytosis. The immunomodulatory action of NSAIDs is low by comparison to glucocorticoids for DED arising from autoimmune diseases, such as Sjögren's syndrome [82]. NSAIDs widely used in ophthalmic formulations include diclofenac sodium, pranoprofen, and bromfenac sodium. Sodium bromfenac ophthalmic solution not only ameliorates the symptoms of DED but it also improves tear production and reduces the onset of inflammation in patients [83]. Furthermore, the inclusion of sodium hyaluronate enhances the suppression of symptoms caused by the treatment of pranoprofen and diclofenac sodium [84,85].

3.8. Vitamin A

Vitamin A is involved in the production of the inner mucin-layer of the tear film, and its deficiency leads to goblet cell atrophy and loss of the mucin-layer [1,86]. Eye drops containing vitamin A protect against inflammation caused by allergens and free radicals. A combination of topical retinoic acid and systemic administration of vitamin A have been studied as a potential treatment for DED [87].

3.9. Autologous serum eye drops

Autologous serum eye drops contain fibronectin, vitamin A, epidermal growth factor, and hepatocyte growth factor. Supplementation of these components helps maintain a healthy ocular surface. Although these preparations have been shown to be highly therapeutic, they are not commercially available because their preparation is specific to each individual [88].

3.10. LFA-1 antagonists

Lifitegrast is a formulation approved by the FDA in 2016 for the treatment of DED. Application of 5% lifitegrast has been found to reduce ocular discomfort and DED scores [89]. The primary ligand for lymphocyte function-associated antigen-1 (LFA-1) is intercellular adhesion molecule-1 (ICAM-1) [90]. Lifitegrast resembles the molecular structure of ICAM-1 and behaves as a competitive antagonist to impede binding of LFA-1 and ICAM-1, preventing the release of inflammatory factors [91].

3.11. Punctal plugs

Punctal plugs are medical devices that can be inserted into the tear duct. The device improves the signs and symptoms of DED by preventing outflow of tears from the lacrimal point through the nasolacrimal duct [92]. After fitting, a follow-up inpatient appointment is recommended to check for plug dropout. Punctal plugs are used in conjunction with artificial tear products.

3.12. New devices for the treatment of DED

An intranasal tear neuro-stimulator is a device that applies a small electric current to stimulate the endings of the mucocutaneous nerves to increase tear secretion. Using this device 4x a day for 180 days is reported to markedly increase the Schirmer score and improve ocular symptoms. Although this treatment is effective for patients with tear deficiency it is costly [93,94]. By contrast, an extranasal tear neuro-stimulator enhances the secretion of lachrymal fluid by applying a microcurrent to the junction of the nasal cartilage and the nasal bone [94]. For patients with an uneven corneal surface, scleral lenses are placed on the sclera. Although this treatment can significantly improve the symptoms of DED it is time consuming and costly to fit [95]. Aero Pump's med spray is a new ophthalmic drug delivery system that allows micro- and nano-technology ophthalmic formulations to be applied directly to an open eye from a short distance without causing a blink reflex. Effective treatment of DED is anticipated by using this device together with commercially available ophthalmic drops [96].

4. Novel drug delivery systems

The use of a DDS *via* ocular administration can minimize the side effects arising from systemic absorption [97]. Moreover, a novel DDS is likely to avoid the need for frequent administration,

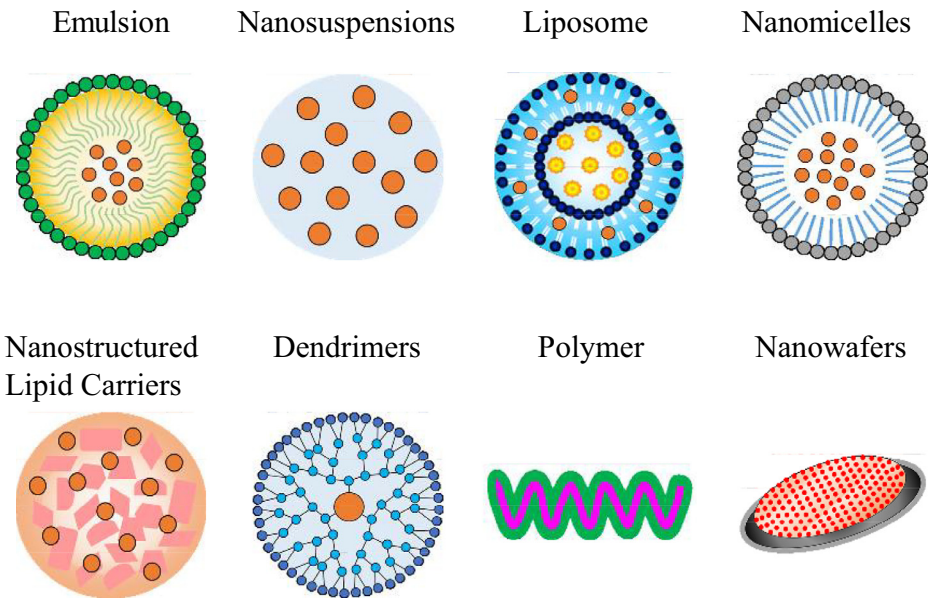

Fig. 5. Illustration of nanoformulations for topical administration in the ophthalmic field.

as well as providing improved ocular bioavailability and reduced side effects. Various types of particulate systems (nanoemulsions, liposomes, nanomicelles, dendrimers, nanocarriers and other's nanoformulations [98]) have been investigated as potential delivery technologies (Fig. 5). Ophthalmic medicine using these systems referred as nanoparticles (colloidal drug carriers of 10 nm-1000 nm) [99,100]. These nanoparticles can deliver both lipophilic and hydrophilic drugs, as well as performing target-specific delivery, efficient drug absorption and sustained drug release [99,101–103]. Nanoparticles for ophthalmic DDS are usually composed of lipids, such as fatty acids and triglycerides together with natural polymers, such as sodium alginate, albumin, gelatin, and chitosan. Synthetic polymers, such as polymethacrylic acid, polycyanoacrylate, Eudragit® (RS100 and RL100), poly(ε-caprolactone), poly(lactic acid-*co*-glycolide) (PLGA) and polyacrylamide are also frequently used [104]. DDS *via* nanoparticles has been employed to treat various ophthalmic diseases, including DED. The rationale for the application of these particulate systems as an ophthalmic DDS includes prolonged residence time and delayed ejection due to the interaction of mucin with bioadhesive polymer chains and the potential for uptake of the particulates into the ocular mucin-layer [105]. Many of these systems are still in the experimental phase, and are being applied to various drugs in clinical use to determine their usefulness. On the other hand, the usefulness and safety of some product has been confirmed, and, FDA-approved nanotherapeutics for DED include nanoemulsions based on CsA, such as Cyclokat® and Restasis®, and nanomicelle formulations, such as Cequa® [106]. This section outlines studies related to various nanotechnology systems for therapeutic DDS suitable for the treatment of DED. A brief overview of the studies is presented in Table 3. In addition, DDS technologies for DED treatment currently in the research phase are also included.

4.1. Emulsions (Microemulsions and Nanoemulsions)

Microemulsions are approximately 100 nm nanodispersions in a one-phase system containing water, oil, and amphiphiles (co-surfactants and surfactants) that have a high spreading coefficient and low surface tension, which enhances diffusion/mixing of drug with tear fluid as well as improving drug contact time on the corneal surface [155]. Therefore, these emulsions are considered to be an effective vehicle for drug delivery [156]. In a recent study, MiDROPS for the delivery of CsA, which is an ocular DDS system based on a microemulsion, was developed and its therapeutic effect found to be higher than that of Restasis® (twice a day) using a mouse model of DED [108]. Furthermore, microemulsions based on the triglyceride of docosahexaenoic acid (TG-DHA) have been reported to be effective at treating a rabbit DED model [112]. Remogen® Omega is also composed of omega-3 fatty acids dissolved in a medium of glycerol/polyacrylic acid/alkyl acrylate crosspolymer as an emollient and hydrating agent [157,158]. Lubricants used in eye drops include a lipofilm microemulsion. These formulations have been shown to enhance the treatment of patients with DED [159]. As a result, it is likely that more biocompatible microemulsion systems will be used to treat DED in the future.

Nanoemulsions are two-phase systems consisting of an aqueous-phase, oil-phase, co-surfactant and a surfactant, with nanoparticles (10 nm-100 nm). These nanoparticles possess a high surface to volume ratio, which can enhance drug diffusion. Increased residence time of nanoemulsion induced drug molecules released into the tear fluid after ophthalmic application is desirable [160]. Oil-in-water nanoemulsions are used as vehicles for CsA, which is a lipophilic drug [117]. Restasis® (nanoemulsion of CsA) is approved in the USA and many other countries for the treatment of DED. The composition of Restasis® includes a 0.05% oil-in-water anionic nanoemulsion of CsA dissolved in polysorbate 80 (surfactant), castor oil (solubilizer) and water. The nanoemulsions containing CsA can possess anionic, cationic or nonionic properties. In general, cationic nanoemulsions of CsA increase drug residence time in the anterior cornea, which consists of an anionic ocular surface [6,117,161]. Lacrinmune® is also available as an ophthalmic formulation with a composition similar to that of Restasis®, but with sodium hyaluronate [162]. The hyaluronic acid derivatives are applied in artificial tear products, such as Opticalmax®, Hyalein®, and Vismed® to treat mild to moderate DED. In addition, Cationorm® and Ikervis® are formulations that utilize nanoemulsion technology for DDS, marketed as oil-in-water cationic nanoemulsions (CNE) containing cetalkonium chloride [62,117]. Cationorm® is also marketed as an OTC drug in some European and South Asian countries [150,163]. Although nanoemulsion technology leads to improved persistence on the ocular surface, its use

Table 3
Studies on novel DDS in DED.

Pharmaceutical technology	Drug	References
Dendrimer	Dexamethasone	[107,108]
Dendrimer	Synthetic sulfonamide derivatives	[109]
Emulsions (microemulsions)	Cyclosporine A	[108,110]
Emulsions (microemulsions)	Riboflavin phosphate and Docosahexaenoic acid in triglyceride form	[111,112]
Emulsions (nanoemulsions)	No drug	[113,114]
Emulsions (nanoemulsions)	Cyclosporine A	[61,115,116]
Emulsions (nanoemulsions)	cetalkonium chloride	[62,117]
Liposomes	No drug	[118]
Liposomes	Astaxanthin	[119]
Liposomes	Azithromycin	[120]
Liposomes	Cyclosporine A	[121]
Liposomes	Heat shock protein 47 (HSP47)	[122]
Liposomes	Medroxyprogesterone	[123]
Liposomes	Phospholipon 90G, cholesterol, α-tocopherol (vitamin E)	[124]
Liposomes	Phosphatidylcholine, cholesterol, and α-tocopherol	[125]
Liposomes	Phosphatidylcholine, cholesterol, vitamins A and E	[126]
Liposomes	Phospholipid	[127]
Liposomes	Sirolimus	[39]
Liposomes	Tetracycline	[128]
Micelles	No drug	[129]
Micelles	Cyclosporine A	[130–137]
Micelles	Pimecrolimus	[138]
Micelles	Vitamin A	[139]
Other's nanoformulations	No drug	[140]
Other's nanoformulations	Amfenac	[141]
Other's nanoformulations	Cyclosporine A	[142–148]
Other's nanoformulations	Epigallocatechin gallate	[149]
Other's nanoformulations	Mineral oil (light & heavy)	[150]
Other's nanoformulations	Petrolatum, lanolin, medium-chain triglycerides (MCT)	[114]
Other's nanoformulations	Phospho sulindac	[151]
Other's nanoformulations	Plasmid coding MUC5AC protein	[152]
Other's nanoformulations	Poly(ethylene glycol) and catechin	[153]
Other's nanoformulations	Sirolimus	[154]

Most of the nanocarrier systems published in the literature were also proposed as alternatives to the commercially available Restasis® CsA ophthalmic emulsion.

is restricted because of stability problems related to aggregation [61]. Therefore, further understanding is needed to expand the clinical application of this technology.

4.2. Nanosuspensions

Nanosuspensions are colloidal dispersions (particle size 1 μm or less) of poorly water-soluble drugs whose dispersion stabilization is ensured by inert polymer resins and surfactants. There are two major methods for preparing nanosuspensions. The breakdown method involves a reduction in the size of large particles by bead milling or high-pressure homogenization. The build-up method generates colloidal dispersions by preventing nucleation and particle growth under appropriate conditions after dissolution [164,165]. Nanosuspensions are generally considered to be better than the previously described nanoemulsions. For example, *in situ* nanosuspensions containing CsA have a particle size of < 505 ± 5 nm, a zeta potential of −0.07 ± 0.05 mV, and a polydispersity index value of 0.23 ± 0.03, which leads to improved drug delivery. Specifically, the concentration of CsA in pig cornea using a nanosuspension was higher than that of Restasis® after a single treatment [i.e., corneal concentration of CsA was 545 ± 137 ng/g using Restasis® and 3165 ± 597 ng/g using a nanosuspension] [166]. Experimental results have also shown that *in situ* nanosuspensions cause less irritation to the rabbit eye compared to Restasis® [167]. Topical vitamin A eye drops prepared by high-pressure homogenizer technology using surfactants, such as Pluronic, benzalkonium chloride, and polysorbate 80, have also been shown to be beneficial for DED therapy [168,169]. Moreover, it was reported that the rebamipide residence time and accumulation on the ocular surface can be increased by regulating the particle size of the Mucosta Ophthalmic Suspension UD 2% to a range of 140–150 nm [170]. Thus, nanosuspension technology provides a safe and effective means of delivering hydrophobic drugs to the ocular surface. However, as with nanoemulsions, the physical stability of nanosuspensions needs to be improved before their applicability can be fully realized.

4.3. Liposomes

Liposomes are spherical vesicles 25 nm to 10 μm in diameter comprising a bilayer of phospholipids. The liposomes adhere to the cornea by coating with an adhesive polymer or by dispersion of liposomes in an adhesive gel, thereby facilitating the efficient delivery of water soluble drugs [171]. Furthermore, liposomes with a positive charge are known to bind efficiently to the negatively charged mucin associated with the corneal epithelium, resulting in enhanced drug delivery (Fig. 6). Liposome formulations for the treatment of DED are referred to as lipid-containing eye drops, such as Vyseo®, Clarimist®, Tears Again®, ActiMist™, and Optrex™. These lipid-containing eye drops are useful for the treatment of patients with mild to moderate evaporative DED. In addition, it has been shown that the lipid-containing eye drops improve stability of the tear fluid and decrease tear fluid osmolarity more effectively than ophthalmic formulations containing hydroxypropyl methylcellulose or sodium hyaluronate [172]. Liposomal sirolimus has also been prepared and this formulation is currently being assessed for the treatment of DED [39,57]. Thus, liposomes can alleviate DED symptoms in patients and enhance the structure and stability of the tear film. However, practical aspects of the application of this system as an ophthalmic DDS are limited due to the difficulty of scale-up and problems associated with stability during the manufacturing process. Further basic research into liposomes for DED therapy are likely to resolve these problems.

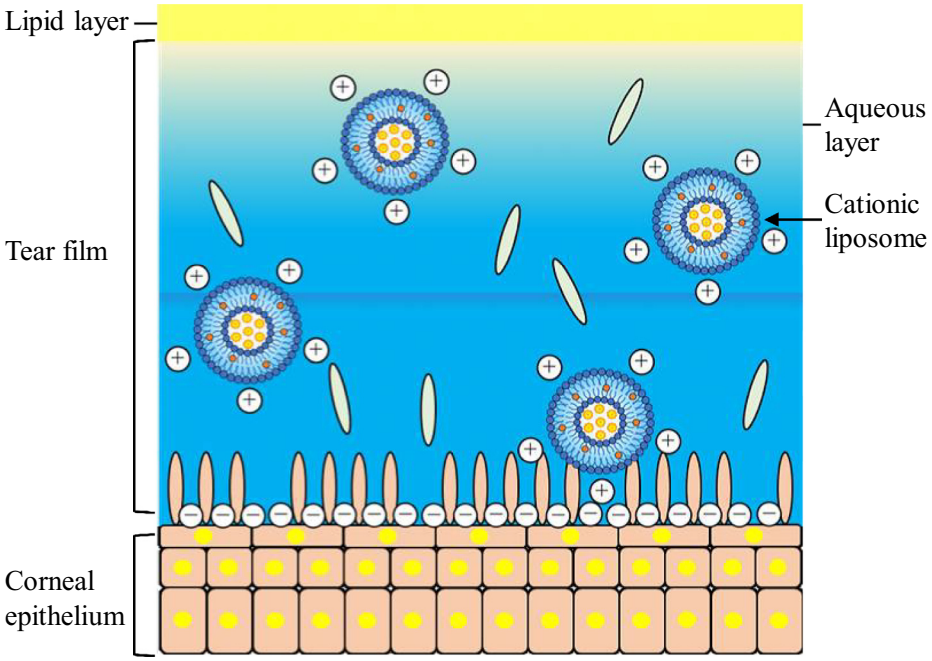

Fig. 6. Illustration showing the interaction of cationic liposomes on the cornea with the negatively charged mucin-layer.

4.4. Nanomicelles

Nanomicelles are colloidal carrier systems with dimensions ranging from 5 nm to 200 nm, which block copolymers and surfactants self-assembling in aqueous solution [173–175]. The nanomicelles synthesized from block copolymers consisting of different hydrophobic and hydrophilic monomer units are called polymeric nanomicelles [176], while nanosized micelles composed of amphiphilic molecules with water loving head groups (anionic, cationic, zwitterionic or nonionic) and hydrophobic tails are referred to as surfactant nanomicelles. Treatment of DED using polymeric nanomicelles and surfactant nanomicelles is described below.

Polymeric micelles represent a promising DDS for the management of DED. It has been reported that methoxy poly(ethylene glycol)-hexyl substituted poly (lactides) (MPEG-hexPLA) polymeric nanomicelles carrying CsA displayed biocompatibility in human corneal epithelial cells and were effective for the treatment of DED [135,177]. Moreover, the pre-corneal residence (327 ng/mL) in rabbits treated with MPEG-hexPLA micelle eye drops loaded with 0.05% CsA was significantly improved compared to Restasis® (142 ng/mL) 3 h after instillation. In addition, the concentration of CsA in rat corneal tissue instilled with MPEG-hexPLA micelles (1540 ng/g tissue) was also significantly higher by comparison with Restasis® (<2 ng/mL) [135,177]. These results using the MPEG-hexPLA micelles containing poorly water-soluble drugs, such as CsA, were applied as ApidSOL™ for the treatment of DED. Soluplus®, a graft copolymer containing polyvinyl acetate, polyvinyl caprolactam, and polyethylene glycol (PVAc-PVCap-PEG, 30/57/13), has also been introduced as a DED treatment [177]. Guo *et al* [178] demonstrated 0.5 mg/mL Soluplus® micelles containing CsA ophthalmic drops were superior to commercial CsA oil-based 10 mg/mL ophthalmic solution in terms of corneal residence of CsA, and suggested that the Soluplus® micelles may be a potential alternative to existing commercial products. Moreover, Soluplus® micelles loaded with α-linolenic acid display prolonged drug corneal residence time, and the therapeutic utility of this system for DED has been investigated [175,179]. Furthermore, it was reported that methoxy poly(ethylene glycol)-poly(lactide) polymer (mPEG-PLA) micelles containing CsA had 4.5 times greater residence, and the effect in the cornea was prolonged in comparison with a 0.05% CsA emulsion [133,134]. Some of these drug-loaded polymeric nanomicelle formulations have been accepted for clinical trials in cancer treatment, but not yet for DED. If these formulations are commercialized, they have the potential to supply an effective and simple treatment for DED patients.On the other hand, surfactant nanomicelles are expected to provide an effective means of delivering therapeutic agents to treat DED. A recent study used a 0.1% CsA self-assembling micellar system with polyethylene glycol-fatty alcohol ether type nonionic surfactants (Sympatens AS or Sympatens ACS) to deliver CsA [137]. The CsA concentration in the cornea of pigs instilled with the micellar CsA solution (1557 ng/g cornea) was higher than that of Restasis® (545 ng/g cornea). In an experimental system using rapamycin nanomicelles with polyethylene glycol-distearoyl phosphatidylethanolamine (PEG-DSPE), autoimmune-induced lacrimal gland inflammation was suppressed [180]. Moreover, lacrimal fluid secretion and ocular surface damage was improved in a non-obese diabetic model mouse of Sjögren's syndrome disease [180]. In addition, Mitra *et al*. prepared a 0.1% CsA nanomicelle system consisting of a mixed polymer of octoxynol-40 and hydrogenated castor oil-40 (0.05:1.0, %), which exhibit very low critical micelle concentrations (0.00707%) [136]. The 0.1% CsA nanomicelle preparation delivered therapeutically significant levels of CsA to the cornea, conjunctiva, and sclera of rabbits [136]. Fig. 7 shows the concentration of CsA in each ocular tissue of the rabbits after a single instillation. Moreover, CsA concentrations in all ocular tissues except the tear and upper eyelid repetitively instilled with a 0.05% CsA nanomicelle formulation (OTX-101, 4 times/day, interval time 2 h) was significantly enhanced over that of Restasis® [181]. These findings may result from superior contact of the outer oil-layer of the tear with the oil-based vehicle. OTX-101 was approved by the US FDA in August 2018 as Cequa® (OTX-101, 0.09%) ophthalmic solution for the treatment of DED in adult patients [162]. Thus, surfactant-based nanomicellar systems could be the key to achieving improved drug treatment for DED.

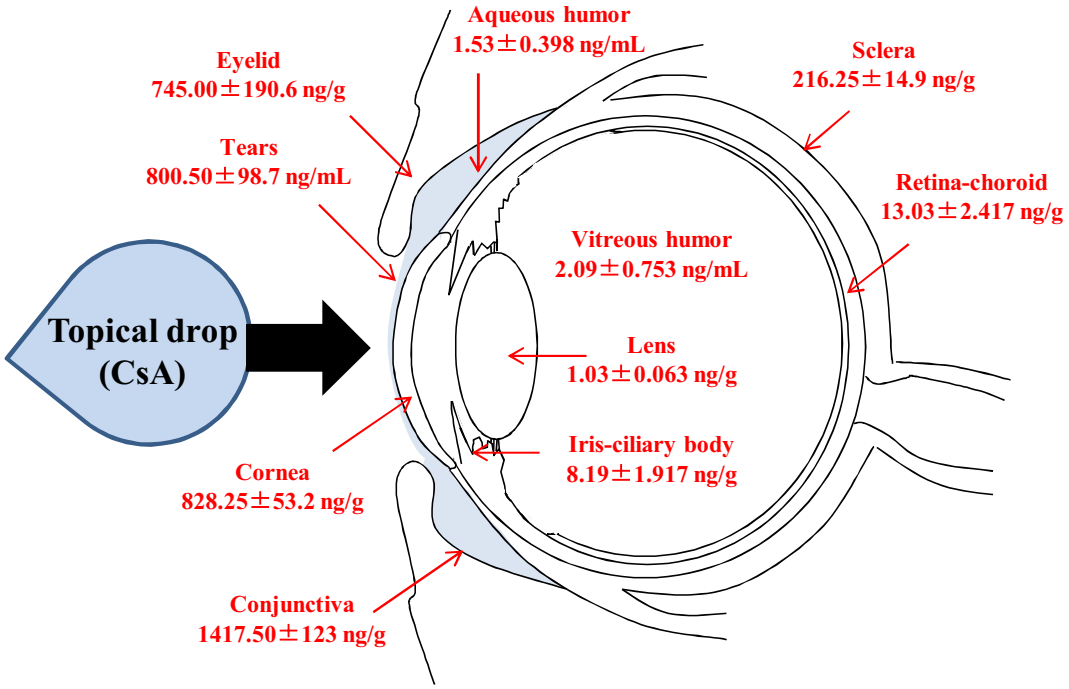

Fig. 7. Ophthalmic distribution of CsA in rabbits instilled with a topical ophthalmic nanomicellar solution of CsA (CEQUA®). Mean ± S.E. n = 4. The data were cited from Ref. 163.

4.5. Nanostructured lipid carriers

Nanostructured lipid carriers (NLCs) contain approximately 30% liquid lipids that lack a crystalline structure in the solid state [182]. As such, NLCs can accommodate more drugs between the fatty acid moieties of the glycerides than solid lipid nanoparticles (SLNs) [183]. NLCs are prepared by melt-emulsification, and Cys-NLC can be generated by incubation with NLCs and thiolated polyethylene glycol monostearate (Cys-PEG-SA). The Cys-NLC provided high residence of CsA in the tear of rabbits for over 6 h without irritation [184]. Moreover, the residence time of CsA in the tear and ocular tissue of rabbits instilled with Cys-NLC were significantly higher in comparison with those of oil or non-thiolated NLC [185]. Thus, Cys-NLC may prove to be valuable for the treatment of DED. In addition, NLC ophthalmic solutions based on phosphatidylcholine and squalene have been reported to be useful as artificial tear products [186]. These NLC ophthalmic solutions form a stable corneal film. Ocular surface residence was good, which offered improved protection to the corneal surface in a model animal (rabbit) of evaporative DED by comparison with polymer-based commercial artificial tear products [186]. However, additional studies are warranted to clarify the safety of the ophthalmic additives prior to clinical application.

4.6. Dendrimers

Dendrimers are a new type of polymer with a radially branched structure that typically adopts a 3D morphology symmetric about the core. The dendrimers can act as nanocapsules because they possess internal spaces that may encapsulate drugs. Moreover, various functional dendrimers can be prepared by attaching biocompatible polymers and functional groups to decorate the dendrimer surface. As such, dendrimers have potential applications for the treatment of DED due to their facile surface modification and good water solubility. For example, polyamidoamine (PAMAM)-based divalent water-soluble dendrimers with two sulfonamide units show high level affinity (nM range) for matrix metalloproteinase 9, which is involved in DED. The efficacy of these formulations has also been demonstrated in a rabbit system for experimental DED [187]. Furthermore, the usefulness of dendrimer-dexamethasone conjugates for DED therapy has been investigated [188]. It was reported that a subconjunctival injection of the formulation conjugate preferentially localized to infiltrating cells in an autoimmune lacrimal gland inflammation-induced rabbit model, and the infiltration was significantly attenuated [188]. However, the long-term safety of dendrimers has not yet been fully demonstrated in the eye, and further safety evaluation is needed [189].

4.7. Polymers

Chitosan is a cationic polymer found in the exoskeleton of crustaceans that displays bioadhesive characteristics. The adhesive properties of chitosan are related to electrostatic interactions, hydrophobic effects and hydrogen bonding [190]. The CsA level in cornea and conjunctiva of rabbits instilled with CsA-loaded chitosan nanoparticles is significantly higher than that of chitosan solutions/suspensions containing CsA [191]. Indeed, chitosan has been used in the preparation of nanoparticles for DED therapy in numerous studies. Moreover, chitosan-coated liposomes of CsA are decorated with the positively charged polymer chitosan, which is also known to prolong drug residence time and enhance drug/-nanocarrier penetration from the membrane surface. These chitosans, which have excellent adhesive properties and can penetrate tight junctions, are approved by the US FDA for treatment of DDS [192]. Thus, the chitosan coating helps bind liposomes to the mucus/lipid membranes of corneal epithelial cells [193].

Several DED treatments with gelatin-based nanoparticles have also been reported. In a previous study, cationized gelatin-based nanoparticles carrying a plasmid encoding a modified MUC5AC protein [pMUC5AC] was generated and the delivery ability of pMUC5AC-nanoparticles assessed using healthy mice and experimental DED model mice [194]. The modified MUC5AC expression in pMUC5AC-nanoparticle-treated mice was elevated compared

to that of the controls. Moreover, inflammation was reduced, and tear production improved in the pMUC5AC-nanoparticle-treated mice. Furthermore, amphenac-loaded poly(catechin) capped-gold nanoparticles was found to inhibit damage to the ocular tissue of a DED rabbit model [195].

PLGA is a synthetic copolymer of polylactic acid and polyglycolic acid that is known for its biocompatibility and biodegradability. As such, PLGA is frequently used in DDS to treat eye conditions [196]. Several PLGA nanoparticles containing CsA have also been investigated for the treatment of DED. For example, it have been reported that PLGA nanoparticles of CsA plus Eudragit®RL (PLGA: Eudragit®RL (75:25) nanoparticles) [148] with positively charged properties increase tear fluid concentration (366.3 ng/g) in comparison with CsA solution in rabbit eyes. Moreover, CsA in phenylboronic acid-modified PLGA nanoparticles generated using a nanoprecipitation method was found to be highly effective in the treatment of a DED mouse model [197]. In addition, phosphosulindac (PS) solution and PS-loaded nanoparticle (PS-NP) formulations have been evaluated as a potential DED therapy. The PS is metabolized to PS sulfone and sulfide after administration, and these three molecules are converted to sulindac. The sulindac is subsequently metabolized to sulindac sulfide and sulphon. The PS levels in the ocular tissue of the eye instilled with PS solution was lower, and the PS metabolite levels higher in comparison with PS-NP [198].

4.8. Nanowafers

Nano-reservoirs called nanowafers are small, transparent, circular discs, which allow a loaded drug to be gradually released from the disc. The polymers used to prepare nanowafers have been approved for human use by the FDA. Therefore, this technology can be applied to clinical studies and tested in humans [199]. Moreover, the nanowafers adhere to the ocular surface even when the eyelid is constantly blinking, and their transparency does not interfere with normal vision. Thus, nanowafers incorporating drugs dissolve slowly in the tear fluid to release the drug over an extended time [200]. The therapeutic effect of nanowafers incorporating dexamethasone and carboxymethylcellulose (once a day for 5 days) was similar to that of dexamethasone eye drops (given twice a day) [201]. Taken together, these findings suggest nanowafers are an attractive treatment option for ocular diseases.

4.9. Other products

4.9.1. Biodegradable DDS

Bioink is a biomaterial used to transport living cells during bioprinting. Commonly used bioinks include gelatin, hyaluronic acid, collagen, fibrinogen, and glycerol. As an application of this bioink for DED treatment, Park et al. [202] produced a novel lens-shaped biodegradable DDS using gelatinous methacrylate and hyaluronic acid. The lens-type biodegradable DDS degrades at 37 °C but not at 4 °C. Exposure to tears after application results in progressive degradation and drug delivery. In addition, due to the nature of the bioink, tears display increased transparency and surface smoothness. Furthermore, lens-type biodegradable DDS can be easily fabricated using a 3D printer. However, further research is required to ensure the visibility of the lenses and to maintain a constant concentration of the drug after degradation. DDS of these lens-type devices has the potential to contribute not only to the protection of the cornea and to facilitate ease of treatment, but also to the regeneration of the epithelium.

4.9.2. Cyclodextrin

Cyclodextrins increase the solubility and sustained release of drugs in tear fluid, as well as improving drug penetration and bioavailability into the eye. CsA aqueous ophthalmic solutions, tacrolimus, loteprednol etabonate, and OCS-02 (anti-TNFα antibody), prepared using these cyclodextrins are reported to be effective for the treatment of DED [203].

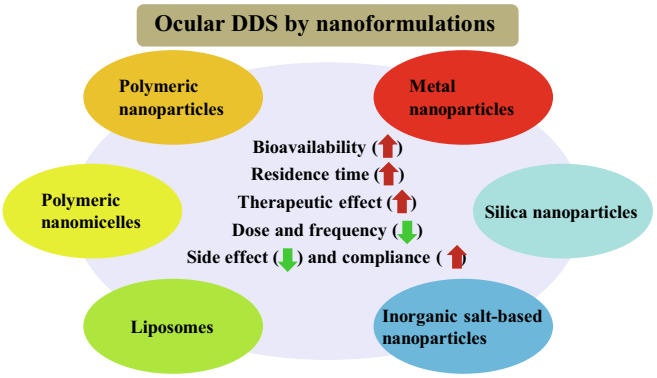

Fig. 8. Schematic diagram outlining the advantages of ophthalmic nanoformulations for topical administration.

4.9.3. kPI-121

Mucus-Permeable Particles (MPPs) are coated nanoparticles with reduced affinity for mucin that are able to transit the mucus barrier. KPI-121 is an ophthalmic suspension that utilizes this strategy to efficiently deposit loteprednol etabonate to ocular tissue. In clinical trials, KPI-121 has been shown to significantly reduce the symptoms and signs of DED compared to placebo. KPI-121 0.25% was granted approval by the FDA in 2020 [204].

5. Conclusion

The development of effective methods to treat DED with minimal impact on physiological function is urgently needed. The introduction of new drugs and colloidal delivery systems will result in more effective treatments for DED. Nanotechnology is a versatile tool for cosmetics, regenerative medicine, diagnostics, drug delivery systems and novel drugs. In particular, recent advances in the design of nanotechnology-based approaches to overcome the limitations of existing ophthalmic formulations for the treatment of anterior eye diseases has been remarkable (Fig. 8). Several nanotherapeutics have been given FDA approval and numerous others are in clinical trials or in the early or late stages of development. It seems only a matter of time before the potential of these agents for the treatment of DED treatment is realized. The use of nanoformulations for ophthalmic drugs is promising, although additional research is still needed to investigate issues related to scale-up, biocompatibility, formulation stability, drug release, and pharmacokinetics.

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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