Hindawi Publishing Corporation
Advances in Pharmaceutics
Volume 2015, Article ID 704946, 12 pages
http://dx.doi.org/10.1155/2015/704946

*Review Article*

# A Comprehensive Review on Dry Eye Disease: Diagnosis, Medical Management, Recent Developments, and Future Challenges

**Suvarna P. Phadatare,[1] Munira Momin,[2] Premanand Nighojkar,[3] Sonali Askarkar,[1] and Kamalinder K. Singh[4]**

[1]*NCRD'S Sterling Institute of Pharmacy, Mumbai University, Nerul, Navi Mumbai, Maharashtra 400706, India*
[2]*SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Mumbai University, Vile Parle (West), Mumbai, Maharashtra 400 056, India*
[3]*Pacific Academy of Higher Education and Research University, Udaipur, Rajasthan 313003, India*
[4]*School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston PR1 2HE, UK*

Correspondence should be addressed to Suvarna P. Phadatare; suphadtare33@yahoo.com
and Kamalinder K. Singh; ksingh1@uclan.ac.uk

Received 30 September 2014; Revised 23 December 2014; Accepted 28 December 2014

Academic Editor: Hidetaka Akita



Dry eye syndrome (DES) or keratoconjunctivitis sicca (KCS) is a common disorder of the tear film caused by decreased tear production or increased evaporation and manifests with a wide variety of signs and symptoms. The present review from interpretation of the literature gives detailed information on the prevalence, definition, causes, diagnostic tests, and medical management of dry eye disease. A number of systems contribute to the physiological integrity of the ocular surface and disruption of system may or may not produce symptoms. Therefore accurate diagnosis of dry eyes with no or minimal disruption of physiological function is necessary. The paper also discusses different colloidal drug delivery systems and current challenges in the development of topical ophthalmic drug delivery systems for treatment of KCS. Due to the wide prevalence and number of factors involved, newer, more sensitive diagnostic techniques and novel therapeutic agents have been developed to provide ocular delivery systems with high therapeutic efficacy. The aim of this review is to provide awareness among the patients, health care professionals, and researchers about diagnosis and treatment of KCS and recent developments and future challenges in management of dry eye disease.

## 1. Introduction

Dry eye syndrome (DES) is a disorder of the preocular tear film that results in damage to the ocular surface and is associated with symptoms of ocular discomfort. DES is also called keratoconjunctivitis sicca (KCS), keratitis sicca, sicca syndrome, xerophthalmia, dry eye disease (DED), ocular surface disease (OSD), or dysfunctional tear syndrome (DTS), or simply dry eyes [1]. Keratoconjunctivitis sicca is a Latin word and its literal translation is "dryness of the cornea and conjunctiva." It may be helpful to know that "sicca" is part of the English word "desiccate." The dry eye syndrome in which the eyes do not produce enough tears is also known as "Sjögren's syndrome" [2].

Dry eye disease is characterized by instability of the tear film that can be due to insufficient amount of tear production or due to poor quality of tear film, which results in increased evaporation of the tears. Dry eye therefore can mainly be divided into two groups, namely,

(1) aqueous production deficient dry eye disease;

(2) evaporative dry eye disease.

Insufficient tears cause damage to the interpalpebral ocular surface and are associated with symptoms of discomfort. The International Dry Eye Workshop (2007) defined dry eye as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular

surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface [1, 3]. DES is associated with decreased ability to perform certain activities such as reading, driving, and computer related work, which require visual attention. Patients experience dry eyes symptoms constantly and severely, affecting their quality of life [4–8].

## 2. Prevalence of Dry Eye

The prevalence of dry eye syndrome increases with age. DES is a common disorder of eyes affecting a significant percentage of the population, especially those older than 50 years of age [9, 10]. Middle-aged and older adults are the most commonly affected group because of the high prevalence of contact lens usage, systemic drug effects, autoimmune diseases, and refractive surgeries in these groups [11–13]. The burden of DES will continue to increase, due to increased life expectancy, as well as projected population growth among the elderly. Surveys have estimated the prevalence of DES varying between 5% and >30% in various age groups across different countries and worldwide [14, 15]. The estimated number of people affected by DES ranges from 25 to 30 million all over the world. Research also shows that DES can affect any race and is more common in women than in men [16, 17]. In women at the age of 50–52 when menopause usually sets in, an imbalance occurs between the oestrogen and androgen hormones. This excites inflammation in lacrimal gland and ocular surface, disrupting the normal homeostatic maintenance of the lacrimal gland and ocular surface. Up to 20% of persons with rheumatoid arthritis have KCS [18, 19]. Other individuals which are likely to be affected include patients with *Helicobacter pylori*, computer users, and long-term contact lens wearers [20, 21].

## 3. Tear Fluid and Composition

Dry eye is recognized as a consequence of disruption of lachrymal functional unit. The lachrymal functional unit consists of lachrymal glands, ocular surface including cornea, conjunctiva, eyelids, meibomian glands, ocular nerves, and goblet cells [22].

The tear film is composed of three main layers. The innermost mucin or mucus layer is the thinnest, produced by cells of conjunctiva. The mucus helps the overlying watery layer to spread evenly over the eye. The middle or aqueous layer is the largest, thickest layer produced by the glands of upper lids and the accessory tear glands and contains essentially a very dilute saltwater solution [23, 24]. This layer keeps the eye moist and helps in the removal of any dust, debris, or foreign particles. Defects of this layer cause DES in most cases [25, 26]. The uppermost layer of tear film is a very thin layer of lipids. These lipids are produced by the meibomian glands and the glands of Zeis (oil glands in the eyelids). This layer helps to decrease evaporation of the watery layer beneath it. The mucous also reduces the surface tension between the lipid layer of the tear film and the water layer, thus contributing to the stability of the tear film [27–29]. The tear fluid also consists of complex mixture of proteins, immunoglobulins, mucins, electrolytes, cytokines, lysozymes, lactoferrin, and growth factors [23, 24, 30]. Lysozyme may act synergistically with IgA in lysis of bacteria. Tears also contain lactoferrin, which has some antibacterial effect [31, 32]. Average glucose concentration of the tears is 2.5 mg/dL and average tear urea level is 0.04 mg/dL. Electrolytes such as K, Na, and Cl occur in higher concentration in the tears than in the blood. Osmolarity of tears is 309 mOsm/liter [24, 33]. Average pH of the tears is 7.25 and refractive index of the tear film is 1.336 [30, 33, 34].

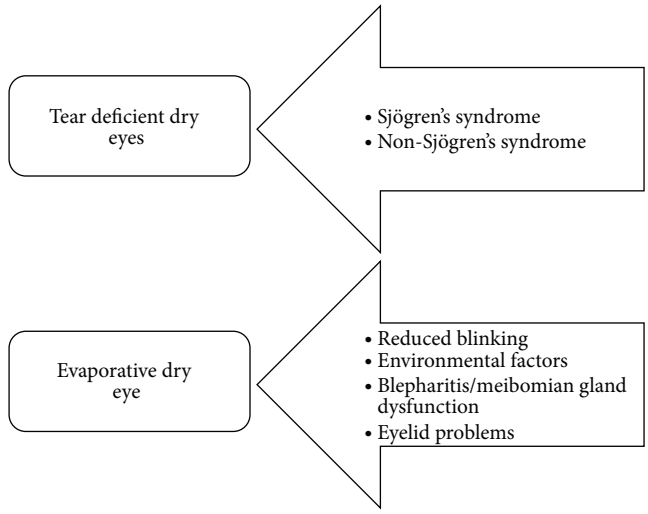


Figure 1: Causes of dry eyes.

## 4. Causes for Dry Eye Syndrome

Causes for DES include decreased tear production, excessive tear evaporation, and abnormality in the production of mucus or lipids of tear layer [24, 25, 31] (Figure 1). A previous report by Lemp in 1995 classified KCS into tear deficient and evaporative dry eyes [25]. Tear deficient dry eye due to poor production of tears by the tear glands is found in older patients, in postmenopausal women, and in patients with autoimmune diseases like primary Sjögren's syndrome and rheumatoid arthritis [13, 16, 19].

Dysfunction of lacrimal functional unit causes changes in composition of the tear fluid and tear film stability [35–37] leading to inflammation of ocular surface. Eye does not produce adequate tears as anti-inflammatory component of eye is lacking and irritation of eye is not controlled. This causes activation of inflammatory cells including T-lymphocytes by immune system of body. T-cells release cytok- ines which causes inflammation of ocular surface and glands, thereby resulting in abnormal tears and dry eye symptoms [38, 39]. An increase in osmolarity of the aqueous layer is suggested as a global feature of DES and is known to trigger inflammation, damaging the ocular surface [25, 31].

Sjögren's syndrome (SS) is characterized by the combination of aqueous tear deficiency (ATD) and dry mouth (xerostomia) [2]. All cases of SS are characterized by

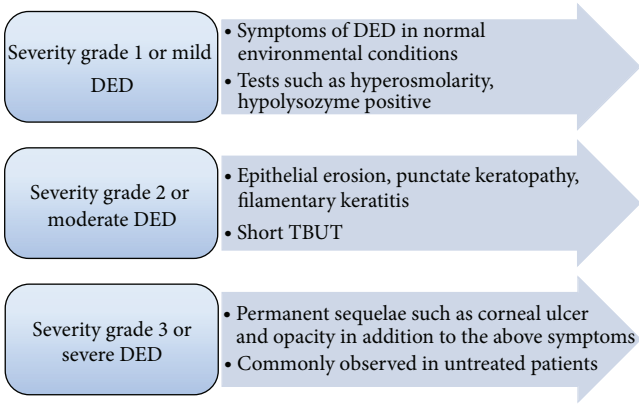


Figure 2: Classification of dry eye disease.

a progressive infiltration of the lacrimal and salivary glands by lymphocytes, leading to disorganization of the normal gland architecture and consequent loss of function [24, 40].

Patients with non-Sjögren's syndrome are associated with disease of the tear gland such as vitamin A deficiency, trachoma, sarcoidosis, and lymphoma [41].

In case of evaporative dry eyes, eyes dry out because of greater tear evaporation as in case of reduced blinking and lid surface anomalies. Environmental factors such as central heating, dry climate, air pollution, wind, chemical burns, contact lens wear, or reduced blinking because of driving, watching TV, and computer work can affect the tear film and proceed up to infection, corneal ulcer, and blindness [42–44]. Evaporative loss of tear fluid and dry eyes are usually associated with inadequate lipid layer. The lipid layer stabilizes and retards evaporation of the underlying aqueous layer [45]. Rosacea, blepharitis, and MGD (meibomian gland dysfunction) are major causes of evaporative dry eyes. In case of ocular disease rosacea, there is abnormal production of lipids due to meibomian gland dysfunction [46].

## 5. Symptoms

The main symptom of dry eyes is dry and gritty feeling in the eyes. The additional symptoms include burning or itching in the eyes, foreign body sensation, excess tearing, pain and redness of the eyes, and photophobia in some cases [47, 48]. Sometimes it is also associated with a stringy discharge and blurred, changing vision. Symptoms are found to worsen in dry weathers, with low humidity and higher temperatures [49]. DED is classified into three grades of clinical severity [1, 50] and the main symptoms are shown in Figure 2.

## 6. Diagnosis of Dry Eyes Syndrome

Diagnostic tests are used for different purposes such as assessing eligibility in a clinical trial and monitoring changes quantitatively [3, 51–53], diagnosing in every day clinical practice by ophthalmologists, and characterizing dry eye as part of clinical syndrome such as Sjögren's syndrome [3, 49, 54]. Recently tests such as tear film breakup time (TBUT), epithelial staining, and ocular surface disease index (OSDI) are used to find correlation between ocular surface disorder, for example, meibomian gland dysfunction, dry eyes, and lifetime computer use/comfort levels [55]. The diagnosis of keratoconjunctivitis sicca (KCS) is made by combining information obtained from the physical examination and performing diagnostic tests. Poor correlation between clinical signs and patient symptoms would require the use of multiple tests. Generally 2 or more tests are performed to permit an absolute diagnosis of DES. Symptom questionnaires can also be used to help establish a diagnosis of DES and to assess the effects of treatments or to grade disease severity.

*6.1. Tear Film Breakup Time (TBUT).* The time required for the tear film to break up following a blink is called TBUT. It is a quantitative test for measurement of tear film stability [3]. The normal time for tear film breakup is 15–20 sec. A fluorescein strip is moistened with saline and applied to the inferior cul-de-sac. After several blinks, the tear film is examined using a broad-beam of slit lamp with a blue filter for the appearance of the first dry spots on the cornea. TBUT values of less than 5–10 seconds indicate tear instability and are observed in patients with mild to moderate dry eye disease [56]. TBUT can also be measured without the addition of fluorescein to the tear film and is called noninvasive BUT (NIBUT). It uses a grid or other patterns directed on the precorneal tear film for observation of image distortion and time from opening the eyes to the first sign of image distortion is measured in seconds [57].

*6.2. Epithelial Staining.* In a staining method, special dyes such as Rose Bengal, lissamine green, and fluorescein are used [58] to determine abnormalities of surface of the eye, quality of tear film, and severity of dryness. It is simple and easy way to recognize the severity of the dryness. Mild cases of DES are detected more easily using Rose Bengal than fluorescein stain and conjunctiva is stained more intensely than the cornea [49, 59]. Staining pattern can be photographed and graded using one of several scoring systems [3].

Fluorescein pools in epithelial erosions, stains degenerating or dead cells, and stains the cornea more than the conjunctiva. Rose Bengal and lissamine green stain dead, devitalized cells as well as healthy cells with inadequate protection [60]. Lissamine green is preferable to Rose Bengal as it avoids the pain, discomfort, and corneal toxicity that are associated with Rose Bengal. However it is somewhat less sensitive and more transient and thus more difficult to appreciate on slit-lamp examination [3].

*6.3. Schirmer Test.* Schirmer test quantitatively measures the tear production by the lacrimal gland during fixed time period [61]. The basic test is performed by instilling topical anaesthetic and then placing a thin strip of filter paper in the inferior cul-de-sac [52, 62]. The patient's eyes are closed for 5 minutes and the amount of tears that wets the paper is measured in terms of length of wet strip. This Schirmer II test measures tear of lacrimal gland by stimulation of lacrimal reflex arc [63] and wetting of <15 mm after 5 minutes is considered abnormal. The results are variable as

any manipulation of the eyelid can alter the results of the test. Further tear drainage can affect the results. Value of less than 6 mm of strip wetting in 5 minutes is accepted as diagnostic marker for aqueous tear deficiency. The Schirmer I test measures both basic and reflex tearing and is performed in a similar way to basic test but without use of a topical anaesthetic [64].

*6.4. Tear Function Index (TFI).* It is a more specific and sensitive test for quantitative measurement of the tears [3, 52]. It evaluates the tear dynamics of production and drainage and helps detect subjects suffering from dry eye. Its numerical value is obtained by dividing the Schirmer II test value in millimeters by tear clearance rate. The higher the numerical value of TFI, the better the ocular surface. Values below 96 suggest dry eyes. It is also called Liverpool modification [65].

*6.5. Tear Osmolarity.* Osmolarity of normal eye is 309–312 mOsm/L and the value increases with severity of dry eye disease. It gives qualitative information of tear production. It is a very sensitive test but lacks specificity. Lemp et al. [66] concluded from a multicenter study that tear osmolarity test was the best single method for diagnosis and severity determination of DES, when compared with other tests such as TBUT, staining, Schirmer test, and meibomian gland grading.

*6.6. Impression Cytology.* The information of etiology of the disease can be obtained from biopsy of conjunctival and lateral lacrimal glands [67]. Impression cytology serves as a minimally invasive alternative to ocular surface biopsy. Progression of ocular surface changes such as marked decrease in goblet cell count and keratinization is monitored by collecting superficial layers and examined microscopically [68]. It is a very sensitive method but requires proper staining and expert microscopic evaluation.

*6.7. Symptom Questionnaires.* Questionnaires explore different aspects of dry eye disease in varying depth, including diagnosis, identification of precipitation factors, and impact on quality of life [51, 69]. The number of questions administered in different questionnaires may range from 3 to 57. Examples of symptom questionnaires include extensive dry eye questionnaire (DEQ) of Begley et al. [69], questionnaire by Schein et al. [70], and OSDI questionnaire by Schiffman et al. [71]. A structured questionnaire to patients helps clinicians in screening patients with potential dry eye disease. A specific questionnaire can be selected depending on intended use of data, for example, for diagnosis use only, for recruiting patients to a clinical trial, or for treatment [72].

Ocular surface disease index (OSDI) questionnaire contains 3 sections: section 1 is based on relative frequency of occurrence of each symptom (e.g., gritty feeling in eye, light sensitivity, and blurred vision), section 2 includes questions indicating limitations on certain activities (reading, driving at night, watching television), and section 3 is based on effect of environmental conditions (wind, low humidity, and air conditioning) on eyes [73].

*6.8. Fluorophotometry.* This method is costly and uses the decay of sodium fluorescein for measurement of tear flow and volume. The tear turnover rate, defined as the percentage by which the fluorescein concentration in tears decreases per minute after instillation, is also reduced in patients with symptomatic DES [49, 54]. Delayed clearance has been associated with increased tear cytokine concentration, which may contribute to chronic inflammation [62].

*6.9. Tear Fluid Protein Immunoassays.* The protein component of tears may be quantified by measuring tear lysozyme, tear lactoferrin, epidermal growth factor (EGF), aquaporin 5, lipocalin, and immunoglobulin A (IgA) concentrations with enzyme-linked immunosorbent assay (ELISA) techniques, as well as tear-film osmolarity [63, 74, 75]. The normal values for total lysozyme reactivity and lactoferrin are given in Table 1. The tear lysozyme accounts for 20–40% of total tear protein and lysozyme reactivity test is used for quantification; however its main disadvantage is its lack of specificity in some eyes disorders. Colorimetric solid-phase and ELISA techniques are used for lactoferrin analysis. Table 1 summarises established normal values for selected tests.

*6.10. Tear Ferning Test (TFT).* The tear ferning test (TFT) can be used to help diagnose the quality of tears/mucin, DES, and hyperosmolarity. A drop of tear fluid is collected from the lower eyelid and then placed onto a microscope slide and allowed to dry by evaporation. Different forms of branching crystallization patterns are observed and classified. The test diagnoses dry eyes on the basis of the fern patterns [76].

*6.11. Other Tests.* Meibomian gland dysfunction (MGD) is diagnosed by techniques such as meibometry, meibography, or meiboscopy [77]. Tear evaporation is tested by means of evaporimetry. Meniscometry is used to help diagnose aqueous rear deficient dry eyes. Lacrimal gland or minor (salivary) gland biopsy may be used for diagnosis of Sjögren's syndrome. Histopathological findings also help to characterize DES and MGD. Reduced tear flow and flushing action are determined by microscopic examination of tear film debris.

The results of diagnostic tests discussed above poorly correlate with symptoms [14]. Though the literature emphasizes hyperosmolarity as a global mechanism of DED, indicating tear osmolarity measurement as a gold standard [61, 78] for diagnosis, unfortunately no single qualitative/quantitative test is capable of assessing integrity of tear film and severity of disease. Therefore the results of multiple abnormal tests can be used to diagnose DES accurately.

## 7. Medical Management

The treatments of keratoconjunctivitis are varied. The goals of treatment are to relieve the symptoms of dry eye, improve the patient's comfort, return the ocular surface and tear film to the normal state, and, whenever possible, prevent corneal damage [3]. Treatment may range from education, environmental or dietary modifications, artificial tear substitutes,

Table 1: Diagnostic tests and normal values.

| Test | Normal values |
|---|---|
| Tear film breakup time (TBUT) | >10 sec |
| Noninvasive breakup time (NIBUT) | 40 sec–60 sec |
| Epithelial staining | No visible staining |
| Schirmer test (basic) | >5 mm after 5 minutes |
| Schirmer I test (without topical anesthesia) | >10 mm after 5 minutes |
| Schirmer II test/Jones test (with anesthesia) | >15 mm after 5 minutes |
| Tear function index | >96 |
| Tear osmolarity | <312–318 mOsm/L |
| Impression cytology | Normal appearance of cells |
| Tear fluid protein immunoassay | Total lysozyme reactivity TLR <1.0<br>Lactoferrin 1.42 mg/mL (abnormal value <1) |

Table 2: Artificial tear products.

| Brand name | Description | Manufacturer |
|---|---|---|
| Tears Naturale Forte Lubricant Eye Drops | Contains special preservative, Polyquad | Alcon Inc. |
| Tears Naturale P.M. eye ointment | Lubricant for night time protection | |
| Systane Ultra lubricant | Demulcent matrix of HP-guar and borate | |
| Refresh Tears Drops | CMC sod. 0.5% w/v | Allergan India Pvt. Ltd. |
| Refresh Endura (for long-term relief) | Contains castor oil to replenish lipid components of tear film, preservative-free | |
| Refresh Celluvisc | Contains CMC sod. 1% w/v; gel-like consistency may cause blurred vision | |
| Refresh Liquigel | Gel drops, CMC sod. 1% w/v, and longer duration of action | |
| Tear Plus lubricant drops | Contains PVA and PVP | |
| Refresh contacts | For dryness and irritation associated with contact lenses | |
| Advanced eye relief environmental lubricant | Eye drops contain propylene glycol and glycerine | Bausch & Lomb Inc. |
| Advanced eye relief lubricant ointment | For lubrication during night time | |
| Soothe XP | Contains mineral oil and an advanced lipid restorative called Restoryl | |
| GenTeal drops and gel | Hydroxy propyl methyl cellulose | Novartis (I) Ltd. |
| Hypo Tears Plus eye drops | Hydroxy propyl methyl cellulose | |

punctal plugs, and topical and/or systemic anti-inflammatory medications to surgery.

*7.1. Artificial Tears.* Artificial tears are lubricant eye drops used to treat the dryness and irritation associated with deficient tear production in KCS. The lubricant tears are available as OTC products and usually are the first line of treatment. Mild disease conditions require the application of lubricant drops four times a day while severe cases need greater frequency (10–12 times a day) of administration. These OTC products mainly vary in their ingredients, indications, and availability of preservatives. Ingredients such as cellulose and polyvinyl derivatives, chondroitin sulfate, and sodium hyaluronate determine their viscosity, retention time, and adhesion to ocular surface [79].

The increase in viscosity of teardrops prolongs the duration of action; however it results in temporary blurred vision [80]. Preservatives are added to multidose containers of artificial tears to reduce the risk of bacterial contamination and to prolong shelf-life. Many ophthalmic products contain preservatives and risk of adverse effects increases with frequency of their administration per day and also duration of their use [81]. The clinician should take into account the sensitivity of patient to preservatives, frequency of use, severity of disease, contamination risk with preservative-free product, and cost while recommending artificial tear product.

Table 2 lists the brand names of few widely used artificial tear products available in the market. "Refresh Tears" by Allergan and "Tears Naturale" and "Bion Tears" by Alcon are few excellent preservative-free artificial teardrops available in the market [81]. Many ophthalmologists use other treatments such as cyclosporin, corticosteroids, and tetracycline in conjunction with artificial tears, in moderate to severe forms of dry eyes, to reduce signs and symptoms. Lubricating tear

ointments can be used during the day, but they generally are used at bedtime due to poor vision after application. An artificial tear insert such as Lacrisert which contains hydroxyl propyl cellulose can also be used every morning [33].

*7.2. Autologous Serum Eye Drops.* Autologous serum eye drops contain different essential tear components such as hepatocyte growth factor, epidermal growth factor, vitamin A, and fibronectin that are important for maintaining healthy ocular surface. All these components are not available in the commercial products and use of these eye drops for treatment of KCS is controversial [82].

*7.3. Nonsteroidal Anti-Inflammatory Drugs and Antibiotics.* NSAID drops containing drugs such as diclofenac sodium and ketorolac reduce the inflammation associated with DES. Ophthalmic ointments containing antibiotics such as erythromycin and bacitracin are used for treatment of meibomian gland dysfunction [83].

Topical ophthalmic aqueous solution of tetracycline has been developed for chronic DES. Tetracyclines are used in DES primarily for their anti-inflammatory effects rather than antibacterial actions [64, 84].

*7.4. Punctal Plugs.* A small medical device called "punctal plug" is inserted into puncta of an eye to block the duct so as to prevent nasolacrimal drainage of tears from eye and thereby dry eyes. Clinical studies have shown that the punctal plugs, as means of occlusion, improve DED symptoms and signs [85]. Punctal plugs are usually reserved for people with moderate to severe KCS and use of artificial tears is necessary after punctal plug insertion. Patient education and close follow-up are recommended to detect plug loss and ensure adequate control of the disease.

*7.5. Corticosteroids.* Topical corticosteroids, such as loteprednol etabonate, dexamethasone, prednisolone, and fluorometholone, are found to be effective in inflammatory conditions associated with KCS and these are approved by the FDA for treating inflammatory conditions of the conjunctiva, cornea, and anterior globe [64, 86, 87]. They are generally recommended for short-term use as prolonged use may result in adverse effects such as ocular infection, glaucoma, and cataracts.

*7.6. Cyclosporin.* Cyclosporin A is effective in a number of ocular immune pathologies. Systemic administration of drug is used in treatment of local ophthalmic conditions involving cytokines, such as corneal graft rejection, autoimmune uveitis, and dry eye syndrome; however it induces severe renal and cardiovascular complications [88]. Local administration avoids the various side effects associated with systemic delivery giving this drug a wide safety profile. Topical cyclosporine A is the first FDA approved medication indicated for treatment of patients with aqueous production deficient dry eye and is better for long-term treatment. It is marketed as "Restasis" 0.05% ophthalmic topical emulsion and as "Cyclomune" by Sun Pharma in India.

It is a highly specific immunomodulator that prevents activation of T lymphocytes and significantly decreases levels of inflammatory cytokines in the conjunctival epithelium with an increase in goblet cells [64, 89]. It also inhibits mitochondrial-mediated pathways of apoptosis [90].

The clinical study demonstrating the use of topical cyclosporine for the treatment of mild, moderate, and severe dry eye disease unresponsive to artificial tears therapy concluded that topical cyclosporine has shown beneficial effects in all categories of dry eye disease [91]. Because of highly hydrophobic properties, topical formulation of cyclosporin A is prepared using different vegetable oils, resulting in a poor local tolerance by the patients [92] and low bioavailability. Multiple studies have supported the use of topical cyclosporine to treat DED caused by insufficient tear production [93, 94]. The use of colloidal carriers such as micelles, nanoparticles, and liposomes is a promising approach to obtain better tolerance and ocular bioavailability and is discussed separately (Section 8) for treatment of DES. Table 3 lists few marketed products other than artificial tears for DED treatment.

*7.7. Vitamin A.* Vitamin A is an essential nutrient present naturally in tear film of healthy eyes. Vitamin A plays an important role in production of the mucin layer, the most innermost lubricating layer of tear film that is crucial for a healthy tear film. Vitamin A deficiency leads to loss of mucin layer and goblet cell atrophy [1, 95]. Vitamin A drops protect the eyes from free radicals, toxins, allergens, and inflammation. Topical retinoic acid therapy in conjunction with systemic administration of vitamin A has been investigated to treat xerophthalmia [96]. Effective amount of one or more retinoids alone may be dispersed in a pharmaceutically acceptable ophthalmic vehicle and topically applied for effective treatment of dry eye disorders.

*7.8. Omega 3 Fatty Acids.* Oral supplementation with essential fatty acids (EFAs) is suggested nowadays by ophthalmologists [64, 97]. EFAs are the precursors of eicosanoids, locally acting hormones involved in mediating inflammatory processes [98]. Essential fatty acids may benefit DED patients by reducing inflammation and by altering the composition of meibomian lipids. Clinicians may suggest dietary intake of n-3 fatty acid to help relieve DES [99]. Some examples of omega 3 gel caps marketed specifically for dry eyes include Thera Tears and Bio Tears.

The study performed by Rashid et al. at the Massachusetts Eye Research Institute demonstrated for the first time the benefit of topical application of a particular fatty acid in treating the signs of dry eye syndrome. Topical alpha-linolenic acid (ALA) treatment has been found to decrease signs of dry eye and inflammatory changes significantly at both cellular and molecular levels [100]. Thus topical application of ALA may be a novel therapy to treat the clinical signs and inflammatory changes in KCS.

Table 3: Few marketed preparations for treatment of keratoconjunctivitis sicca.

| Manufacturer | Brand | Content | Delivery system and indication |
|---|---|---|---|
| Allergan, Inc. | Restasis (by prescription) | Cyclosporin A 0.05% w/v | Oil-based emulsion<br>DED treatment |
| | Refresh Optive | Contains 2 osmolytes L-carnitine and erythritol and CMC sodium 5 mg | Eye drops |
| Sun Pharma Ind. Ltd. | Cyclomune | Cyclosporin A 0.05% w/v | Drops<br>DED treatment |
| Bausch & Lomb Inc. | Lotemax | Loteprednol etabonate 0.5% | Suspension drops (steroid) for short-term therapy |
| Novartis Ltd. | Voltaren | Diclofenac sodium ophthalmic solution) 0.1% | Drops |
| FDC Ltd. | ZO-D eye drops | Ofloxacin and dexamethasone | Drops |
| Allergan India Pvt. Ltd. | Acular LS | Ketorolac tromethamine 0.4% | Drops |
| | Toba | Tobramycin USP | |
| | Toba DM | Tobramycin and dexamethasone | Drops |
| | Toba F | Tobramycin and fluorometholone | |
| Ocusoft, Inc. | Retaine<br>MGD | Cationic O/W emulsion technology | Hypotonic emulsion provides lubrication |
| Otsuka Pharmaceuticals | Mucosta ophthalmic suspension UD2% | Rebamipide | Marketed in China, Japan, Indonesia, Malaysia, and Thailand |
| Advanced Vision Research | Thera tears nutrition | Omega 3 fatty acids | Gel capsules |

## 8. Colloidal Carrier Systems for Treatment of KCS

The rationale for the use of microparticulate systems for the delivery of ophthalmic drugs is based on possible entrapment of the small particles in the ocular mucus layer and the interaction of bioadhesive polymer chains with mucins inducing a prolonged residence and slow drainage [101]. Colloidal carriers are promising systems among a variety of topical drug delivery systems as they fulfill the requirements such as nontoxicity, ease of application as drops, drug loading capacity, possibility of drug targeting, controlled release characteristics, and chemical and physical storage stability [102]. Colloidal carriers are small particles of 100–400 nm in diameter. Colloidal systems including liposomes and nanoparticles have the convenience of a drop, which is able to maintain drug activity at its site of action and is suitable for poorly water-soluble drugs [103].

Lipid based ophthalmic drug delivery systems may offer a number of advantages for use in treatment of KCS. Lipophilic matrices are not susceptible to erosion and drug encapsulated in small lipid particle ensures close contact and selective drug delivery to cornea and conjunctiva. Examples of carrier systems include liposomes, solid lipid nanoparticles, lipid suspensions and emulsions, lipid microbubbles, and lipid microspheres [104, 105].

Liposomes are the microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments with a diameter ranging from 25 nm to 100 $\mu$m. Adherence to the corneal or conjunctival surface can be improved by dispersion of the liposomes in mucoadhesive gels or coating the liposomes with mucoadhesive polymers [106]. Lipospheres are solid microparticles (0.2–100 $\mu$m), composed of solid hydrophobic fat core stabilized by a monolayer of phospholipids molecules. Prodispersion liposphere formulation of cyclosporine has been prepared and its topical use in treatment of DES can be investigated [93].

Microspheres and nanoparticles have important potential applications for site specific drug delivery. A number of studies deal with the preparation and application of ophthalmic drugs loaded to micro- and nanospheres. Bioadhesive PLGA and lipid microspheres have been developed to prolong residence time of cyclosporin A in preocular area [44, 107]. A novel topical polymeric micelle formulation based on methoxy poly(ethylene) glycol- (MPEG-) hexyl-substituted poly(lactides) (hexPLA) has been shown to provide a selective delivery of cyclosporine A into the cornea, avoiding systemic absorption and without compromising the ocular surface stability [108].

Nanoparticles are colloidal particles ranging in size from 10 nm to 1000 nm. Formulations containing drug loaded nanoparticles such as polymeric and lipid nanoparticles have been prepared to obtain sustained ophthalmic delivery. Cyclosporine A loaded solid lipid nanoparticles for topical ophthalmic applications have been prepared by high shear homogenization and ultrasound method [94]. Drug loaded polymeric nanoparticles (DNPs) are subnanosized colloidal structures composed of synthetic or semisynthetic polymers offering favourable biological properties such as biodegradability, nontoxicity, biocompatibility, and mucoadhesiveness. These submicron particles are better than conventional ophthalmic dosage forms to enhance bioavailability without blurring the vision [109].

## 9. Current Challenges and Future Aspects

Dry eye syndrome is the most common ophthalmic manifestation and untreated dry eye can cause increased risk of ocular infection, corneal ulcer, and blindness. The clinical diagnosis of dry eye is challenging due to extensive variety of signs and symptoms and the ambiguity in the etiology and pathophysiology of the disease. Unclear symptoms could confuse the clinician with symptoms of other condition, such as conjunctivochalasis (which can easily induce an unstable tear film) or delayed tear clearance (which is a frequent cause of ocular irritation) [110].

Conventional tests for diagnosis include Schirmer test, TBUT, and ocular staining; as mentioned above, some of them have low degree of standardization and some are invasive. The invasive nature of some diagnostic tests can make interpretation challenging. A tear film is a dynamic, open system subject to numerous internal and environmental variations leading to misinterpretations of the obtained result [74]. Recent studies have shown that less than 60% of subjects with other objective evidence of DED are symptomatic [111]. Thus the use of symptoms alone will result in missing a significant percentage of DED patients. Clinically, osmolarity has been shown to be the best single metric for diagnosis of dry eyes and is directly related to increasing severity of disease. Clinical examination and other assessments determine the subtype of disease. In conclusion, an accurate testing and differential diagnosis of dry eye which is crucial for medical management of disease are difficult and results of multiple tests measuring tear volume and biological components have been used by ophthalmologists to diagnose KCS accurately. Therefore the clinicians play challenging role in identification of symptoms of dry eye, selection of appropriate diagnostic tests and products, interpretation, and instructing patients on the proper use of medications.

Ophthalmic drugs constitute a prominent segment of the global pharmaceutical market, with sales of over $20 bn. Accordingly, the number of pharmaceutical industries has tendency towards the development of new drugs for DED to control the inflammation or to stimulate mucin and tear secretion. Current available therapies such as lubricants and anti-inflammatory drugs alleviate symptoms and reduce signs of DED; however the underlying cause of disease remains unattended. A number of drugs and different delivery systems of existing drugs are under development or in preclinical and clinical research pipeline [106–109]. In this section of review, we also discuss recently marketed novel medications and few new drugs under clinical trials that may find the way for marketing.

Most exciting drugs in R&D pipeline include diquafosol and rebamipide. Diquafosol (INS 365) acts by stimulating tear components and rebamipide, an amino acid analogue of quinolinone causes mucin secretion [112, 113]. Jumblatt and Jumblatt demonstrated that functional P2Y2 nucleotide receptors of rabbit and human conjunctival cells are stimulated by diquafosol, thereby stimulating mucociliary clearance and hydration of mucosal surface [114]. Clinical studies conducted by Santen Pharmaceutical Co., Ltd. demonstrated the effectiveness of diquafosol at an optimal dose of 3% six times a day [115]. Topical administration of diquafosol was shown to be safe and effective in alleviating signs and symptoms of DES as demonstrated with Schirmer test and corneal staining.

Some drugs used to treat gastric ulcers also stimulate the secretion of mucin like substances of cornea in animal experiments, for example, rebamipide and gefarnate. The drug rebamipide was launched for the treatment of dry eye syndrome in Japan in 2012 as Mucosta ophthalmic suspension UD2%. It increases the level of mucin in the tear film covering the conjunctiva and cornea [116]. A comparison of 2% rebamipide ophthalmic suspension with 0.1% sodium hyaluronate in a randomized multicenter Phase 3 study showed marked improvement in signs and symptoms of DED as compared to sodium hyaluronate [117]. Otsuka Pharmaceutical Co., Ltd. in partnership with Acucela Inc. has initiated Phase 3 clinical trial to determine the efficacy and safety of 2% rebamipide ophthalmic suspension in US patients with DES [118].

Gefarnate ointment on topical application to eyes in the rabbit and cat dry eye models has been found to stimulate *in vitro* secretion of mucin like glycoprotein in conjunctival tissue and ameliorate corneal epithelial damage [119]. There are significant numbers of promising drugs that show better results and lesser side effects in preclinical and clinical trials [120–123]. SARcode Bioscience has conducted a year-long safety study (SONATA) of lifitegrast 5% ophthalmic solution after completion of Phase 3 trial which demonstrated a superior reduction in the signs and symptoms of DED [121]. Few other new drugs [122, 124] presently in Phase 2 and 3 clinical trials for treatment of KCS include AL-2178/rimexolone 1% (Alcon/Novartis, ClinicalTrials.gov Identifier: NCT00471419), MIM-D3 (Mimetogen Pharmaceuticals, ClinicalTrials.gov Identifier: NCT01257607), rituximab (IDEC Pharmaceuticals, ClinicalTrials.gov Identifier: NCT00740948), ecabet sodium (Bausch & Lomb Inc., ClinicalTrials.gov Identifier: NCT00667004), sirolimus or rapamycin (Santen Pharmaceutical, ClinicalTrials.gov Identifier: NCT00814944), ESBA-105 (Alcon and ESBATech, ClinicalTrials.gov Identifier: NCT01338610), RX-10045 (Resolvyx Pharmaceuticals, ClinicalTrials.gov Identifier: NCT00799552), CF 101 (OphthaliX Company-Can-Fite BioPharma, ClinicalTrials.gov Identifier: NCT01235234), DE-101/rivoglitazone (Santen pharmaceuticals, ClinicalTrials.gov Identifier: NCT01118754), difluprednate (Alcon, ClinicalTrials.gov Identifier: NCT01276223), RGN-259/thymosin beta 4 (RegeneRx Biopharmaceuticals, ClinicalTrials.gov Identifier: NCT01387347), and cyclosporine (Restasis X) (Allergan, ClinicalTrials.gov Identifier: NCT02013791).

Most of these potential new drugs center their action towards controlling inflammation and restoring normal amount of tears, but none of them attend the main cause of disease. Thus there is a need for effective therapeutic agents that target the causative mechanism of disease. Possibility of use of old drugs (e.g., rebamipide) for new use in DED treatment should be considered after understanding the main cause of disease and mechanism of action of old drug as it will result in reduced R&D cost and approval time. FDA approval

is another challenge for candidate DED drugs. A number of companies failed in securing FDA approval for new dry eye drugs mainly in the United States [124]. Lack of clarity in symptoms evaluation or insufficient diagnosis data is one of the reasons for frequent failure. A very few dry eye agents pass successfully through tight clinical trials regulations of USA as compared to Asia and Europe. Rebamipide, being developed for dry eye syndrome in the United States, is marketed in Japan under the trade name Mucosta by Otsuka Pharmaceutical [118]. Thus there is a need for better understanding of the FDA approval system of different countries including protocol development, the inclusion/exclusion of signs and symptoms, and patient selection. Patients with less disease variability should be selected after considering type of dry eyes, severity level, and other factors, namely, age, gender, lifestyle, and history of poor therapeutic response.

The current treatment is based on the use of topically applied artificial tears: tear retention management, stimulation of tear secretion, and use of anti-inflammatory drugs [125, 126]. New therapeutic strategies and novel drug delivery systems using future pharmaceutical compounds designed to reduce key inflammatory pathways and restore healthy tear film along with incorporation of improved endpoints for clinical trials will lead to successful management of dry eyes or keratoconjunctivitis sicca in the future.

## 10. Conclusion

The overarching complexity of the dry eye disease makes it challenging to diagnose and manage accurately. With development of objective tests with precise diagnostic value and minimal disruption of physiological function, accurate diagnosis of disease is possible. Recent knowledge about causes, symptoms, and diagnostic tests of KCS provides better opportunities for improving medical management. Development of new potential drugs and different colloidal delivery systems definitely provides a ray of hope for more effective treatment of this widely prevalent and debilitating disease.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this review article.

## References


[1] M. A. Lemp, C. Baudouin, J. Baum et al., "The definition and classification of dry eye disease: report of the definition and classification subcommittee of the international Dry Eye WorkShop," *Ocular Surface*, vol. 5, no. 2, pp. 75–92, 2007.

[2] N. Delaleu, R. Jonsson, and M. M. Koller, "Sjögren's syndrome," *European Journal of Oral Sciences*, vol. 113, no. 2, pp. 101–113, 2005.

[3] "Methodologies to diagnose and monitor dry eye disease: report of the diagnostic methodology subcommittee of the international dry eye workshop (2007)," *The Ocular Surface*, vol. 5, no. 2, pp. 108–152, 2007.

[4] M. Uchino, Y. Uchino, M. Dogru et al., "Dry eye disease and work productivity loss in visual display users: the Osaka study," *The American Journal of Ophthalmology*, vol. 157, no. 2, pp. 294–300, 2014.

[5] J. R. Grubbs Jr., S. Tolleson-Rinehart, K. Huynh, and R. M. Davis, "A review of quality of life measures in dry eye questionnaires," *Cornea*, vol. 33, no. 2, pp. 215–218, 2014.

[6] A. J. Paulsen, K. J. Cruickshanks, M. E. Fischer et al., "Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life," *American Journal of Ophthalmology*, vol. 157, no. 4, pp. 799–806, 2014.

[7] B. Miljanović, R. Dana, D. A. Sullivan, and D. A. Schaumberg, "Impact of dry eye syndrome on vision-related quality of life," *American Journal of Ophthalmology*, vol. 143, no. 3, pp. 409.e2–415.e2, 2007.

[8] L. Tong, S. Waduthantri, T. Y. Wong et al., "Impact of symptomatic dry eye on vision-related daily activities: the Singapore malay eye study," *Eye*, vol. 24, no. 9, pp. 1486–1491, 2010.

[9] D. A. Schaumberg, R. Dana, J. E. Buring, and D. A. Sullivan, "Prevalence of dry eye disease among US men: estimates from the physicians' health studies," *Archives of Ophthalmology*, vol. 127, no. 6, pp. 763–768, 2009.

[10] A. Sharma and H. B. Hindman, "Aging: a predisposition to dry eyes," *Journal of Ophthalmology*, vol. 2014, Article ID 781683, 8 pages, 2014.

[11] S. E. Moss, R. Klein, and B. E. K. Klein, "Prevalance of and risk factors for dry eye syndrome," *Archives of Ophthalmology*, vol. 118, no. 9, pp. 1264–1268, 2000.

[12] S. C. Pflugfelder, "Prevalence, burden, and pharmacoeconomics of dry eye disease," *The American Journal of Managed Care*, vol. 14, no. 3, supplement, pp. S102–S106, 2008.

[13] O. D. Schein, B. Munuz, J. M. Tielsch, K. Bandeen-Roche, and S. West, "Prevalence of dry eye among the elderly," *The American Journal of Ophthalmology*, vol. 124, no. 6, pp. 723–728, 1997.

[14] J. A. Smith, J. Albenz, C. Begley et al., "The epidemiology of dry eye disease: report of the epidemiology subcommittee of the international Dry Eye WorkShop (2007)," *Ocular Surface*, vol. 5, no. 2, pp. 93–107, 2007.

[15] M. A. Lemp, "Advances in understanding and managing dry eye disease," *The American Journal of Ophthalmology*, vol. 146, no. 3, pp. 350.e1–356.e1, 2008.

[16] D. A. Schaumberg, D. A. Sullivan, and M. R. Dana, "Epidemiology of dry eye syndrome," *Advances in Experimental Medicine and Biology*, vol. 506, pp. 989–998, 2002.

[17] D. A. Schaumberg, J. E. Buring, D. A. Sullivan, and M. Reza Dana, "Hormone replacement therapy and dry eye syndrome," *The Journal of the American Medical Association*, vol. 286, no. 17, pp. 2114–2119, 2001.

[18] S. S. Kassan and H. M. Moutsopoulos, "Clinical manifestations and early diagnosis of Sjögren syndrome," *Archives of Internal Medicine*, vol. 164, no. 12, pp. 1275–1284, 2004.

[19] M. Fujita, T. Igarashi, T. Kurai, M. Sakane, S. Yoshino, and H. Takahashi, "Correlation between dry eye and rheumatoid arthritis activity," *The American Journal of Ophthalmology*, vol. 140, no. 5, pp. 808–813, 2005.

[20] S. C. Sacca, A. Poscotto, G. M. Venturino et al., "Prevalence and treatment of *Helicobacter pylori* in patients with blepharitis," *Investigative Ophthalmology & Visual Science*, vol. 47, pp. 501–508, 2006.

[21] C. Blehm, S. Vishnu, A. Khattak, S. Mitra, and R. W. Yee, "Computer vision syndrome: a review," *Survey of Ophthalmology*, vol. 50, no. 3, pp. 253–262, 2005.

[22] J. C. Lang and R. E. Roehrs, "Ophthalmic preparations," in *Remington: The Science and Practice of Pharmacy*, D. B. Troy, Ed., vol. 1, pp. 850–854, Lippincott Williaims Wilkins, Philadelphia, Pa, USA, 21st edition, 2005.

[23] J. Lakshmi Prabha, "Tear secretion—a short review," *Journal of Pharmaceutical Sciences and Research*, vol. 6, no. 3, pp. 155–157, 2014.

[24] E. Peters and K. Colby, "The tear film," in *Foundation Volume 2: Physiology of the Eye and Visual System*, W. Tasman and E. A. Jaeger, Eds., Duane's Foundations of Clinical Ophthalmology, Lippincott Williams & Wilkins, Philadelphia, Pa, USA, 2006, Duanes Ophthalmology on CD rom.

[25] M. A. Lemp, "Report of the national eye institute/industry workshop on clinical trials in dry eyes," *CLAO Journal*, vol. 21, no. 4, pp. 221–232, 1995.

[26] S. Agarwal, A. Agarwal, D. J. Apple, L. Buratto, and J. L. Alió, "Tear film physiology," in *Textbook of Ophthalmology: Basic Sciences Optics and Refraction Neuro-Ophthalmology Strabismus*, J. P. Vij, Ed., vol. 1, pp. 39–45, Jaypee Brothers Medical Publishers, New Delhi, India, 1st edition, 2002.

[27] J. P. Craig and A. Tomlinson, "Importance of the lipid layer in human tear film stability and evaporation," *Optometry and Vision Science*, vol. 74, no. 1, pp. 8–13, 1997.

[28] J. P. McCulley and W. E. Shine, "The lipid layer of tears: dependent on meibomian gland function," *Experimental Eye Research*, vol. 78, no. 3, pp. 361–365, 2004.

[29] H. M. Tabery, "The mucus in the preocular tear film," in *Keratoconjunctivitis Sicca and Filamentary Keratopathy: In Vivo Morphology in the Human Cornea and Conjunctiva*, H. M. Tabery, Ed., pp. 1–14, Springer, Berlin, Germany, 2012.

[30] J. M. Tiffany, "Tears in health and disease," *Eye*, vol. 17, no. 8, pp. 923–926, 2003.

[31] M. E. Johnson and P. J. Murphy, "Changes in the tear film and ocular surface from dry eye syndrome," *Progress in Retinal and Eye Research*, vol. 23, no. 4, pp. 449–474, 2004.

[32] F. Tsuji and K. Kawazu, "Biomarker identification of tear fluid," *Metabolomics*, vol. 2, article 105, 2012.

[33] S. A. Mengi and S. G. Deshpande, "Ocular drug delivery," in *Controlled and Novel Drug Delivery*, N. K. Jain, Ed., pp. 82–90, CBS Publishers and Distributors, New Delhi, India, 1997.

[34] C. Snyder and R. J. Fullard, "Clinical profiles of non dry eye patients and correlations with tear protein levels," *International Ophthalmology*, vol. 15, no. 6, pp. 383–389, 1991.

[35] M. E. Stern, J. Gao, K. F. Siemasko, R. W. Beuerman, and S. C. Pflugfelder, "The role of the lacrimal functional unit in the pathophysiology of dry eye," *Experimental Eye Research*, vol. 78, no. 3, pp. 409–416, 2004.

[36] M. E. Stern and S. C. Pflugfelder, "Inflammation in dry eye," *Ocular Surface*, vol. 2, no. 2, pp. 124–130, 2004.

[37] J. I. Prydal, P. Artal, H. Woon, and F. W. Campbell, "Study of human precorneal tear film thickness and structure using laser interferometry," *Investigative Ophthalmology & Visual Science*, vol. 33, no. 6, pp. 2006–2011, 1992.

[38] J. Y. Niederkorn and H. J. Kaplan, "Immune response and the eye," *Chemical Immunology and Allergy*, vol. 92, pp. 176–184, 2007.

[39] J. Y. Niederkorn, "Regulatory T cells and the eye," *Chemical Immunology and Allergy*, vol. 92, pp. 131–139, 2007.

[40] P. J. Driver and M. A. Lemp, "Meibomian gland dysfunction," *Survey of Ophthalmology*, vol. 40, no. 5, pp. 343–367, 1996.

[41] M. Guzey, I. Ozardali, E. Basar, G. Aslan, A. Satici, and S. Karadede, "A survey of trachoma: the histopathology and the mechanism of progressive cicatrization of eyelid tissues," *Ophthalmologica*, vol. 214, no. 4, pp. 277–284, 2000.

[42] R. W. Yee, H. G. Sperling, A. Kattek et al., "Isolation of the ocular surface to treat dysfunctional tear syndrome associated with computer use," *Ocular Surface*, vol. 5, no. 4, pp. 308–315, 2007.

[43] P. Versura, P. Nanni, A. Bavelloni et al., "Tear proteomics in evaporative dry eye disease," *Eye*, vol. 24, no. 8, pp. 1396–1402, 2010.

[44] V. D. Wagh and D. U. Apar, "Cyclosporine a loaded PLGA nanoparticles for dry eye disease: *in vitro* characterization studies," *Journal of Nanotechnology*, vol. 2014, Article ID 683153, 10 pages, 2014.

[45] W. E. Shine and J. P. McCulley, "Keratoconjunctivitis sicca associated with meibomian secretion polar lipid abnormality," *Archives of Ophthalmology*, vol. 116, no. 7, pp. 849–852, 1998.

[46] G. N. Foulks, K. K. Nichols, A. J. Bron, E. J. Holland, M. B. McDonald, and J. Daniel Nelson, "Improving awareness, identification, and management of meibomian gland dysfunction," *Ophthalmology*, vol. 119, no. 10, supplement, pp. S1–S12, 2012.

[47] Y. Ohashi, R. Ishida, T. Kojima et al., "Abnormal protein profiles in tears with dry eye syndrome," *The American Journal of Ophthalmology*, vol. 136, no. 2, pp. 291–299, 2003.

[48] A. Solomon, D. Dursun, Z. Liu, Y. Xie, A. Macri, and S. C. Pflugfelder, "Pro- and anti-inflammatory forms of interleukin-1 in the tear fluid and conjunctiva of patients with dry-eye disease," *Investigative Ophthalmology and Visual Science*, vol. 42, no. 10, pp. 2283–2292, 2001.

[49] T. Kaercher and A. Bron, "Classification and diagnosis of dry eye," in *Surgery for the Dry Eye*, G. Geerling and H. Brewitt, Eds., vol. 41 of *Developments in Ophthalmology*, pp. 36–53, 2008.

[50] J. Murube, J. Németh, H. Höh et al., "The triple classification of dry eye for practical clinical use," *European Journal of Ophthalmology*, vol. 15, no. 6, pp. 660–667, 2005.

[51] S. C. Pflugfelder, S. C. G. Tseng, O. Sanabria et al., "Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation," *Cornea*, vol. 17, no. 1, pp. 38–56, 1998.

[52] N. Yokoi and A. Komuro, "Non-invasive methods of assessing the tear film," *Experimental Eye Research*, vol. 78, no. 3, pp. 399–407, 2004.

[53] A. J. Bron, "Diagnosis of dry eye," *Survey of Ophthalmology*, vol. 45, supplement 2, pp. S221–S226, 2001.

[54] G. Petroutsos, C. A. Paschides, K. X. Karakostas, and K. Psilas, "Diagnostic tests for dry eye disease in normals and dry eye patients with and without Sjogren's syndrome," *Ophthalmic Research*, vol. 24, no. 6, pp. 326–331, 1992.

[55] M. Rosenfield, "Computer vision syndrome: a review of ocular causes and potential treatments," *Ophthalmic and Physiological Optics*, vol. 31, no. 5, pp. 502–515, 2011.

[56] M. B. Abelson, G. W. Ousler III, L. A. Nally, D. Welch, and K. Krenzer, "Alternative reference values for tear film break up time in normal and dry eye populations," *Advances in Experimental Medicine and Biology*, vol. 506, pp. 1121–1125, 2002.

[57] L. S. Mengher, A. J. Bron, S. R. Tonge, and D. J. Gilbert, "A non-invasive instrument for clinical assessment of the pre-corneal tear film stability," *Current Eye Research*, vol. 4, no. 1, pp. 1–7, 1985.

[58] A. J. Bron, V. E. Evans, and J. A. Smith, "Grading of corneal and conjunctival staining in the context of other dry eye tests," *Cornea*, vol. 22, no. 7, pp. 640–650, 2003.

[59] H. Watanabe and M. Tanaka, "Rose bengal staining and expression of mucin-like glycoprotein in cornea epithelium," *Investigative Ophthalmology & Visual Science*, vol. 37, p. S357, 1996.

[60] D. J. Kim and G. N. Foulks, "Evaluation of the effect of lissamine green and rose bengal on human corneal epithelial cells," *Cornea*, vol. 18, no. 3, pp. 328–332, 1999.

[61] S. C. Pflugfelder, A. Solomon, and M. E. Stern, "The diagnosis and management of dry eye: a twenty-five-year review," *Cornea*, vol. 19, no. 5, pp. 644–649, 2000.

[62] A. A. Afonso, D. Monroy, M. E. Stern, W. J. Feuer, S. C. G. Tseng, and S. C. Pflugfelder, "Correlation of tear fluorescein clearance and Schirmer test scores with ocular irritation symptoms," *Ophthalmology*, vol. 106, no. 4, pp. 803–810, 1999.

[63] K. Tsubota, M. Kaido, Y. Yagi, T. Fujihara, and S. Shimmura, "Diseases associated with ocular surface abnormalities: the importance of reflex tearing," *British Journal of Ophthalmology*, vol. 83, no. 1, pp. 89–91, 1999.

[64] M.-A. Javadi and S. Feizi, "Dry eye syndrome," *Journal of Ophthalmic and Vision Research*, vol. 6, no. 3, pp. 192–198, 2011.

[65] A. J. Mackor and O. P. van Bijsterveld, "Tear function parameters in Keratoconjunctivitis sicca with and without the association of Sjogren's syndrome," *Ophthalmologica*, vol. 196, no. 4, pp. 169–174, 1988.

[66] M. A. Lemp, A. J. Bron, C. Baudouin et al., "Tear osmolarity in the diagnosis and management of dry eye disease," *The American Journal of Ophthalmology*, vol. 151, no. 5, pp. 792–798, 2011.

[67] M. Rolando, F. Terragna, G. Giordano, and G. Calabria, "Conjunctival surface damage distribution in keratoconjunctivitis sicca. An impression cytology study," *Ophthalmologica*, vol. 200, no. 4, pp. 170–176, 1990.

[68] M. Calonge, Y. Diebold, V. Sáez et al., "Impression cytology of the ocular surface: a review," *Experimental Eye Research*, vol. 78, no. 3, pp. 457–472, 2004.

[69] C. G. Begley, B. Caffery, R. L. Chalmers, and G. L. Mitchell, "Use of the dry eye questionnaire to measure symptoms of ocular irritation in patients with aqueous tear deficient dry eye," *Cornea*, vol. 21, no. 7, pp. 664–670, 2002.

[70] O. D. Schein, J. M. Tielsch, B. Munoz, K. Bandeen-Roche, and S. West, "Relation between signs and symptoms of dry eye in the elderly: a population-based perspective," *Ophthalmology*, vol. 104, no. 9, pp. 1395–1401, 1997.

[71] R. M. Schiffman, M. D. Christianson, G. Jacobsen, J. D. Hirsch, and B. L. Reis, "Reliability and validity of the ocular surface disease index," *Archives of Ophthalmology*, vol. 118, no. 5, pp. 615–621, 2000.

[72] A. Sahai and P. Malik, "Dry eye: prevalence and attributable risk factors in a hospital-based population," *Indian Journal of Ophthalmology*, vol. 53, no. 2, pp. 87–91, 2005.

[73] H. D. Perry and E. D. Donnenfeld, "Dry eye diagnosis and management in 2004," *Current Opinion in Ophthalmology*, vol. 15, no. 4, pp. 299–304, 2004.

[74] K. K. Nichols, G. L. Mitchell, and K. Zadnik, "The repeatability of clinical measurements of dry eye," *Cornea*, vol. 23, no. 3, pp. 272–285, 2004.

[75] C. Garcher, "CA 19-9 ELISA test: a new method for studying mucus changes in tears," *British Journal of Ophthalmology*, vol. 82, no. 1, pp. 88–90, 1998.

[76] E. Vaikoussis, P. Georgiou, and D. Nomicarios, "Tear mucus ferning in patients with Sjogren's syndrome," *Documenta Ophthalmologica*, vol. 87, no. 2, pp. 145–151, 1994.

[77] K. K. Nichols, G. N. Foulks, A. J. Bron et al., "The international workshop on meibomian gland dysfunction: executive summary," *Investigative Ophthalmology & Visual Science*, vol. 52, no. 4, pp. 1922–1929, 2011.

[78] A. Tomlinson, S. Khanal, K. Ramaesh, C. Diaper, and A. McFadyen, "Tear film osmolarity: determination of a referent for dry eye diagnosis," *Investigative Ophthalmology and Visual Science*, vol. 47, no. 10, pp. 4309–4315, 2006.

[79] M. F. Saettone, D. Monti, M. T. Torracca, and P. Chetoni, "Mucoadhesive ophthalmic vehicles: evaluation of polymeric low-viscosity formulations," *Journal of Ocular Pharmacology*, vol. 10, no. 1, pp. 83–92, 2009.

[80] G. J. Berdy, M. B. Abelson, L. M. Smith, and M. A. George, "Preservative-free artificial tear preparations: assessment of corneal epithelial toxic effects," *Archives of Ophthalmology*, vol. 110, no. 4, pp. 528–532, 1992.

[81] W. S. Pray, "Ophthalmic conditions," in *Nonprescription Product Therapeutics*, pp. 435–445, Lippincott Williams & Wilkins, Baltimore, Md, USA, 2nd edition, 2006.

[82] G. Geerling, S. MacLennan, and D. Hartwig, "Autologous serum eye drops for ocular surface disorders," *British Journal of Ophthalmology*, vol. 88, no. 11, pp. 1467–1474, 2004.

[83] H. D. Perry, S. Doshi-Carnevale, E. D. Donnenfeld, R. Solomon, S. A. Biser, and A. H. Bloom, "Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction," *Cornea*, vol. 25, no. 2, pp. 171–175, 2006.

[84] J. P. Gilbard, "Ophthalmic solution with tetracycline for topical treatment of dry eye disease," Advanced Vision Research EP 1105139 B1, PCT/US 1999/017185, 2004.

[85] M. Balaram, D. A. Schaumberg, and M. R. Dana, "Efficacy and tolerability outcomes after punctal occlusion with silicone plugs in dry eye syndrome," *The American Journal of Ophthalmology*, vol. 131, no. 1, pp. 30–36, 2001.

[86] G. N. Foulks, "Pharmacological management of dry eye in the elderly patient," *Drugs and Aging*, vol. 25, no. 2, pp. 105–118, 2008.

[87] S. C. Pflugfelder and M. E. Stern, "Therapy of lacrimal keratoconjunctivitis," in *Dry Eye and Ocular Surface Disorders*, S. C. Pflugfelder and W. B. Roger, Eds., pp. 309–320, Marcel Dekker, New York, NY, USA, 2004.

[88] O. D. Schein, B. Muñoz, J. M. Tielsch, K. Bandeen-Roche, and S. K. West, "An epidemiologic study of medication use and symptoms of dry eye," *Investigative Ophthalmology and Visual Science*, vol. 38, no. 4, p. S213, 1997.

[89] K. S. Kunert, A. S. Tisdale, M. E. Stern, J. A. Smith, and I. K. Gipson, "Analysis of topical cyclosporine treatment of patients with dry eye syndrome: effect on conjunctival lymphocytes," *Archives of Ophthalmology*, vol. 118, no. 11, pp. 1489–1496, 2000.

[90] S. Matsuda and S. Koyasu, "Mechanisms of action of cyclosporine," *Immunopharmacology*, vol. 47, no. 2-3, pp. 119–125, 2000.

[91] H. D. Perry, R. Solomon, E. D. Donnenfeld et al., "Evaluation of topical cyclosporine for the treatment of dry eye disease," *Archives of Ophthalmology*, vol. 126, no. 8, pp. 1046–1050, 2008.

[92] J. P. Gilbard, "Non-toxic ophthalmic preparations and methods of preparing them," Patent no. EP0205279 B1, 1991.

[93] A. Avramoff, W. Khan, A. Ezra, A. Elgart, A. Hoffman, and A. J. Domb, "Cyclosporin pro-dispersion liposphere formulation," *Journal of Controlled Release*, vol. 160, no. 2, pp. 401–406, 2012.

[94] E. H. Gokce, G. Sandri, M. C. Bonferoni et al., "Cyclosporine A loaded SLNs: evaluation of cellular uptake and corneal cytotoxicity," *International Journal of Pharmaceutics*, vol. 364, no. 1, pp. 76–86, 2008.

[95] A. J. Bron and L. S. Mengher, "The ocular surface in keratoconjunctivitis sicca," *Eye*, vol. 3, no. 4, pp. 428–437, 1989.

[96] A. Sommer and N. Emran, "Topical retinoic acid in the treatment of corneal xerophthalmia," *The American Journal of Ophthalmology*, vol. 86, no. 5, pp. 615–617, 1978.

[97] A. M. Al Mahmood and S. A. Al-Swailem, "Essential fatty acids in the treatment of dry eye syndrome: a myth or reality?" *Saudi Journal of Ophthalmology*, vol. 28, no. 3, pp. 195–197, 2014.

[98] E. S. Rosenberg and P. A. Asbell, "Essential fatty acids in the treatment of dry eye," *Ocular Surface*, vol. 8, no. 1, pp. 18–28, 2010.

[99] B. Miljanović, K. A. Trivedi, M. R. Dana, J. P. Gilbard, J. E. Buring, and D. A. Schaumberg, "The relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women," *American Journal of Clinical Nutrition*, vol. 82, no. 4, pp. 887–893, 2005.

[100] S. Rashid, Y. Jin, T. Ecoiffier, S. Barabino, D. A. Schaumberg, and M. R. Dana, "Topical omega-3 and omega-6 fatty acids for treatment of dry eye," *Archives of Ophthalmology*, vol. 126, no. 2, pp. 219–225, 2008.

[101] A. Ludwig, "The use of mucoadhesive polymers in ocular drug delivery," *Advanced Drug Delivery Reviews*, vol. 57, no. 11, pp. 1595–1639, 2005.

[102] A. Joshi, "Microparticulates for ophthalmic drug delivery," *Journal of Ocular Pharmacology*, vol. 10, no. 1, pp. 29–45, 1994.

[103] C. le Bourlais, L. Acar, H. Zia, P. A. Sado, T. Needham, and R. Leverge, "Ophthalmic drug delivery systems—recent advances," *Progress in Retinal and Eye Research*, vol. 17, no. 1, pp. 33–58, 1998.

[104] R. M. Gilhotra, P. Vishva, and D. N. Mishra, "A comparative review of recently developed particulate drug carrier systems," *Targeted Drug Delivery Systems*, vol. 7, no. 3, pp. 1–12, 2009.

[105] R. H. Müller, K. Mäder, and S. Gohla, "Solid lipid nanoparticles (SLN) for controlled drug delivery—a review of the state of the art," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 50, no. 1, pp. 161–177, 2000.

[106] D. Meisner and M. Mezei, "Liposome ocular delivery systems," *Advanced Drug Delivery Reviews*, vol. 16, no. 1, pp. 75–93, 1995.

[107] A. Yanagawa, Y. Mizushima, A. Komatsu, M. Horiuchi, E. Shirasawa, and R. Igarashi, "Application of a drug delivery system to a steroidal ophthalmic preparation with lipid microspheres," *Journal of Microencapsulation*, vol. 4, no. 4, pp. 329–331, 1987.

[108] C. di Tommaso, F. Valamanesh, F. Miller et al., "A novel cyclosporin a aqueous formulation for dry eye treatment: in vitro and in vivo evaluation," *Investigative Ophthalmology and Visual Science*, vol. 53, no. 4, pp. 2292–2299, 2012.

[109] R. C. Nagarwal, S. Kant, P. N. Singh, P. Maiti, and J. K. Pandit, "Polymeric nanoparticulate system: a potential approach for ocular drug delivery," *Journal of Controlled Release*, vol. 136, no. 1, pp. 2–13, 2009.

[110] G. Savini, P. Prabhawasat, T. Kojima et al., "The challenge of dry eye diagnosis," *Clinical Ophthalmoogy*, vol. 2, no. 1, pp. 31–55, 2008.

[111] A. J. Bron, A. Tomlinson, G. N. Foulks et al., "Rethinking dry eye disease: a perspective on clinical implications," *Ocular Surface*, vol. 12, supplement, no. 2, pp. S1–S31, 2014.

[112] A. Peral, C. O. Domínguez-Godínez, G. Carracedo, and J. Pintor, "Therapeutic targets in dry eye syndrome," *Drug News & Perspectives*, vol. 21, no. 3, pp. 166–176, 2008.

[113] A. Y. Matsumoto, Y. Ohashi, H. Watanabe, and K. Tsubota, "Efficacy and safety of diquafosol ophthalmic solution in patients with dry eye syndrome: a Japanese phase 2 clinical trial," *Ophthalmology*, vol. 119, no. 10, pp. 1954–1960, 2012.

[114] J. E. Jumblatt and M. M. Jumblatt, "Regulation of ocular mucin secretion by P2Y2 nucleotide receptors in rabbit and human conjunctiva," *Experimental Eye Research*, vol. 67, no. 3, pp. 341–346, 1998.

[115] M. Nakamura, T. Imanaka, and A. Sakamoto, "Diquafosol ophthalmic solution for dry eye treatment," *Advances in Therapy*, vol. 29, no. 7, pp. 579–589, 2012.

[116] Otsuka Pharmaceutical Company, Acucela and Otsuka pharmaceutical announce the initiation of a phase 3 clinical trial to evaluate rebamipide ophthalmic suspension in patients with dry eye syndrome, http://www.otsuka.co.jp/en/release/2012/0719_02.html.

[117] S. Kinoshita, K. Oshiden, S. Awamura, H. Suzuki, N. Nakamichi, and N. Yokoi, "A randomized, multicenter phase 3 study comparing 2% rebamipide (OPC-12759) with 0.1% sodium hyaluronate in the treatment of dry eye," *Ophthalmology*, vol. 120, no. 6, pp. 1158–1165, 2013.

[118] "Acucela and Otsuka Pharmaceutical Announce the Initiation of a Phase 3 Clinical Trial to Evaluate Rebamipide Ophthalmic Suspension in Patients with Dry Eye Syndrome," http://www.acucela.com/Read-About-Us/Press-Releases.

[119] A. Dota, Y. Takaoka-Shichijo, and M. Nakamura, "Gefarnate stimulates mucin-like glycoprotein secretion in conjunctival tissue and ameliorates corneal epithelial damage in animal dry-eye models," *Clinical Ophthalmology*, vol. 7, pp. 211–217, 2013.

[120] B. Colligris and J. Pintor, "Dry eye disease compounds currently under evaluation in clinical trials," *Anales de la Real Academia Nacional de Farmacia*, vol. 80, no. 1, pp. 151–178, 2014.

[121] C. Semba, "Safety study of lifitegrast to treat dry eye (SONATA)," Clinical Trials Identifier: NCT01636206, https://clinicaltrials.gov/ct2/show/NCT01636206.

[122] M. Ono, E. Takamura, K. Shinozaki et al., "Therapeutic effect of cevimeline on dry eye in patients with Sjögren's syndrome: a randomized, double-blind clinical study," *The American Journal of Ophthalmology*, vol. 138, no. 1, pp. 6–17, 2004.

[123] I. Avni, H. J. Garzozi, I. S. Barequet et al., "Treatment of dry eye syndrome with orally administered CF101: data from a phase 2 clinical trial," *Ophthalmology*, vol. 117, no. 7, pp. 1287–1293, 2010.

[124] P. M. Karpecki, "Why dry eye trials often fail," *Review of Optometry*, vol. 150, no. 1, p. 50, 2013.

[125] H. Lin and S. C. Yiu, "Dry eye disease: a review of diagnostic approaches and treatments," *Saudi Journal of Ophthalmology*, vol. 28, no. 3, pp. 173–181, 2014.

[126] B. Colligris, H. A. Alkozi, and J. Pintor, "Recent developments on dry eye disease treatment compounds," *Saudi Journal of Ophthalmology*, vol. 28, no. 1, pp. 19–30, 2014.