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REVIEW



Toward patient-centered, phenotype-driven care for dry eye disease: a review of advances in artificial tear formulation

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ABSTRACT

Introduction: The tear film is part of the ocular surface and forms a highly complex interface between the corneal and conjunctival epithelium and the environment. As a key refracting surface, it is essential in maintaining clear vision, as well as supporting the health and integrity of the entire ocular surface.

Areas covered: This review describes the structure and stability of the tear film, a complex, dynamic, trilayered combination of mucins, aqueous components, and lipids. It discusses how loss of this stability leads to inflammation, ocular surface damage, eye dryness, and discomfort that can significantly impair vision and quality of life. Finally, it summarizes the current and future state of dry eye disease (DED) management. Over-the-counter artificial tear eye drops remain a therapeutic cornerstone and represent part of first-line therapy for most patients. Artificial tears are typically multi-component formulations and differ in their active ingredients, preservative content, electrolytes, vehicle formulation, and concentration and consistency.

Expert opinion: A nuanced, phenotype-driven approach to artificial tear selection, rather than viewing tear substitutes as interchangeable therapies, is necessary. Clinicians should aim to align formulation characteristics with disease etiology, symptom profile, lifestyle factors, and patient preferences to achieve more specific targeted disease management.

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1. Introduction

The tear film is part of the ocular surface and forms a complex, multilayered interface between the corneal and conjunctival epithelium and the environment [1,2]. It plays a key role in the optical properties of the cornea, and in maintaining the health, healing, and integrity of the ocular surface, by clearing debris, preventing infection, and maintaining ocular comfort [1–3]. Loss of tear film homeostasis underpins the pathology of dry eye disease (DED) and leads to a self-perpetuating cycle of tear film instability, reduced tear quality and hyperosmolarity, ocular surface inflammation and injury, and neurosensory abnormalities [4–8].

DED is one of the most common reasons for visiting an eye care professional [4]. Estimated global prevalence ranges from 5% to 50%, with inconsistent reporting and/or diagnostic criteria contributing to the variation, and exacerbated by clinical ambiguity and delayed or missed diagnoses [6,9–12]. DED

is estimated to affect over 16 million adults in the United States, with prevalence estimates ranging from 5% to 15%; European prevalence is estimated at 10–30%, and 20–52% in Southeast Asia (20% in Asia overall) [12–15]. Across regions, DED incidence increases with age, is more common in women than men, and recent studies suggest a higher than expected impact in younger people driven by increased screentime, the COVID-19 pandemic, diet, and lifestyle changes [6,9,10,16–18]. In children (<18 years of age), the prevalence of DED ranges from 6% to 24%, including one study in Mexico indicating a prevalence of 65% [10,17]; a separate study in 21–30-year-old young adults reported that more than 99% experienced DED symptoms [16].

Regardless of age, patients can experience a range of symptoms, including itching, burning, and stinging, leading to chronic discomfort and visual disturbances, which may progress to vision impairment and can significantly impact

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Article highlights

- The tear film structure is a complex, dynamic trilayer forming an essential barrier against pathogens and particulates; disruptions to the tear film in dry eye disease (DED) compromise these functions.
- Artificial tears remain the most common primary therapy for DED, but artificial tears encompass a wide range of formulations with different effects on pathophysiology.
- The efficacy of artificial tears is affected more by the overall composition of the formulation than the inclusion of individual components and ingredients.
- Because DED etiologies differ, identifying patient-specific drivers of DED enables personalized selection of artificial tear formulations most likely to address a patient's DED signs and symptoms.
- Support for a patient with DED should include more than selection of artificial tears alone, with dietary, environmental and lifestyle factors also essential to consider.

their daily lives and well-being [5–8,19]. DED is associated with reduced physical and mental health, including increased risk of depression, with impact increasing with symptom severity, and patients with moderate-to-severe DED may experience a quality-of-life impact similar to that observed in patients with moderate-to-severe angina [20,21].

Over-the-counter artificial tear formulations, designed to replenish and stabilize the tear film, offer accessible symptom relief and remain one of the mainstays of DED management [22–25]. The recent update from the Tear Film & Ocular Surface Society Dry Eye Workshop (TFOS DEWS III) represents the third iteration of an evidence-based expert consensus on DED management, emphasizing early use of artificial tears and a patient-centered, stepwise approach to care [22].

In this review, we summarize the structure and complexity of the tear film, its role in ocular surface lubrication, and the consequences of its disruption in DED pathophysiology. With a focus on over-the-counter rather than prescription products, we review recent evidence on approved artificial tears ingredients, and their role in artificial tear drop formulations in the

context of the TFOS DEWS III report and current evidence-based recommendations for DED management.

2. The tear film structure

Current evidence indicates that the tear film is broadly arranged as a dynamic trilayer consisting of a mucin gradient within an aqueous layer, and a thin lipid layer surface (Figure 1) [2,26–28]. A stable, intact tear film is essential for maintaining a barrier against pathogens and environmental particulates, enabling ocular lubrication, and providing a smooth, transparent refractive surface [1–4]. Disruptions in tear film dynamics and stability can compromise these functions, resulting in optical aberrations and visual disturbances [1–4,26].

The aqueous layer is primarily produced by the main lacrimal glands, contains tightly controlled levels of functionally important electrolytes, nutrients, and proteins, and includes a gradient of secreted mucin glycoproteins produced by goblet cells [1–3]. Secreted mucins enhance tear film stability and ability to spread over the corneal epithelium to maintain its barrier function, by forming a cross-linked gel matrix within the tear film aqueous layer that protects from eyelid friction; the mucin matrix supports persistence of secreted tear components, and has been found to clear pathogens and debris [2,4,26,28]. Ocular membrane-associated mucins anchor to the hydrophobic plasma membrane of apical epithelial cells to form a hydrophilic glycocalyx that maintains wetness, lubricates blink dynamics, and stabilizes the tear film (Figure 1) [26,28].

The tear film lipid layer includes both polar and nonpolar lipids, primarily secreted from the meibomian glands, and contributes to a smooth and refractive optical surface, maintains effective tear film distribution during blink cycles, and preserves the aqueous layer by reducing evaporation (Figure 1) [2,26,29]. The polar lipids, including omega-acyl hydroxy fatty acids and phospholipids, are arranged to

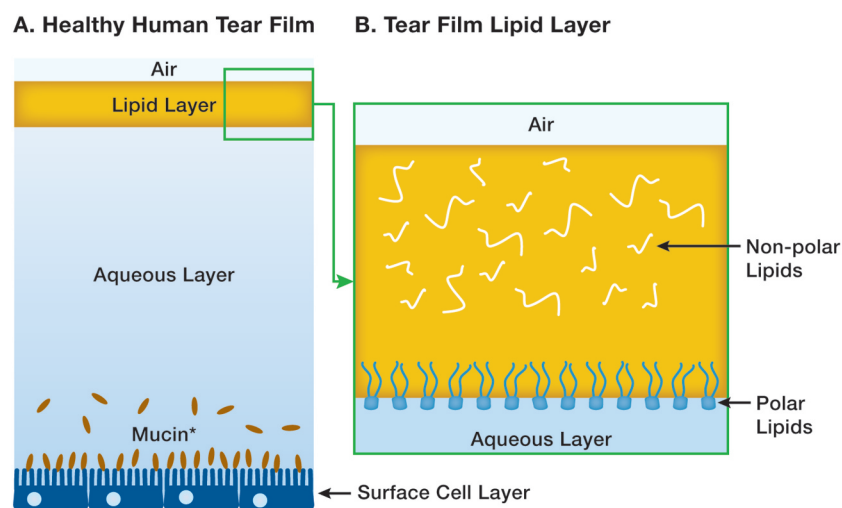


Figure 1. Structure of the tear film.

Developed based on Labetoulle et al. 2022 [23]. <https://creativecommons.org/licenses/by/4.0/>.

*Mucin has historically described as a layer.

interface with the aqueous-mucin layer, where they alter local surface tension and contribute to a smooth optical surface for light refraction. The nonpolar lipids (including mono-, di-, and triglycerides, cholesterol, cholesterol esters, and wax esters) form a thicker layer that interfaces with the air, acting as a barrier to decelerate water evaporation [2,26,29]. The lipid layer reduces tear film surface tension and contributes to its interfacial viscoelasticity, which stabilizes the tear film and prevents tear breakup, reducing friction between the eyelid and ocular surface, and avoiding discomfort, inflammation, and tissue injury [2,3,26,29].

Natural basal tears contain more than 1,500 proteins, including cytokines/chemokines, growth factors, immunoglobulins, and neuropeptides, many of which have anti-inflammatory or antimicrobial properties; additional tear components include fibronectin and other molecules essential for maintaining epithelial barrier function [1–3]. Nutrients, including vitamins A and E, contribute to corneal health, while essential electrolytes (sodium, calcium, potassium, and magnesium cations, and chloride, phosphate, and bicarbonate anions) help maintain osmolarity and function [2,22,26,27].

Tear film changes can indicate the presence of ocular disorders, such as meibomian gland dysfunction (MGD), and/or chronic systemic inflammatory conditions seen in individuals with autoimmune disorders, diabetes, collagen vascular diseases, obesity, overweight, or Sjögren's syndrome [2,27,30,31]. An unstable tear film is characterized by hallmarks of tear dysfunction, including altered tear composition or osmolarity, or disrupted lipid spreading and focal thinning during blink cycles, and is associated with increased tear evaporation and hyperosmolarity, which drives a vicious cycle of further destabilization [1,2,4,26]. Tear film hyperosmolarity leads to inflammation and injury, by triggering stress-induced responses and apoptosis in corneal and conjunctival epithelial cells, and can contribute to DED-associated pain alongside neurosensory factors [4,7,22,23].

3. The multifactorial origins and impacts of DED

Disrupted tear film homeostasis characterizes DED, which is broadly classified as either evaporative or aqueous deficient, with many patients having a combination of both [4–7,32]. The resulting symptoms include redness, irritation, burning, eye dryness, pain, blurred vision, fluctuating vision, photophobia, eye fatigue, and twitching, all of which can be chronic and impact quality of life and well-being [4–7,32]. The persistent, daily impact of symptoms can negatively affect patients' perception of their physical and mental well-being, is associated with anxiety and depression, and can also have a considerable economic impact related to lost productivity [21].

DED is a heterogeneous inflammatory condition, with diverse triggers of tear film dysfunction that may act concurrently and evolve over time with patient age and life stage [4–6,22,31]. Patient lifestyle plays a critical role in the development and severity of DED symptoms, with the TFOS DEWS III report identifying excessive digital device use as a major and growing contributor related to altered blink dynamics

[4,22]. Other lifestyle behaviors can exacerbate or trigger DED symptoms, including poor sleep, cosmetic and tobacco use, and consumption of highly processed foods low in essential nutrients such as omega-3 fatty acids [22]. TFOS DEWS III also summarizes recent evidence from the TFOS Lifestyle Report demonstrating the direct and indirect influence of environmental factors on the tear film and ocular surface [22,33]. These include external climate factors (sunlight, temperature, humidity, and wind speed), exposure to pollutants and allergens, and internal environmental conditions, such as recycled air, which are associated with sick building syndrome [22,33].

Individual patient characteristics, such as preexisting ocular conditions, systemic inflammatory diseases, medication use, age, gender, body mass index, and overall well-being, also play significant roles in DED progression and symptom severity [4–6,22,30,34]. There is a recognized association between obesity and altered tear quality, with a recent review summarizing the impact of inflammation in individuals with overweight or obesity on their DED symptom severity and disrupted tear composition [30].

4. Non-prescription approaches to DED management

Improvements in diet and physical activity can positively affect inflammation and tear quality in healthy individuals, smokers, and those with elevated body mass index, emphasizing the importance of patient-specific, modifiable factors as part of a whole-person approach to managing DED [30,35–37]. As a first-line approach, educating and supporting patients in adopting sustainable changes to improve overall wellness can contribute to long-term DED symptom reduction [4,6,22,30]. Education on lifestyle and person-specific environmental changes can include improving sleep quality, optimizing nutrition and physical activity, ensuring adequate hydration, limiting alcohol intake, and stopping smoking [4,6,22,30].

Artificial tears, warm compresses, eyelid hygiene, and nutraceuticals all remain central non-prescription options to long-term DED management [4,22]. The primary goals of artificial tears are to restore tear film homeostasis, improve the ocular surface microenvironment, and disrupt the inflammatory cycle driving DED progression, with recent findings suggesting that their use can complement and enhance the benefits of other lifestyle changes [22–25,38].

5. Artificial tear formulations

Artificial tears for DED are formulated to address tear insufficiency by replenishing, stabilizing, and/or enhancing the tear film by mimicking key tear characteristics and/or replenishing natural tear components [22–24]. They are often readily available as over-the-counter products that differ in ingredients, use of preservatives, and dispensing bottle design; any of these characteristics may influence their suitability for different DED etiologies, and alignment with patient and clinician preferences [24,25].

Table 1. Summary of key types of artificial tear components and their role in restoring the tear film in DED.

Component category	Function	Examples	References
Polymers	Large macromolecules composed of repeating subunits. Broad range of functions: • Viscosity enhancers to improve residence time on the eye and/or improve drop rheology to mimic natural tears and provide protection during blink cycles • Replenishers/stabilizers of the aqueous tear film layer • Compounds with mucoadhesive and mucomimetic properties • Wound-healing and anti-inflammatory properties	Naturally existing polymers • Hyaluronic acid • Gellan gum • Xanthan gum • Chitosan Semisynthetic polymers (cellulose derivatives) • Hydroxypropyl methylcellulose • Carboxymethylcellulose Synthetic polymers • Carbomers • Polyethylene glycol • Polyvinyl pyrrolidone • Polyvinyl alcohols	[23,41]
Osmoprotectants	Small organic molecules that act to prevent DED-induced cell apoptosis by helping cells to withstand osmotic stress and protect from tear hyperosmolarity. Includes demulcents, such as glycerol, that can soothe inflammation.	• L-carnitine • Erythritol • Trehalose • Betaine • Sorbitol • Ectoine • Glycerol (glycerin)	[23,42]
Lipids and surfactants	Supplement the tear film lipid layer, particularly in evaporative DED, contribute to the smooth corneal surface for improved vision quality, and prevent aqueous evaporation to maintain correct tear osmolarity. Often formulated as liposomes, oil nano-droplets, or oil-in-water emulsions.	• Phospholipids (phosphatidylcholine and hydrogenated phospholipid) • Medium-chain triglycerides • Omega-3 fatty acids • Mineral oil • Castor oil • Coconut oil • Lecithin • Paraffin	[23,24,29]
Antioxidants and vitamins	Topical application of vitamins primarily has an antioxidant role to address DED-associated oxidative stress of ocular surface cells, which can lead to tissue damage.	• Vitamin A, C, E, B12, and • Co-enzyme q10 • Lipoic acid	[22,23,26,43,44], [45–47]

(Continued)

Table 1. (Continued).

Component category	Function	Examples	References
Preservatives*	Protect against bacterial contamination and eye infections by disrupting bacterial membranes and biochemical processes, including protein synthesis, or chelating critical components.	Quaternary ammonium compounds • Benzalkonium chloride (found in around 70% of eye drop formulations) • Polyquaternium 1 • Cetrimide Alcohols • Chlorobutanol 'Transient' or 'vanishing' preservatives • Stabilized oxychloro complex or sodium chlorite • Sodium perborate Other compounds • Chlorhexidine • Sorbic acid • Potassium sorbate • Boric acid • Biguanides • SofZia (boric acid, zinc, sorbitol, and propylene glycol) • Sodium perborate • EDTA	[22,23,48,49]
Electrolytes	Electrolytes to restore the salt composition of the tear film aqueous layer.	• Sodium • Potassium • Chloride • Magnesium • Calcium	[22,23,44,45,50], [46,47]
Others	• Buffers to maintain tear film pH (7.4), and regulate tonicity • Herbal additives, with potential antioxidant, anti-inflammatory, protective, or restorative effects, although clinical evidence is lacking • Amino acids with some evidence for a role in the cornea and rationale for use in topical dry eye drop formulations	• pH buffers (bicarbonate, phosphate, citrate, and borate) • Eyebright and fucoidan (anti-inflammatory and protective) • Aloe vera (anti-inflammatory and healing) • Glycine, proline, and lysine	[23,24,26,51,52]

*Standards for preservative effectiveness are specified for the relevant regions in the European Pharmacopoeia, including -A and -B criteria for antimicrobial activity, and in the United States Pharmacopoeia and the Japanese Pharmacopoeia [53–55].
DED, dry eye disease; EDTA, ethylenediaminetetraacetic acid.

Most available artificial tear formulations are aqueous-based, with components added according to their defined activity on DED pathophysiology [22–24,39,40]. The formulations of artificial tears also aim to achieve longer ocular residence, enhanced comfort, reduced dosing frequency, and targeted DED management, including anti-inflammatory effects in some cases, to enhance the level and longevity of relief [24,34]. Table 1 summarizes the roles for key types of artificial tear ingredients.

Artificial tears can be classified according to their interaction with the eye: wetting agents lubricate the ocular surface with a limited residence time, multiple-action tear substitutes can improve tear film quality and quantity without interacting with the ocular surface, and other artificial tear formulations contain ingredients that interact with and influence the ocular surface to address DED symptoms [23,56]. Artificial tears differ in their physical properties and fluid behavior (rheological characteristics), affecting how they interact with patients’ individual tear properties or other medications they use for co-existing ocular conditions; this has implications for treatment decisions on how topical ophthalmological agents are

combined to ensure product efficacy and avoid mechanistic redundancy [57]. Figure 2 illustrates how various artificial tears components can act at different levels of the tear film.

Technological development and innovations in artificial tear ingredients have enabled combinations into novel formulations that incorporate bioengineered elements such as hydrogels, multi-polymer systems, and lipid-based nanocarriers (Table 2) [23,24,26,34]. Table 3 summarizes key features of artificial tear formulations.

The TFOS DEWS III report and recent reviews highlight that the efficacy of artificial tears depends on their delivery system and the overall formulation, including the relative composition of and interactions between ingredients, rather than individual components [22–24]. Most artificial tear ingredients exert mechanical and/or biological actions on DED pathophysiology and/or overall ocular health, and are included in formulations based on their properties that contribute to lubrication, retention, and/or hydration [22–24]. This means that, while some ingredients may be considered ‘active’ based on the US Food and Drug Administration monograph in which they are listed, ‘inactive’ components or excipients in the formulation that are

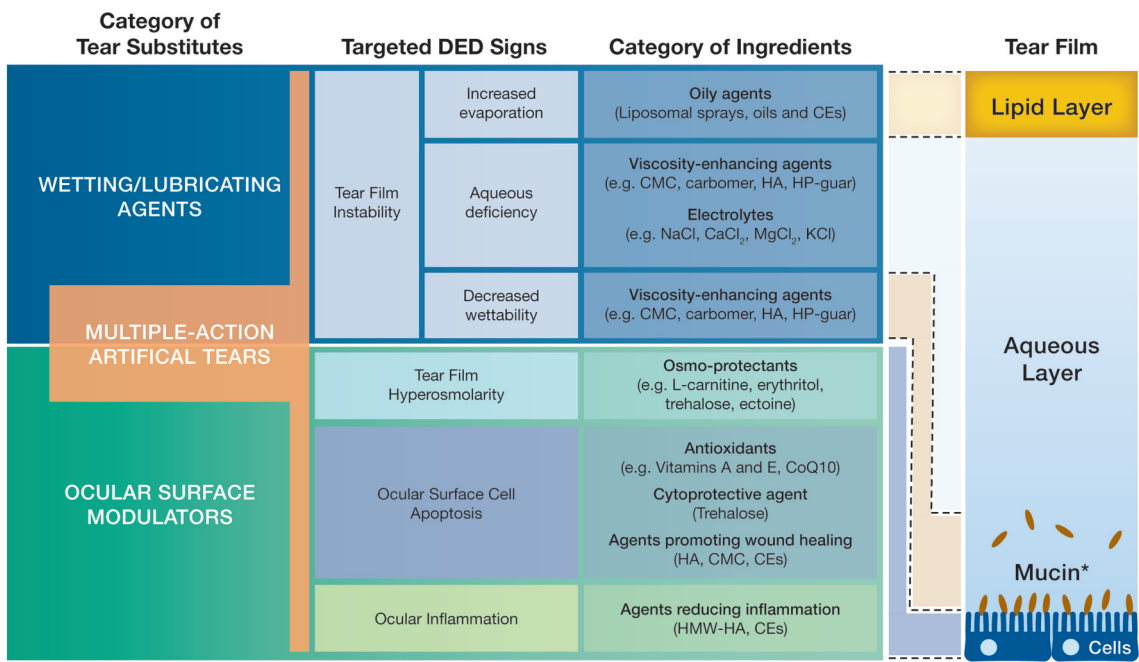


Figure 2. Interaction and impact of artificial tear ingredients on the tear film. Developed based on Labetoulle et al 2022 [23]. <https://creativecommons.org/licenses/by/4.0/>.

*Mucin has historically described as a layer.
Abbreviations: CE, cationic emulsion; CMC, carboxymethylcellulose; DED, dry eye disease; HA, hyaluronic acid; HMW, high molecular weight; HP-guar, hydroxypropyl guar.

Table 2. Summary of artificial tear formulations.

- Polymer-based drops: Enhance viscosity and lubrication, prolonging ocular surface residence time. Common ingredients include hyaluronic acid, carboxymethylcellulose, hydroxypropyl methylcellulose, and hydroxypropyl guar.
- Osmoprotectant-containing drops: Ingredients include trehalose, betaine, and L-carnitine to protect ocular cells from hyperosmolarity-related stress.
- Lipid-based drops: Target the tear film lipid layer, particularly beneficial in evaporative dry eye caused by meibomian gland dysfunction. May include nanoemulsions or liposomal sprays.
- Combination formulations: Blend polymers, lipids, and osmoprotectants for enhanced efficacy, supporting healing, lubrication, and comfort. Preservative-free options and those integrating vitamins and antioxidants are among recent advances.

Table 3. Key features of artificial tear formulations.

Ingredient(s)	Formulation/ ingredient combinations	Key properties	Clinical effects/study findings	References
Polymer combinations	CMC, HPMC, PEG, HA, propylene glycol, and xanthan gum	Hydrate, lubricate, retain moisture, anti-inflammatory, and promote healing	Accelerated corneal healing and improved conjunctival health, increased goblet cell density and epithelial repair, improved DED signs/symptoms and tear film stability (reduced corneal staining and redness, enhanced tear film stability/TBUT, and reduced osmolarity), and extended retention. Dual-polymer drops outperform single-polymer, better OSDI scores, increased goblet cell density, and reduced corneal staining. 0.2% xanthan gum outperformed CMC, similar efficacy to PEG/propylene glycol, symptom relief after 1 month. High molecular weight HA has demonstrated better efficacy than low molecular weight in animal models of dry eye. Artificial tears containing 0.10% and 0.15% HA have shown similar effects to IPL therapy for DED.	[22,39,58]
Osmoprotectant-containing	Trehalose Ectoine Fucoidans	Stabilizes proteins/ membranes, limits oxidative damage, and enhances autophagy Bacterial extremolyte. Shields proteins/osmo-sensitive macromolecules and cell membranes by binding water to form a protective hydro-layer. Antioxidant, immunomodulatory, and anti-inflammatory.	Restores goblet cells, reduces inflammation, and improves comfort, TBUT, corneal staining. Highly favorable safety profile; effective in peri-/post-menopausal women, and also post-cataract surgery. Reduces DED symptoms; increases TBUT, protects cornea, restores regularity, and reduces inflammation. In vitro protection of human corneal epithelial cells from hyperosmotic stress; algae species-specific improvement in tear secretion in vivo.	[22–24,42,59–61]
Lipid-based	Lipid-based emulsions, phospholipid nanoemulsions, and combinations with HP-guar	Improves tear film lipid layer, preventing aqueous evaporation and improving hydration; phospholipids may migrate within the tear film to replenishes the lipid layer and reduce friction during blinking; improves surface retention of other ingredients.	Symptom relief, reduced lid wiper epitheliopathy, and improved TBUT and comfort. Mineral oil/phosphatidylglycerol nanoemulsion can stabilize the tear film for up to 8 hours and improve burning/stinging symptoms, and increase contact lens comfort. Castor oil/CMC combination can reduce feelings of grittiness. Omega-3–containing drops can significantly increase lipid layer thickness. Phospholipid-containing drops can improve TBUT and significantly increase lipid layer grade. HP-guar phospholipid nanoemulsions improve TBUT and comfort for up to 8 hours, with reductions in dryness, burning, and stinging.	[26,29,40]
Antioxidant- and vitamin-containing	Alpha-lipoic acid, selenium, vitamin E, ubiquinol, ascorbate, and glutathione Vitamin A, beta-carotene, B12, and Vitamin C	Antioxidant and anti-inflammatory properties; support tear stability as part of combinations with lipids and viscosity-enhancing agents.	Limited clinical data. Improved corneal staining and TBUT, and boosted antioxidant enzyme levels. Topical alpha-lipoic acid improved outcomes vs hydroxypropyl methylcellulose alone; selenium supplementation beneficial. Beta-carotene delivery can be enhanced with HA, leading to reduced oxidative stress.	[22–24,58,62]

Abbreviations: CMC, carboxymethylcellulose; DED, dry eye disease; HA, hyaluronic acid; HP-guar, hydroxypropyl guar; HPMC, hydroxypropyl methylcellulose; IPL, intense pulsed light; OSDI, Ocular Surface Disease Index; PEG, polyethylene glycol; TBUT, tear breakup time.

approved for in-human use may also have biological activity, and therefore contribute to symptomatic relief [22,23,63,64].

5.1. Polymer-based formulations

Polymers in artificial tear formulations can function as viscosity-enhancing agents, lubricants, or demulcents [22–24]. By increasing viscosity through mucoadhesive properties, polymers prolong the residence time of artificial tears on the ocular surface to provide sustained relief relative to baseline DED severity [22–24].

Carboxymethylcellulose (CMC) is the most commonly used viscosity-enhancing agent in artificial tear formulations and, along with hydroxypropyl methylcellulose (HPMC) it is plant-derived, and has negatively charged subunits that enhance binding to the surface of corneal epithelial cells [23,24]. Hydroxypropyl guar (HP-guar) is a high molecular weight, viscosity-enhancing polymer that forms a gel in solution, and when combined with other lubricants, forms a protective hydrated scaffold on the ocular surface [22]. DED artificial tear formulations combining HP-guar with polyethylene glycols (PEG) or propylene glycol (PG) have a favorable safety profile and can also improve tear osmolarity [24].

Hyaluronic acid (HA) is a naturally occurring humectant polymer, rich in hydroxyl groups, that attracts and retains water molecules, improving eye drop viscosity and elasticity, and thickening and stabilizing the tear film [23,24,39]. With 30 years of clinical use, extensive data have shown HA to be effective in improving symptoms and objective measures of DED, and it is frequently used as an active comparator in clinical studies, although the optimal drop frequency and formulation for HA-containing artificial tears have not been clinically established [23,24,39]. HA-containing drops recently demonstrated similar effects to intense pulsed light therapy for the treatment of DED [58], and a synthetic soft hydrogel of cross-linked HA recently demonstrated high biocompatibility and therapeutic potential as a long-acting DED treatment [65,66]. HA is also under investigation in a novel formulation to deliver the antioxidant beta-carotene to the eye as part of a nano-supramolecular delivery system consisting of polycyclodextrin and HA, with initial data indicating improved residence time and corneal penetrance of beta-carotene [62].

The physical properties of HA vary depending upon its molecular weight: high molecular weight HA has established anti-inflammatory, immunosuppressive, and antiangiogenic activity, including pro-inflammatory cytokine and chemokine suppression, whereas lower molecular weight HA may have pro-inflammatory effects [24,39]. A recent small study demonstrated that an artificial tears formulation containing 2.5 MDa HA exhibited rheological behavior more aligned with that of the tear film, versus one containing 1.3 MDa HA, although both drops were associated with significant reductions in DED symptoms [67]. Very-low molecular weight and high molecular weight HA (800–15,000 Da and >1 MDa, respectively) both demonstrated minimal toxicity to corneal keratinocytes in vitro, highlighting the importance of precise formulations in optimizing outcomes with artificial tears [68].

Other naturally occurring polymers, such as xanthan gum, a bacterially derived polysaccharide, and tamarind plant seed polysaccharide, contribute mucoadhesive properties to mimic natural tears [22,24].

Multi-polymer combinations can optimize drop rheology to enhance ocular surface protection and improve tear film stability, and can also contribute to reduced inflammation and epithelial healing [22–24,69]. For example, HA has demonstrated increased ocular residence time compared with HPMC, increasing HA concentration in HP-guar-based drops improves drop retention, and recent data found that the HP-guar/HA combination is more effective at stabilizing the tear film than HA alone [70,71].

Synthetic polymers can also act as viscosity-enhancing agents and include carbomer (polyacrylic acid), PEG and PE, polyvinyl alcohol, and povidone (polyvinylpyrrolidone) [22,23]. Like HP-guar, carbomer increases viscosity at ocular surface pH and forms a gel when mixed with tears [23]. Data comparing synthetic and natural polymers are inconclusive, with some suggesting HA could be more effective than carbomers and others finding no difference [24]. Novel polymers are contributing to the complex landscape of artificial tear ingredients, including biocompatible, highly water-attracting polymers designed to mimic the cell membrane, which demonstrated efficacy in a small study of contact lens wearers with DED in combination with HPMC [72].

5.2. Osmoprotectants

Maintaining tear film osmotic balance is essential to prevent corneal injury, and the addition of osmoprotectants to artificial tears supports epithelial cell stress responses and survival under DED-associated hyperosmotic conditions [22–25]. Common osmoprotectants, including trehalose and glycerol (glycerin), are listed in Table 1, and some polymers, such as xanthan gum, have also shown osmoprotective properties [22,23].

Trehalose is a naturally occurring disaccharide that acts as a bioprotectant by forming a stabilizing, protective gel layer around proteins, cell membranes, and cell components, including enzymes [73,74]. The protective properties were demonstrated in experimental models of wound healing, tissue injury, and UV damage, with outcomes including protection from oxidative stress, inflammation, and dehydration [73]. In the context of DED, trehalose demonstrated efficacy in both in vitro and in vivo models, preventing cell membrane damage that would normally occur in dry eye environments, while also providing well-studied safety and efficacy in DED clinical trials [24,59,73,75]. As for polymer combinations, combining osmoprotectants demonstrated utility in protecting cells from osmotic stress in vitro, and most studies of trehalose have been in combination formulations, most often HA, to enhance its effects [23,24,59].

The polysaccharide erythritol and amino acid L-carnitine are both naturally present in the tear film and are common osmoprotectants in artificial tear formulations [74]. Alone or as combinations, erythritol and L-carnitine can protect corneal epithelial cells from hyperosmolar stress, decrease

inflammatory markers, reduce tear osmolarity, and provide symptomatic relief of DED [23,74].

Glycerol is a small, three-carbon polyol, with hygroscopic and humectant properties that allow it to attract and retain moisture from the environment, as well as hydrate and protect ocular surface cells from dehydration and environmental stress [60]. Glycerol also increases the viscosity of artificial tear formulations to improve tear film stability, and, although less extensively studied, has anti-irritant and anti-inflammatory properties, especially as part of multi-component formulations with other polymers and/or lipids or surfactants, which can also extend the duration of its effects [23,24,60]. Its size means glycerol may be retained for less time than larger molecules, such as L-carnitine, and may therefore be most useful in multi-ingredient formulations containing osmoprotectants that act with different kinetics [76].

The bacterial extremolyte ectoine is a derivative of a naturally occurring amino acid enables cell survival in extreme-stress environments by protecting cells against temperature, UV radiation, or salt [61]. Based on its chemical structure and dual charge, ectoine exhibits strong water-binding and kosmotrope properties in aqueous solutions: it can organize and enhance water molecule structure and stability by enhancing the properties of local hydrogen bonds to form protective and stabilizing water shells around macromolecules and cell membranes [42,77]. The organizational properties of ectoine also have implications for the tear film lipid layer, where it can affect polar lipid packing and fluidity [78]. Ectoine has been well-studied in in vivo DED models and demonstrated normalization of inflammatory markers and significant reduction in corneal cell damage [79–81]. Ectoine has also demonstrated efficacy in patients with DED when combined with HA and CMC by improving tear film stability, and signs and symptoms [82,83].

Fucoidans are sulfated heteropolysaccharides found in the extracellular matrix and cell walls of various species of brown algae, with antioxidant, immunomodulatory, and anti-inflammatory properties [84–86]. Oral administration in vivo indicated an algae species-specific impact for fucoidan on tear secretion and corneal injury in rats [84,86], as well as in vitro protection from hyperosmotic stress in human corneal epithelial cells [86]. Clinical trial data evaluating the efficacy and safety of fucoidan in patients with DED are currently lacking, and research evaluating an additional role as a drug-carrying molecule is ongoing [85].

To complement the effects of osmoprotectants, artificial tears also typically include electrolytes, such as sodium, potassium, chloride, magnesium, and calcium, which provide ions essential to maintain an osmolarity supportive of healthy corneal epithelial cells, and reduce inflammatory responses [22,23,50].

5.3. Lipid-based formulations

Dysfunction of the polar and nonpolar lipids of the tear film lipid layer is commonly associated with evaporative DED, which accounts for 60–75% of patients with DED [29,87]. Thinning or insufficiency of the lipid bilayer often results

from MGD and causes the tears to evaporate quickly, leading to tear film instability [29,87]. Oily/lipid-based agents and surfactants are a category of artificial tear ingredients that aim to supplement and stabilize the tear film lipid layer, support its restoration, and also maintain a smooth optical surface to enhance refraction and quality of vision [22–24,29,87].

Lipid-based artificial tears incorporate ingredients such as mineral oil, castor oil, phospholipids, omega-3 fatty acids, and medium-chain triglycerides [22–24,29,87]. Clinical data highlight sustained tear film stability and improved DED symptoms with mineral oil-containing artificial tears, increased lipid layer thickness with omega-3-containing drops, improved tear film spread and lipid layer quality with drops containing phospholipids, and improved symptoms and ocular health with a carbomer-based drop containing a CMC/medium-chain triglyceride combination [29]. However, recent findings suggest that available formulations do not achieve robust reductions in tear evaporation and, depending on the viscosity of the formulation, can cause temporary blurred vision, stinging, or foreign body sensation immediately after instillation [87,88]. In addition, appropriate lipid-based artificial tear formulations have been associated with greater subjective symptom relief and patient satisfaction in contact lens wearers [22]; however, some oil-based ingredients may deposit on the lens material [89].

Delivery of lipid-based formulations can include nanoemulsion eye drops and vesicle-based liposomal sprays, with the lipid component frequently combined with additional agents to enhance product performance [4,5,22–24,29,87]. These include electrolytes to regulate homeostasis, synthetic and natural polymers (including CMC, polypropylene glycol, HP-guar, and HA) to enhance long-term relief and tear stability, and ectoine to improve ocular retention [22,24,90].

Emulsions are formed by combining oil nano-droplets, polymers, and surfactants in an aqueous base to generate a biocompatible formulation with structural similarities to the three-layer tear film that has anti-inflammatory properties and distinct rheological behavior [23,40,65]. Innovations in new-generation emulsions include the addition of ingredients that impart a cationic (positive) charge to the oil droplets, which improves interaction between the positively charged droplets and the negatively charged tear film mucin layer, and supports tear film stability [23,40]. Findings from pilot and larger DED clinical studies of emulsions demonstrate increased tear volume and stability, and improvement in both objective and subjective DED outcomes; their use is also associated with improved recovery from corneal damage after refractive surgery [40].

Liposomes are made of phospholipids that form a spherical vesicle of one or more concentric lipid bilayers around aqueous compartments to encapsulate and/or integrate active ingredients [23,65,91]. Liposomes mimic the cell membrane and have a positive surface charge that supports interaction with the tear film mucin layer, and this interaction can be enhanced by coating liposomes with adhesive polymers or HA, or by combining with polysaccharides [65,91]. Clinical studies have demonstrated improved tear film stability and lipid layer thickness with liposomal sprays, as well as increased

patient comfort [23,65,91]. Available data suggest possible dose-dependent efficacy at higher liposomal concentration in artificial tears [24].

5.4. Antioxidant-containing formulations

Antioxidants and certain vitamins are included in some artificial tear formulations as part of a wider approach to address the oxidative stress-induced tissue damage and inflammation implicated in DED pathology [4,5,22,23].

Vitamin A improves mucin secretion, goblet cell density, and wound healing in ocular surface models, and has demonstrated clinical efficacy in reducing DED symptoms, including in combination with vitamin D and omega-3, although is historically unstable in liquid formulations [23,43].

Dexpanthenol is a provitamin and analog of vitamin B5 (pantothenic acid) that can promote epithelial healing and has demonstrated in vitro efficacy in corneal and conjunctival epithelial cells [43]. Vitamin B12 has antioxidant, anti-inflammatory, and nerve and tissue regenerative properties [92], and in vitro studies have demonstrated that the protective effects of HA drops may be enhanced by the addition of vitamin B12 [44]. B12-containing artificial tears have also demonstrated benefits in specific groups of patients with DED, including improved signs and symptoms in postmenopausal women and patients with severe DED or Sjögren's syndrome, when combined with HA and a range of electrolytes [22].

Alpha-lipoic acid (ALA) is a potent antioxidant that protects cell membranes by interacting with vitamin C and glutathione [93,94]. ALA has demonstrated antioxidant and anti-inflammatory effects in oxidative stress models, and extensive studies have established its therapeutic potential in neurosensory abnormalities as a beneficial antioxidant, anti-inflammatory, and metal chelator [94]. The antioxidant, free radical-scavenging properties of ALA are associated with reducing oxidative damage to the meibomian glands, preserving their function, and decreasing inflammation [94]. Recent findings for a topical emulsion containing ALA and HA indicated that this combination resulted in improvements in corneal damage, ocular redness, goblet cell density, and meibomian gland blockage, and reduced inflammatory markers, especially in patients with high levels of inflammation at baseline [93]. In patients with diabetes and DED, ALA administration can reduce ocular inflammation and oxidative stress, improve tear film parameters, protect corneal cells, and reduce corneal defects, as well as improve glycemic control [94,95].

Antioxidant vitamins C and E, and the antioxidant N-acetylcysteine have all demonstrated utility in in vivo corneal wound healing assays [45]. Although vitamin C is more commonly given as an oral supplement, several artificial tear formulations include combinations of vitamin E, co-enzyme q10, or lipoic acid, and a recent review identified 106 in vitro, in vivo, and preclinical publications examining the role of topical N-acetylcysteine in ocular therapeutics [23,96]. Vitamin B5 and its precursor, D-panthenol, have potential in terms of corneal healing, especially in combination with HA, although larger studies are needed [46,47].

5.5. Combining artificial tear ingredients

Evidence supports combination formulations as more effective than artificial tears containing a single active ingredient, with studies evaluating newer formulations in different countries including combinations of naturally derived and synthetic polymers, osmoprotectants, and/or lipids that impart complementary mechanisms (rheology, osmoprotection, and/or evaporation control) [24,69,70,90,97–99]. Examples in a review of available data include studies indicating that combining CMC and HA is more effective than either alone, and the addition of trehalose to HA-containing formulations enhances patient-reported benefit and satisfaction [24]. A separate review specific to HPMC studies concluded that artificial tears containing HPMC in combination with other therapeutic ingredients seemed more effective than HPMC alone [98]. In agreement, data indicate that newer versions of currently available artificial tears, which have more complex formulations, appear to perform better than the original drops as treatments for DED [24].

In addition, components like glycerol, xanthan gum, and several polymers each offer multiple benefits based on their chemical characteristics, including moisture and lubrication, viscosity, anti-inflammatory properties, and osmoprotection, making them versatile additions to artificial tear formulations [22–24,60]. The addition of glycerol to artificial tears enhances the benefits of CMC alone, in terms of improved DED signs and symptoms [60,100], and is effective as part of combination formulations with polymers and/or lipids or surfactants to reduce DED signs and symptoms [23,24,60].

The combination of ectoine and HA has demonstrated initial promise in patients with dry eye symptoms after cataract surgery, in terms of benefiting tear film stability [82], suggesting potential for their complementary properties in the management of dry eye symptoms, although further studies are needed.

Combining liposomes with viscosity-enhancing agents, electrolytes, and osmoprotectants may more closely reflect the tear film, and the combination of lipids with ectoine alters the physicochemical structure of the lipid layers to enhance drop fluidity, with implications for the impact on DED symptoms [23,101]. In addition, including lipids in artificial tears that have high electrolyte content can supporting aqueous tear retention and help prevent the associated increases in osmolarity that could otherwise worsen DED-associated tear film hyperosmolarity [23].

5.6. Preservatives and preservative-free formulations

Maintaining sterility is essential for topical eye drops to prevent vision-threatening infections, and can be achieved by including chemical preservatives as part of the drop formulation, by using preservative-free single-dose unit packaging, or through specific dispenser design features that enable multi-dose instillation of preservative-free drops while preventing microbial contamination [63,102]. While preservatives are primarily included in topical ophthalmic formulations to maintain sterility for long-term therapeutic applications, such as glaucoma treatment, they may also contribute to improved drug

delivery by modifying molecular interactions and enhancing corneal penetration [48]. Most regulatory bodies have historically required the inclusion of preservative ingredients in multidose ophthalmic formulations, and these ingredients can offer convenience of longer shelf-life and room temperature storage [48,49,103].

Data comparing various preservatives in artificial tears are not expansive, and there is currently no consensus regarding their use, with recommendations to consider preservative-free formulations, based on DED symptom severity [24,48]. Different preservatives have varying effects on the ocular surface, and there is a broad association between chronic, multi-use exposure to the preservative benzalkonium chloride and symptoms of ocular surface disease [49,104]. While recent descriptive and literature findings from Nordic countries indicated a potential association between aggravated DED symptoms and long-term use of preservatives in artificial tears, these observations may only apply to individuals with preexisting sensitivities or receiving multiple preservative-containing topical ophthalmic treatments [48,103,105].

The 'transient' or 'vanishing' preservatives purite and sodium perborate are present in many artificial tear formulations [63]. On instillation, both are converted by ocular catalase into oxygen and water, as well as sodium chloride in the case of purite, reducing their toxicity and potentially offering a less damaging alternative to traditional preservatives [63]. There is increasing interest in both alternatives to widely used preservatives, such as polyquaternium (Table 1), and single-dose bottle designs that prevent microorganism entry and support the use of preservative-free formulations without compromising sterility or increasing packaging [23,24,48,49].

6. The role of compliance in artificial tear effectiveness

Appropriate and consistent long-term use is essential for patients to obtain the full therapeutic benefits of artificial tears, and TFOS DEWS III indicates from available evidence that patients should experience symptomatic improvement after 1 month of four-times-daily use [22,24]. Clinical studies commonly assess DED outcomes after 4 weeks of regular artificial tears use, although clinically visible ocular surface changes indicating improved ocular health may take longer and vary with baseline severity and formulation [22,24]. These findings highlight the importance of long-term compliance to achieve meaningful improvements in DED signs and symptoms.

A prospective case-control study found that the DED severity can affect the impact of artificial tears on fluctuating or poor-quality vision, suggesting that evaluating visual quality may help assess the impact of these agents on DED and provide support for individualized treatment approaches [106].

Mode of drop administration may also have implications for patient compliance, based on usability and/or patient preference: the practical features of different bottle designs can affect how easy they are to use, and packaging materials and formats can have varying environmental impact, both of which may influence patient willingness to comply with their

treatment [22,24]. Recommended storage conditions may also contribute to patient preference, as some prefer refrigerated storage to enhance symptomatic relief, which may be incompatible with product performance and affect characteristics such as viscosity that are important for product effectiveness [22,24].

7. Patient-based selection of artificial tears

The TFOS DEWS III report concludes that 'the management of DED requires a personalized, multifaceted approach that considers the underlying causes and patient-specific factors' [22]. This approach requires consideration of patient-specific lifestyle factors and necessary changes, and selection of the most suitable drop formulation according to the DED type and severity, guided by an evidence-based treatment algorithm [22]. This means that decisions around selecting artificial tears must shift from simply increasing ocular lubrication, to a more nuanced, phenotype-driven approach incorporating considerations around DED subtype, patient-specific etiology and symptoms.

The importance of enhanced patient-clinician communication and patient education to guide artificial tears selection was highlighted during a roundtable discussion in 2006 [107], underscoring the importance of patients seeking guidance from a clinician [108,109]. Patient preferences for dry eye management approaches should also not be underestimated [110], and highlights the necessity for clinician education to support informed, shared decision-making that will be essential to enhance compliance and increase the likelihood of successful disease and symptom control.

In identifying patient groups who may benefit from specific artificial tear formulations, a recent review of available data suggests that, while drops targeting individual layers of the tear film seem equally effective, DED subtype at presentation (baseline) can be used to predict the most effective drop [24]. Evidence indicates that lipid-rich artificial tears, specifically those containing high concentrations of liposomes, are more effective in patients with evaporative DED, or DED caused by MGD, whereas osmoprotectants are more beneficial in patients with hyperosmolarity-predominant [22,24]. Clinical diagnostic tests can play an important role in the diagnosis of DED subtypes, and therefore contribute to phenotype-driven artificial tear selection, based on tear patient-specific tear film deficit [22,111]. For example, Schirmer's test values can be used to diagnose aqueous tear deficiency that requires supplementation of the tear film aqueous layer with artificial tears containing viscosity enhancing polymers (eg. carboxymethylcellulose or xanthan gum) or humectants (eg. hyaluronic acid); osmolarity testing can highlight the need for osmoprotectant-containing drops (eg. L-carnitine, erythritol or trehalose); imaging tests and/or tear breakup time can indicate MGD, or tear film instability requiring lipid-based or surfactant-containing artificial tear formulations that include ingredients such as phosphatidylcholine, medium-chain triglycerides or omega-3 fatty acids [22-24,111].

For those patients experiencing DED-associated pain, while artificial tears do not directly modulate ion channels or nerve function, their instillation may dilute pro-inflammatory

mediators and reduce hyperosmotic and mechanical stimuli that could trigger nociceptive ion channels, thereby producing indirect effects [112]. Osmoprotectants, such as trehalose, may reduce the activation of osmolarity-sensitive ion channels, and the action of lipid-based formulations may protect cold-sensitive neurons from activation by reducing evaporative loss [112].

Patient satisfaction responses highlighted by TFOS DEWS III suggest that contact lens wearers may prefer lipid-based drops [22,24], and the TFOS report also cited recent studies indicating the benefit of HA plus trehalose or B12 in peri- and post-menopausal women and in patients with Sjögren's syndrome or post-cataract surgery [22,113,114].

Preservative-free formulations are increasingly popular to minimize the risk of additional ocular surface damage in sensitive individuals, including those suffering from post-surgical DED or after ocular injury; these options may also be more suited to patients on multiple, long-term ophthalmic medications [22,24].

The ability and preference of patients to use different types of artificial tear bottles, sprays, or single-use dispensers should also be integrated into the prescribing process, including considering the ease with which sprays or rigid bottles can be used by patients with reduced manual dexterity, and patient opinion on environmental sustainability [24]. It is notable that preservative-free multidose packaging can mitigate cost and waste compared with single-use packaging, which may contribute to patient preference regarding drop selection [115].

7.1. Interpreting available evidence

Despite the expanding artificial tears landscape, with plentiful data for various formulations, there is a lack of high-quality, comparative data to define the relative superiority of individual artificial tear components and support definitive recommendations for optimal ingredient concentrations, combinations, and drop frequency [22–25,29,59,98]. Well-designed, long-term studies involving adequate numbers of patients with comparable DED criteria and severity, and the reporting of standardized treatment outcomes are needed [22–25,29,59,98].

The levels of evidence for the impact of individual artificial tears ingredients on DED pathology also varies, ranging hierarchically from preclinical in vitro and in vivo studies, to observational clinical data, randomized clinical trials, along with systematic reviews and meta-analyses. Of the ingredients considered in this article, HA, CMC, and trehalose have the broadest evidence base, with direct data from all five levels; glycerol, CMC, and ectoine have strong multi-level evidence, including randomized clinical trials. Several ingredients, including gellan gum, xanthan gum, polyvinyl alcohol, povidone, coconut oil, lecithin, paraffin, eyebright, and amino acids have limited data directly associated with artificial tears, and evidence for electrolytes is primarily from combined solutions in animal models and in vitro ion-channel experiments. Supplementary Table S1 summarizes evidence available for the ingredients considered in this article, based on the cited studies.

While some artificial tear ingredients can address a specific DED pathology, for example lipids for MGD-associated evaporative dry eye, most ingredients provide relief by acting on several pathological mechanisms simultaneously [22–25,29]. This precludes artificial tears selection based on a single-symptom/single-ingredient association, and necessitates a patient-centered approach to address multifactorial DED pathology by aligning formulation characteristics with disease etiology, symptom profile, lifestyle factors, and patient preferences [22].

8. Future directions for artificial tear formulations and topical DED treatment

Identification of novel artificial tears ingredients that can enhance or synergize with established components is contributing to improved, hypoosmotic formulations and innovative ingredient combinations [24]. For example, γ -polyglutamic acid is a naturally occurring polymer that demonstrated preclinical potential in enhancing the lubricating effects of HA, and may also support corneal healing in vivo [116].

Improved understanding of the role of electrolytes and other solutes in the aqueous phase of the tear film indicate that trace hydroxyl-containing solutes, including sodium and potassium hydrogen phosphate and glucose, are required for thin fluid film stability and dynamics [50]. These molecules influence tear film surface tension and viscosity by forming hydrogen bonds that delay dewetting, changing the behavior of hydroxyl-containing tear film components and artificial tear ingredients, including mucins and HA [50].

Ocular bioavailability affects the efficacy of artificial tear ingredients and can be improved by increasing their residence time on the ocular surface [117]; however, while increasing viscosity can support increased ocular residence, there is increased potential for irritation and/or transient visual blur [118]. Physiological barriers to ingredients achieving their full effects include dilution with tears, removal through nasolacrimal drainage or blinking, or metabolic degradation [65]. Nano-technologies represent a new focus of research and, along with liposomes and emulsions, include nano-spheres, nano-capsules, and highly branched dendrimer nanocarriers, all of which aim to improve topical bioavailability and efficacy while reducing the required frequency of administration [65,91]. In addition, solid lipid nanoparticles represent an approach to improve bioavailability and sustained release of components to treat DED and other ocular conditions [119].

Artificial tears combining viscosity-enhancing agents with natural anti-inflammatory and protective ingredients, such as aloe vera and *Artemia salina* extracts, are under investigation [51,120]. New topical DED approaches, beyond artificial tears, include application of mucosal protective or immunosuppressive agents, topical insulin or the antibiotic azithromycin, or blood-derived platelet-rich plasma eye drops [121–125]. Nonpharmacological approaches to promote tear secretion may be beneficial, along with alternative therapeutic approaches, including acupuncture, as an adjunct to artificial tears for patients with DED [126,127].

Ultimately, developments in topical artificial tear formulations, and their delivery systems, aim to broaden the range of available ingredient combinations to enable more personalized, phenotype-driven customization of drop selection, based on individual patients' underlying DED etiology, subtype and symptom impact [22], [111]. In the future, integrating emerging multi-omics approaches, including evaluation of genomic, proteomic, and metabolomic data could support disease stratification by etiological drivers. [128]

9. Conclusion

The future of DED management lies in addressing patient-specific tear film deficits rather than just increasing tear volume. The evolving landscape of artificial tears offers clinicians and patients an expanding range of accessible options for the management of DED. Direct comparative clinical data defining the relative superiority of individual artificial tear components and formulations remain limited, reflecting formulation complexity and the diverse nature of DED etiology, symptoms and patient experience. Emerging guidance supports a more nuanced, phenotype-driven approach to artificial tear selection, incorporating patient-specific factors, rather than viewing tear substitutes as interchangeable therapies.

10. Expert opinion

Artificial tears remain the initial, and often primary, therapy for DED, serving as a cornerstone of DED management, with innovations in component chemistry supporting the development of more comprehensive and effective formulations [22–25]. This article examines how the combined properties of artificial tear components can contribute to the action of artificial tear formulations in the management of DED signs and symptoms, taking into consideration the broad applicability of these components to DED pathophysiology and ocular health, without categorizing them as 'active' or 'inactive' [63].

The TFOS DEWS III report and recent reviews highlight that the efficacy of artificial tears depends on their overall formulation, including the relative composition of and interactions between ingredients and the delivery system, rather than the efficacy of individual components [22–24]. Indeed, most artificial tear ingredients exert mechanical and/or biological actions on DED physiology and/or ocular health and their inclusion in formulations is based on their properties contributing to lubrication, retention, and/or hydration [22–24].

While the expanding landscape of artificial tears potentially offers increased flexibility in DED treatment, there remains the need for each patient to receive the most appropriately formulated drop, to address their specific tear film deficits rather than just increasing tear volume. The recent TFOS DEWS III care algorithm emphasizes the importance of patient-centered care that extends beyond generalized treatment of symptoms [22,23]. Fundamentally, this must begin with improvements in diagnosis and identification of the underlying etiology of a patient's disease, to ensure that an appropriate, individualized treatment regimen can be designed.

Different DED etiologies mean that the tear film dysfunction experienced by patients with DED is not universal, in terms of specific changes in composition and behavior [22,23]. Identifying patient-specific etiological drivers, DED subtype and severity, and associated tear deficiencies and ocular surface changes provides an opportunity to match patients with artificial tear formulations that are most likely to effectively address their signs and symptoms based on a phenotype-driven approach [22,23,111]. Integrating information from multi-omics approaches could be key to more precise patient stratification according to phenotype, and individualized artificial selection [128].

The pace of artificial tear innovation and the multi-symptom impacts of individual ingredients, along with the complexity of recruiting adequate numbers of comparable patients and matched controls, makes establishing head-to-head trials challenging. As such, there is a paucity of high-quality, comparative data to define the relative superiority of increasingly complex artificial tear formulations and support clinical decision-making [22–25,29,59,98]. There is a need for phenotype-stratified randomized trials, with standardized diagnostic criteria and core outcome measures (including patient-reported outcomes), and appropriate follow-up, masking and comparator selection; pragmatic comparative-effectiveness studies could also provide insight into real-world use of artificial tears.

Although some evidence suggests that certain formulations may be more suited to specific DED etiologies and patient groups, the current evidence gaps preclude a purely data-driven approach. When selecting the most appropriate artificial tear drop, clinicians should consider the patient's key problematic symptoms, any coexisting sensitivities, and patient preferences [22–24]. Aligning formulation characteristics with disease etiology, symptom profile, lifestyle factors, and patient preferences is increasingly recognized as central to optimizing adherence and therapeutic benefit. Patient education and personalized management strategies, including matching artificial tear formulations to DED phenotype and patient context, are therefore essential to improving long-term outcomes and quality of life for individuals affected by this chronic condition.

As part of comprehensive support for patients with DED, optimized blinking, dietary adjustment and supplementation with vitamins and antioxidants, and modifying environmental factors play a crucial role in long-term management; education on the importance of integrating these changes is essential for sustained symptom relief [22–24]. Emphasizing the importance of consistent, appropriate artificial tear use is also critical to support patients in achieving long-term benefits associated with their use [24]. Future patient-specific considerations, which were beyond the scope of this review, include the impact of the surface microbiome, digital eye strain as a modern driver of DED, and the limitations of artificial tears in addressing inflammatory and neuropathic components of DED.

The chronic nature of DED means causes, impacts, and patient circumstances can change over time, making a dynamic, individualized, shared-decision approach fundamental to ensure that treatment and the choice of eye drops are continuously tailored to the developing needs of each patient.

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