

The Right Artificial Tear Substitute

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Abstract

Dry Eye Disease (DED) is one of the most common ocular conditions, affecting millions of people worldwide. Its prevalence is increasing day by day. The first line of therapy for its management is artificial tear substitutes. The name “Artificial tear substitutes” is a misnomer. They contain a variety of active ingredients, biologically active excipients with/without preservatives. Each ingredient has a specific mechanical and pharmacological role. A better understanding of these ingredients will guide the ophthalmologist to choose a better artificial tear substitute for the patient. An approach has been described in the article for the selection of the most appropriate tear substitute, but the choice should still be tailor-made for the patient.

Keywords: Dry eye disease, Artificial tear substitutes, Ocular surface, Hyperosmolarity, Preservatives.

INTRODUCTION

Dry eye disease (DED) may affect nearly 5 to 50% of the population, depending upon age, sex and ethnicity.¹ TFOS DEWS II report defines DED as “Ocular surface disease characterised by loss of homeostasis of tear film and accompanied by ocular signs, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles”.¹ Amongst all the treatment options available for DED, artificial tear substitutes (ATS) are the mainstay of treatment. It is also the first medication to be started in DED, with the aim of supplementing the existing deficiency of the patient’s tear film. Artificial tear substitutes are available with various types of ingredients. Each ingredient has a slightly different mechanism of action. In 2016, a Cochrane systematic review highlighted the deficiencies in clinical trials, rendering it impossible to directly compare different types of lubricants in terms of efficacy, safety and tolerability. Even after so many years, we still stand in nearly the same position.

Ingredients of Artificial Tear Substitutes

Recently, Barabino *et al.*² tried to summarise the results of a consensus meeting held by a group of experts in DED. He proposed new terminologies for the ingredients of tear substitutes, i.e., wetting agents, multiple-action tear substitutes, or ocular surface modulators. Tear substitutes are electrolyte solutions consisting of different buffers and with widely different properties in terms of composition, presence

and type of preservatives, duration of action, viscosity, osmolarity/ osmolality and pH.³ Mohan *et al.*⁴ proposed a new classification recently. In their article, the authors classified ingredients of lubricants into three categories based on their degree of interaction with the ocular surface. This classification will be described here.

Ingredients of artificial tear substitutes can be classified as

- Active ingredients
- Biologically active excipients
- Preservatives

Active Ingredients/Viscosity Enhancing agents/ Demulcents

Demulcent is primarily a water-soluble polymer that is applied topically to the eye to protect and lubricate mucous membrane surfaces and relieve dryness and irritation. Table 1 elaborates the FDA-approved demulcents, which include cellulose derivatives, dextran 70, gelatin, liquid polyols and polymers. Any ATS should have a minimum of one and a maximum of three demulcents to classify as an ATS. This is

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Table 1: Viscosity enhancing agents/active ingredient/demulcents

<i>Viscosity-enhancing agents (demulcents/active ingredients)</i>	<i>Features</i>
Cellulose derivatives (0.2–2.5%) • Carboxymethylcellulose (CMC) • Hydroxypropyl methylcellulose (HPMC) • Hydroxy methylcellulose • Methylcellulose	• Boosts viscosity (thickener) • Stabilizes emulsions • Cross-links upon contact with the tear film due to the pH difference to increase viscosity
Dextran 70 (0.1%)	• Improves the mechanical strength of the tear film
Gelatin 0.01%	• Gelling agent
Liquid polyols (0.2–1%) • Glycerin	• Reduces the damaging effects of hyperosmolarity on the ocular surface • Stimulates epithelial cell growth
• Polyethylene glycol—PEG 300 • Polyethylene glycol—PEG 400 • Polypropylene glycol—PG	• Boosts viscosity • Forms a protective layer over the mucous membrane to relieve irritation • Forms a protective layer over mucous membranes, relieving inflammation • Increases viscosity • Holds up to 3x own weight in water
Polymers • Carbomer • Polyvinyl alcohol (PVA) 0.1–4% • Polyvinyl pyrrolidone (Povidone) 0.1–2%	• Incorporates with the existing oil layer, increases retention time, and reduces evaporation • Lowers tear viscosity • Integrates with the existing oil layer, thickening it and reducing evaporation

mandatory to obtain regulatory approval, although regulations may have slight variations in different countries. Currently, CMC, hypromellose, dextran, glycerin, polyethylene glycol 400, polysorbate 80, polyvinyl alcohol and povidone are commonly used active ingredients in commercially available ATS. These agents are known to be mucoadhesive and mucomimetic due to their branched structure, similar to mucin-1 (formed by goblet cells).⁵ It has also been observed that a combination of CMC and HA gives better effects than either of them alone.⁶ Similar results were also seen with a combination of HA with HP-guar.⁷ Three formulations from Systane – Original, ultra and gel, contain propylene glycol with polyethylene glycol as active ingredients, but differ in their physicochemical properties, especially viscosity and biological properties.

Some of these viscosity-enhancing agents, when administered as a liquid on the eye, form a gel upon mixing with tears. The trigger for sol-gel transition can be different for different ingredients: for HP- guar, it is contact with borates and divalent ions from tears, but for carbomers, it is simply the pH of the ocular surface.⁸ Due to such mechanisms, they are able to partially compensate for the mucin layer deficiency, hence helping to increase the residence time of ATS on the ocular surface.

Biologically active excipients/ Inactive Ingredients/Humectant

They complement the active ingredient of ATS in relieving the dry eye disease. Hence, although named as inactive ingredients, they are not inactive. Instead, they have a protective and/or modulatory role. Biologically active excipients are briefly described as follows. Their action is detailed in Table 2.

- Osmoprotectants – they play an important cytoprotective role for corneal and conjunctival epithelial cells to prevent their apoptosis, which is the underlying etiology of DED. They also reduce matrix metalloproteinase (MMP) synthesis, oxidative stress and regulate the autophagy.
- Humectants - Hygroscopic agents or humectants (e.g., Sodium hyaluronate or HP Guar) are also included in this group. They help in increasing the viscosity as well as the ocular residence time. In some places, they are included in the demulcent group.
- Oily agents and surfactants – Their addition is especially useful in the deficiency of the lipid layer as seen in MGD. They are commercially available in two formulations – liposomes and oil-in-water emulsions.⁹ Initial studies with liposomes have shown promising results, but more studies need to be performed.
- Oil-in-water emulsions are made of oily droplets stabilised in water using surfactants or emulsifiers. Emulsifiers can be non-ionic, anionic, or cationic. Cationic emulsions are special because positively charged oil droplets can interact with the negatively charged mucin layer of the tear film, helping in the stabilisation of the tear film.¹⁰ It has also been shown that polar lipid abnormalities may be involved in DED. Studies have highlighted the fact that cationic emulsions containing cetalkonium chloride (polar lipid) were superior in DED as compared to HA.¹⁰ Systane Balance and Systane Complete have identical composition, but have significantly different physicochemical characteristics, with Systane Balance as a microemulsion and Systane Complete as a nanodrop formulation.
- Electrolytes – As is well known, one of the mechanisms leading to DED is hyperosmolarity. Use of hypotonic

Table 2: Biologically active excipients in artificial tears substitutes

Category	Biologically active excipients	Features
A. Osmoprotectants	Carbohydrates	• Protects from corneal epithelial cell apoptosis, Anti-inflammatory, protects from dysregulated autophagy. • Prevents inflammation and shrinkage of cells. • Promotes epithelial cell growth.
A. Osmoprotectants	Polys	• Lowers the viscosity of gelling agents. Dissipates quickly, improving viscosity. • Protects epithelial cells exposed to increased osmotic stress. • Shields epithelial cells exposed to hyperosmolar stress. Absorbed by dehydrated cells to promote hydration.
Amino acids (Zwitterions)	Glycine, proline, taurine, betaine, ectoin	-
Amino acids (Zwitterions)	Methylamines/Methyl sulfonium solutes	• L-carnitine, L-carnosine
B. Humectants (Hygroscopic agents)	Hyaluronic acid (HA), Hydroxypropyl (HP) guar	• Binds multiples of its weight in water. Lowers tear osmolarity. • Adheres to ocular surface. • Stabilizes the tear film. • Highly viscous until blink thins it out. • Improves cell-cell adhesion. • Increases viscosity. • Imitates the mucin layer of the eye. • Binds to cornea and aqueous layer. • Prolongs the efficacy of active ingredients. • Actively cross links/gels at pH above pH 7.
C. Oily agents and surfactants	Oil in Water Emulsions	• Due to its high lipophilicity, it is strongly associated to oil nanodroplets at the oil/water interface in oil-in-water emulsions, offering a positive charge at the surface of the oil nanodroplets. • Stabilizes the emulsion by producing an electrostatic repulsion between the nanodroplets and the negatively charged cell epithelium. • Spreads and stabilizes the lipid layer upon instillation. • Stabilizes tear film, enhances lipid layer thickness, and prevents evaporation. • Replaces or thickens lipid layer to increase tear stability and TBUT. • Surfactant and mucolytic agents. • Emulsifying agents.
D. Electrolytes	Na ⁺ /K ⁺ /Cl ⁻ /Mg ⁺⁺ /Ca ⁺⁺ Buffers	• Preserves osmotic balance. • Obtains a pH for the artificial tear that is healthy and comfortable for the eye.
E. Antioxidants	Vitamin E, B6, B12, C, Panthotenic acid, Coenzyme Q10, Lipoic acid	• Free radical scavengers. • Improve tear film stability.
F. Agents that promote wound healing	High Molecular Weight (HMW)-HA, T-LysYal, Cationic emulsions	• Hastens wound healing of epithelium, Anti-inflammatory, promotes a higher TBUT and reduces ocular surface cell apoptosis. • Replenishes corneal epithelial cells. • Anti-inflammatory. • Replenishes lipid layer. • Prevents release of pro-inflammatory cytokines.

substitutes has been shown to reduce the signs of DED.¹¹ Some electrolytes, e.g., boric acid, can act both as buffering agents (by stabilizing the pH of formulations) and as preservative agents (when combined with sorbitol, zinc and propylene glycol – Sofzia).¹² Hence, electrolytes are important in maintaining the osmolarity of the tear film by providing essential ions for the maintenance of corneal epithelial cells and counterbalancing the hyperosmolarity of the tear film induced by DED.

- Antioxidants – DED is known to be associated with oxidative stress, which induces tissue damage and increases inflammation.¹³ Erythritol and trehalose, which

are used as osmoprotectants, can also protect the cell from oxidative stress.¹⁴ The antioxidants mentioned in the list have been used in different studies.¹⁵ More clinical studies are required to assess the effects of antioxidants, to better understand their role in DED.

- Agents promoting wound healing and reducing inflammation – HMW-HA accelerates wound healing. It is most likely due to the presence of ligands on the HMW-HA molecule that can bind to CD44 receptors on human corneal epithelial cells.¹⁶ Recently, HA has been combined with other agents to further improve its activity. T-LysYal is composed of lysine HA, thymine and sodium

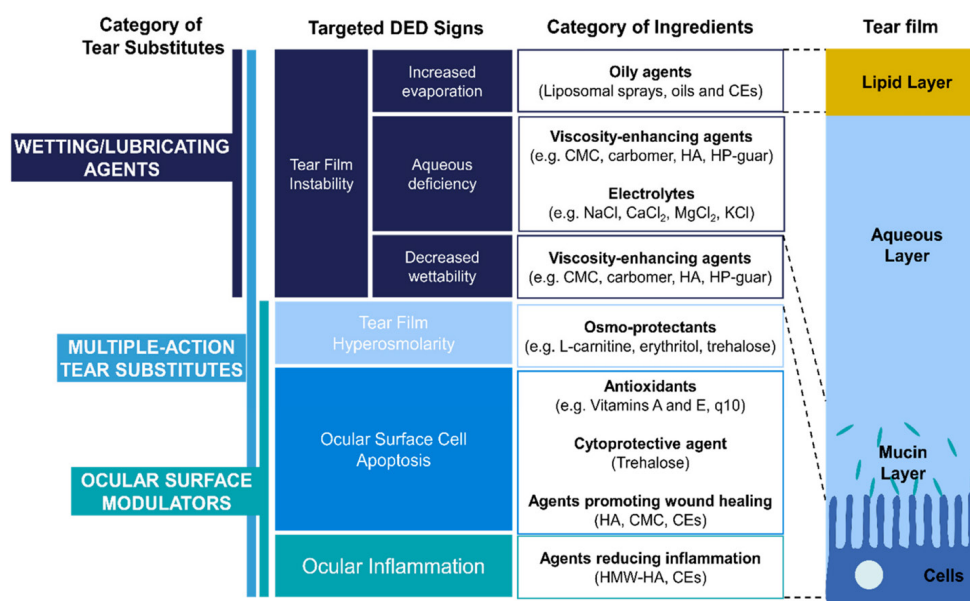


Figure 1: Category of ingredients of artificial tears targeted DED signs. ADDE = Aqueous Deficiency Dry Eye; CEs = Cationic emulsions; CMC = Carboxymethylcellulose; EDE = Evaporative Dry Eye; HA=Hyaluronic acid; HMW =high molecular weight; HP-guar = hydroxypropyl guar¹⁹

Table 3: Preservatives in artificial tears substitutes

Category	Preservative	Features
Oxidative preservatives	Purite (stabilized oxychloro complex)	• Produces chlorine dioxide free radicals which provides it's oxidizing antimicrobial activity • Converts to sodium and chloride ions, oxygen and water upon instillation in the eye
	OcuPure	• Stabilized oxychloro complex with sodium chlorite
	Sodium perborate tetrahydrate	• Breaks down to sodium and chloride ions, oxygen, and water on exposure to light • Uses enzymes present on the ocular surface, such as catalase, to decompose to oxygen and water
Ionic buffer system	Sofzia (borate, sorbitol, propylene glycol and zinc)	• Behaves similarly to oxidative preservatives by breaking down into harmless components
Detergent preservatives	Polyquad (polyquaternium-1)	• Anti-bacterial activity, disrupts microbial cell membranes • Repelled by human corneal epithelial cells
	Chlorobutol, Chlorobutanol	• Alcohol that increases lipid solubility and can pass across the bacterial lipid layer • Anti-bacterial action, causing cell lysis by disruption of microbial cell membrane lipid configuration
	Chlorhexidine gluconate	• Lethally alters the transcription of bacterial DNA
	Benzyl alcohol	• Integrates into bacterial cell walls, disrupting the membrane • Increases drug penetration • Disrupts tight junctions • Hastens epithelial desquamation
	Cetrimide	• Anti-bacterial
	Edetate disodium 0.1% and sorbic acid 0.1%	• Chelating agent that binds metals which inactivates them • Enhances the activity of quaternary ammonium bases and sorbate
	Polyhexamethylene biguanide (PHMB)	• Has activity against bacteria and acanthamoeba • Lethally alters the transcription of bacterial DNA
	Benzalkonium chloride	• Integrates into bacterial cell walls, disrupting the membrane • Water soluble • Surfactant/detergent properties • Causes bacterial cell death by interacting with lipid components in the cell membrane

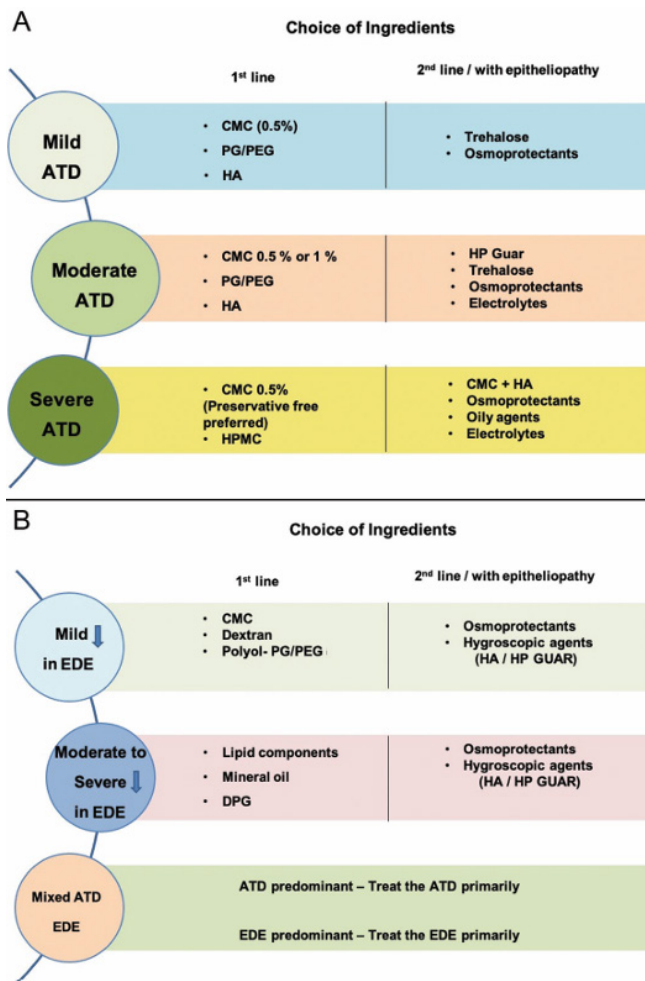


Figure 2: (A) A broad guideline for the choice of ingredients in varying grades of severity of aqueous tear deficiency (ATD). (B) A broad guideline for the choice of ingredients in varying grades of severity of evaporative dry eye (EDE). The predominant component is treated first in eyes with mixed dry eye disease. PG: polypropylene glycol, PEG: polyethylene glycol, HA: hyaluronic acid, CMC: carboxymethylcellulose, DPG: dimyristoyl phosphatidylglycerol¹⁴

chloride and has shown excellent in vitro efficacy.¹⁷ Cationic emulsions have demonstrated a reduction in expression and secretion of pro-inflammatory factors from corneal epithelial cells in *in-vitro* studies.¹⁸

Preservatives

Preservatives are mandatory in any topical preparations to prevent infection. Older preservatives included detergents, e.g., benzalkonium chloride, polyhexamethylene biguanide and ethylene diamine tetraacetic acid. But these induced a lot of ocular surface toxicity. So newer preservatives are preferred, which have lesser toxicity (chlorbutanol, polyquaternium-1), or those which disintegrate on coming in contact with the ocular surface (Purite, sodium perborate). Preservative-free units are best for the ocular surface as there is no toxicity due to preservatives. They can be prescribed in unit dose containers, suitable for a day. Multidose containers with a special cap design so as to allow unidirectional flow of

drops can also be used for preservative-free lubricants. But it increases the cost of the drops. Classification of preservatives has been detailed in Table 3.

Choosing the Right Artificial Tear Substitute

ATS should ideally target the deficient component of tear, but there is no such ATS to simplify its application in a particular type of dry eye.

It should be tailored to suit the grade and type of dry eye. Hence, understanding the benefits of the main ingredients along with the excipients is important for the prescription of drugs. ATS are used to treat patient symptoms as well as to prevent corneal damage.

Guidelines for deciding the main ingredients can be as follows-

Depending Upon Ingredients

- Demulcents - aqueous tear deficiency
- Humectants or oil emulsion- evaporative eye disease
- Osmoprotectants - hyperosmolarity
- Osmoprotectants and hygroscopic agents - epithelial damage

Labetoulle *et al.*¹⁹ have described the key pathologies (Figure 1) in dry eye disease and ingredients used in lubricants that will treat these problems.

Depending on severity

Higher viscosity agents will be preferred in more severe disease for obvious reasons, and vice-versa. Gels or ointments can be given for nighttime protection in moderate to severe disease. A simplified guideline for choosing the ingredient⁴, depending upon the severity of dry eye disease, is given the following (Figure 2).

Preserved vs. Preservative-free

A patient with mild dry eye can be treated with preserved eye drops. But a moderate dry eye disease patient should receive preservative-free eye drops. Because a moderate dry eye patient will require more frequent instillation of ATS (4-6 times), hence the preservative will cause more damage.

Combination Therapy

There are multiple causes of dry eyes, and the ATS acts by various mechanisms, so we may try mix and match with the ingredients of ATS to decide what works best.

Tailored Therapy

It is good to start treatment with more than or equal to two ATS in severe dry eye disease. It helps in rapidly restoring the ocular surface to near normal. Such cases should be followed up frequently to look for a response to therapy. If the condition improves, the ATS can be tapered to reach an optimum level.

Switching to another ATS

If one particular ATS fails to give the desired effect in a reasonable time, it may be wise to switch to another ATS with a different mechanism of action. Even one particular

brand of ATS fails to give similar results, in the same type and severity of dry eye disease. It may be attributed to various factors. Hence, one must not hesitate to change the ATS in the absence of the desired effect.

Stopping the ATS

It is very important to understand that none of the ATS treat the etiology of dry eye disease. Hence, the ATS is providing only symptomatic relief. A patient with mild dry eye can enjoy an eye drop-free interval depending on the environmental conditions. But a moderate to severe dry eye disease patient will require regular ATS eye drops at varying frequencies.

Add-on Therapies

If the symptoms do not get relieved by ATS alone, one must look for a systemic cause and treat accordingly. Level 3 and 4 management of dry eye must be given as and when required.

CONCLUSION

Dry eye is a common disease nowadays and is seen in nearly all age groups. Since the etiology of dry eye disease cannot be treated in the majority of cases, it is very important to provide the patient with symptomatic relief. No one group of lubricants is superior to another. Only by proper understanding of ingredients, their main action and by evaluation of the response in individual patients, can we make our own algorithm of use of ATS. The strategy of treating ophthalmologists should be to target *all* the main issues simultaneously – tear film quality and stability, epithelial morphofunctional changes and obvious and subclinical inflammation. The therapeutic approaches cannot be unique and fixed throughout the course of the disease; instead, they should be dynamic, adapting to the changes on the ocular surface.²⁰

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