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*Review*

# Formulation Considerations for the Management of Dry Eye Disease

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**Abstract:** Dry eye disease (DED) is one of the most common ocular surface disorders characterised by a deficiency in quality and/or quantity of the tear fluid. Due to its multifactorial nature involving several inter-related underlying pathologies, it can rapidly accelerate to become a chronic refractory condition. Therefore, several therapeutic interventions are often simultaneously recommended to manage DED efficiently. Typically, artificial tear supplements are the first line of treatment, followed by topical application of medicated eyedrops. However, the bioavailability of topical eyedrops is generally low as the well-developed protective mechanisms of the eye ensure their rapid clearance from the precorneal space, thus limiting ocular penetration of the incorporated drug. Moreover, excipients commonly used in eyedrops can potentially exhibit ocular toxicity and further exacerbate the signs and symptoms of DED. Therefore, formulation development of topical eyedrops is rather challenging. This review highlights the challenges typically faced in eyedrop development, in particular, those intended for the management of DED. Firstly, various artificial tear supplements currently on the market, their mechanisms of action, as well as their application, are discussed. Furthermore, formulation strategies generally used to enhance ocular drug delivery, their advantages and limitations, as well as their application in commercially available DED eyedrops are described.

**Keywords:** dry eye disease; ocular drug delivery; artificial tears; cyclosporine A



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## 1. Introduction

Dry eye disease (DED) is one of the most prevalent ocular surface disorders affecting tens of millions of individuals globally [1]. Recently, the Definition and Classification Subcommittee of the second Tear Film and Ocular Surface Society Dry Eye Workshop (TFOS DEWS II) reviewed the existing literature to achieve an international consensus on the current working knowledge of DED and defined it as "a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play aetiological roles" [2]. Although DED is not sight-threatening in most patients, visual impairment associated with low spatial frequency and contrast sensitivity, increased glare, blurred vision and eye fatigue are frequently reported [3–5]. In addition to these direct pathological manifestations, DED also tends to compromise physical functioning, social interaction and general health and well-being of patients, resulting in a significant deterioration in their quality of life [6–8].

DED is often classified into two primary subtypes: aqueous tear-deficient dry eye (ADDE), characterised by inefficiency or inability of the lacrimal glands to produce tears, and evaporative dry eye (EDE), typically attributed to excessive evaporation of the tear fluid. ADDE may or may not have an autoimmune origin and is generally attributed to a compromise in the integrity of the lacrimal functional unit. EDE is the more common form of DED and is frequently associated with meibomian gland dysfunction (MGD)

characterised by modification or reduction of tear fluid lipids, due to which, integrity and quality of the tear fluid may be compromised [9,10]. A number of pathological mechanisms, including inflammation, microbial contamination and lipid deficiencies can trigger MGD [11]. Although traditionally, DED has been classified into these two subtypes, it is acknowledged that there is considerable overlap between them [2]. As such, chronic conditions are most often characterised by a "hybrid" or "mixed" form of the disease, wherein each DED subtype eventually adopts some clinical features of the other [12,13]. It is now understood that the various DED pathologies are not exclusive of each other, but rather, they tend to initiate and exacerbate each other forming a "vicious circle" of DED and MGD [2,14]. Consequently, multiple therapeutic strategies are often employed simultaneously to target DED pathologies with topically applied tear supplements typically being the first line of intervention.

Topical application, being simple, convenient, and painless, is the preferred route for administration of prescription drugs to treat ocular surface conditions as it reduces systemic side effects by localising the drug close to the target site. Moreover, for a number of drugs, it is the only means of achieving therapeutic concentrations in the eye, since the blood-aqueous barrier otherwise prevents systemically administered drugs from reaching anterior segment tissues [15]. Not surprisingly, over 90% of ophthalmic formulations currently on the market are topical eyedrops [16]. However, the efficacy of topically applied formulations is limited by the various protective mechanisms of the eye which reduce drug bioavailability, thus necessitating frequent eyedrop administration over prolonged periods. This in turn is often associated with reduced patient compliance further limiting treatment efficacy. Concomitant administration of multiple eyedrops, as is often necessary to manage DED, may further complicate the treatment regimen and reduce compliance. This review discusses the challenges encountered in developing topical formulations, specifically highlighting those attenuated by the ocular surface compromise typically observed in DED. Additionally, formulations generally used in the management of DED to target the different underlying pathologies, their postulated benefits and their formulation characteristics are also discussed.

## 2. Formulation Challenges

### *2.1. Rapid Precorneal Clearance*

The dynamic nature of the ocular surface results in rapid clearance of foreign substances from the eye due to blinking, nasolacrimal drainage and reflex and basal tearing. The conjunctival sac, which serves as a reservoir for topically applied formulations, has a volume of approximately 7–8 μL and can distend to a maximum capacity of 30 μL without blinking [17]. Meanwhile, eyedrops instilled with commercial droppers typically have a volume of 40 μL or more [18]. The eye attempts to achieve homeostasis immediately after eyedrop instillation by reflex blinking and tearing to expel foreign substances and restore the normal tear volume, which results in immediate overflow and expulsion of excess fluid [17,19]. It has been estimated that less than 10 μL of the applied dose remains on the ocular surface following a single blink, leaving a short window of approximately 5–7 min for drug absorption, especially when the rapid tear fluid turnover (19.7 ± 6.5%/min) is taken into account [20].

Concomitant administration of two or more eyedrops, as is often necessary for DED, can further reduce precorneal residence time and ocular bioavailability by increasing competition for volume in the precorneal space [21], with the time interval between eyedrop administration negatively correlating with corneal bioavailability [22,23]. On the other hand, corneal drug concentration post-administration of a single eyedrop formulation containing two drugs is reportedly similar to that observed after administration of eyedrops containing equivalent amounts of each drug, individually [22]. Thus, combination eyedrop formulations capable of simultaneously treating more than one of the underlying DED pathologies could potentially improve the ocular bioavailability and treatment efficacy.

### 2.2. Poor Drug Penetration

In addition to the rapid clearance of topically applied medications from the ocular surface, the ocular bioavailability of drugs from medicated eyedrops is further limited by the nature of the tear fluid and ocular tissues, which together pose a formidable barrier to intraocular transport of drugs (Figure 1).

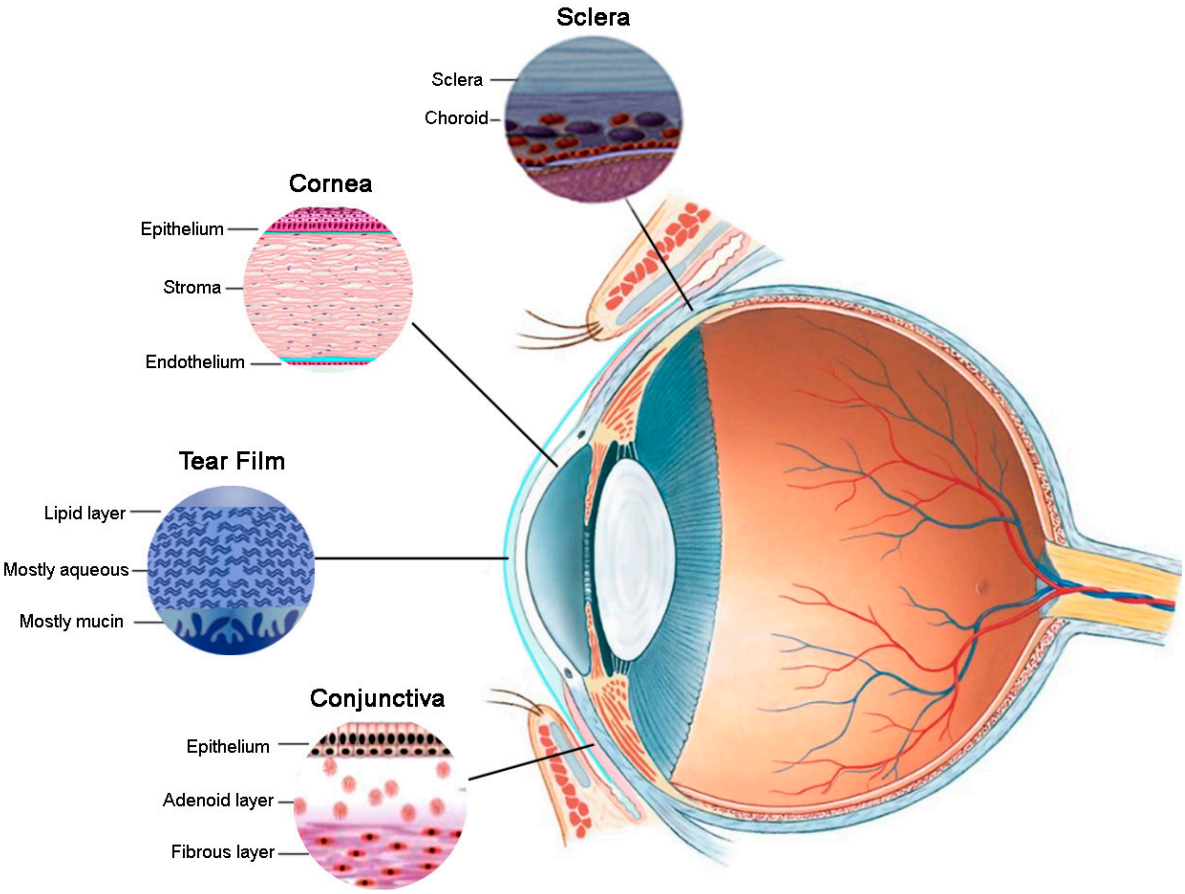


**Figure 1.** Penetration barriers to topical drug delivery.

The tear film is the eye's first line of defence with its various components working synergistically to minimise exposure to foreign substances. Superficially, it comprises a thin lipid layer which limits access of aqueous formulations to the corneal interface while also minimising excessive tear evaporation. Underlying the lipid layer is the aqueous phase of the tear film, rich in enzymes, proteins, and mucins that can inactivate drugs by protein binding or enzymatic degradation, and thus reduce their bioavailability [24]. The region of the aqueous layer closest to the goblet cells is the most concentrated in mucins which can entrap drug particles by the formation of low affinity polyvalent adhesive interactions, rapidly eliminating them from the ocular surface [25,26].

The cornea is the most anterior ocular tissue and consists of alternating hydrophobic and hydrophilic layers. The hydrophobic corneal epithelium is the major barrier to drug transport. It is composed of 5–7 layers of epithelial cells with tight intercellular junctions, therefore, only very small molecules can traverse paracellularly through the cornea. Transcellular transport, on the other hand, is generally only possible for smaller molecular weight lipophilic drugs [27]. Underlying the hydrophobic epithelium is the hydrophilic stroma which favours the penetration of low molecular weight hydrophilic drugs while hindering the passage of lipophilic drugs. Therefore, hydrophobic drugs tend to be retained in the corneal epithelium from where they are released very slowly into

the posterior tissues [28]. Overall, it has been estimated that less than 10% of a topically applied dose reaches the intraocular environment through the cornea [29].

While traditionally not considered a major drug delivery route, ocular drug penetration may also occur via the conjunctival-scleral pathway which provides a much larger surface area for drug absorption than the cornea [28]. The conjunctival epithelium is relatively leaky and hydrophilic, with intercellular spaces being approximately 230-fold larger than those in the cornea, rendering it permeable even to large biomolecules, such as proteins and peptides [30,31]. The conjunctival epithelium is more permeable to hydrophilic drugs with the permeability of hydrophilic polyethylene glycol mixtures reportedly being the highest in the conjunctiva, followed by the sclera and cornea, respectively [31]. However, since the sclera and conjunctiva are richly perfused by blood vessels, a large fraction of drug absorbed via this route may be lost to the systemic circulation [32].

### *2.3. Dose Volume*

Due to limited precorneal space, a smaller eyedrop volume (5–15 μL) is preferable to minimise drug wastage and reduce the risk of systemic toxicity. The dose-volume can be controlled to some extent by training the patient in eyedrop administration and by modifying the dropper tip and angle [33,34]. Piezoelectric micro-dosing systems have also been developed to consistently deliver a very small eyedrop volume [35]; however, these devices are rather expensive. Physical characteristics of the formulation, such as surface tension, cohesive forces, viscosity and density can also influence the drop size [36]. For instance, in situ gelling systems, such as hydroxypropyl-guar Systane®, by virtue of their lower viscosity, reduce dosing errors in comparison to viscous gels [37]. Surfactants and penetration enhancers, such as tetracaine, polysorbate 80 and benzalkonium chloride (BAK), can also reduce the drop size to some extent by reducing the surface tension of the formulation [33]; however, due to the toxicity typically associated with these excipients, their inclusion is rarely justified for the purpose of reducing drop size alone. Certain non-aqueous liquids, such as semifluorinated alkanes (SFAs), which inherently have lower surface tension and viscosity than aqueous eyedrops, may help in achieving a smaller drop size and minimise overflow [38].

### *2.4. Visual Disturbance*

Transiently reduced visual acuity post-instillation is another limitation of eyedrops that correlates with their viscosity and refractive index. For example, mid-viscosity Refresh Liquigel® can cause more blurring than low viscosity Refresh Tears® [39]. Blurring of vision is also commonly reported with in situ gelling systems, likely due to a sudden change in viscosity post-instillation [40]. To minimise visual disturbance, topically applied eyedrops should be optically transparent and ideally have a refractive index identical to that of the tear fluid (1.336–1.338) [41]. Nevertheless, the refractive index of most formulations currently on the market is relatively high (oily eyedrops typically have a refractive index of 1.44–1.50), resulting in frequent complaints of blurred vision and foreign body sensation [42].

### *2.5. Preservative Toxicity*

Several experimental and clinical studies have demonstrated that most preservatives used in ophthalmic formulations have pronounced ocular toxicity. BAK, the most commonly used preservative in topical eyedrops, has repeatedly been shown to be toxic to the ocular surface, leading to exacerbated DED symptoms [43,44]. BAK disrupts the integrity of corneal tight junctions which may compromise its barrier properties and elevate the toxicity potential of other drugs and excipients. Therefore, eyedrops preserved with BAK not only have a direct detrimental effect on the ocular surface but may also potentiate the toxicity of other excipients in the same formulation or those applied concomitantly. In fact, one study has suggested that with each additional dose, eyedrops containing BAK increase the risk of ocular surface disease two-fold [45]. However, despite the overwhelming evi-

dence of its toxicity, a number of products containing BAK remain commercially available and are not infrequently used in the treatment of DED [46].

Significant ocular toxicity has also been associated with other antimicrobial agents used in eyedrops, including parabens, sodium perborate, chlorobutanol, stabilised thiomersal, and ethylenediamine tetraacetic acid (EDTA) [47]. Meanwhile, the cytotoxic effect of newer generation preservatives, such as Polyquad®, Purite®, and SofZia®, is comparatively low [48], although their long-term effect on tear film stability is currently unknown. It should be noted that the toxicity of preservatives may incidentally be enhanced by viscosity-building agents present in eyedrops. For instance, corneal epithelial damage has been observed when the thickening agent hydroxyethylcellulose is used with BAK, although no such effect was observed when either excipient was used alone [49]. Similarly, punctal plugs, commonly used in DED therapy to reduce tear drainage, can increase the exposure to toxic preservatives enhancing their detrimental effects.

To enable the delivery of preservative-free eyedrops to the ocular surface, preparations may be supplied in single-dose units; however, such eyedrops can cost 5–10 times more than multidose formulations and are often difficult to handle [50]. Multidose preservative-free dosing systems have thus been developed to overcome these limitations. One such dosing system is the third generation ABAK® bottle (Théa Laboratories, Clermont-Ferrand, France) which uses a bi-functional membrane with antimicrobial properties to maintain sterility for up to three months after opening. Sterile filters are also used in the Clear Eyes® bottle (Prestige Consumer Healthcare, Greenburgh, NY, USA) and the hydraSENSE® delivery system (Bayer, Leverkusen, Germany), while the COMOD® dosage system (Ursapharm, Saarbrücken, Germany) uses a one-way valve to maintain sterility for up to six months after opening [46]. Although these systems reduce the difficulties associated with handling single-dose products, their cost remains significantly higher than that of conventionally preserved eyedrops.

### *2.6. Poor Tolerability of Formulation Excipients*

In view of recent clinical experience and literature evidence, the TFOS DEWS II Iatrogenic Subcommittee listed several formulation excipients, including surfactants, pH modifiers and antioxidants, in addition to preservatives, as agents with the potential to cause DED [51]. However, almost all of these compounds are commonly found in over-the-counter artificial tear supplements and DED medications currently on the market. An increased incidence of local adverse effects, such as stinging, burning and excessive tearing, has been reported due to high surfactant concentrations in topical formulations. The risk of toxicity is particularly high in novel colloidal drug delivery systems, such as micelles, micro- or nanoemulsions, liposomes and nanoparticles, due to the higher proportion of surfactants and co-surfactants used compared to conventional formulations [52,53]. Surfactants and co-surfactants can further destabilise the tear film exacerbating DED symptoms [51,54]. Consequently, iatrogenic ocular surface disease, caused by "commission" rather than the "omission" of treatment, is a significant concern with eyedrops.

As discussed earlier, excipient toxicity too may be exacerbated by concomitant administration of multiple eyedrops. For example, Restasis® and Refresh® Endura artificial tear supplements both contain polysorbate 80, which can reportedly trigger DED [51]. However, these eyedrops are frequently recommended in combination for DED therapy [55] and this practice may significantly increase the toxicity potential by increasing the overall exposure. Finally, adverse effects may also become more pronounced on exposure to multiple iatrogenic excipients (in addition to preservatives) simultaneously.

### *2.7. Poor Patient Compliance*

Non-compliance with treatment regimens is one of the biggest challenges in treating ocular surface disorders. In a phone survey performed in 239 patients [56], 37–53% of patients with prescribed topical eyedrops had discontinued use. Inter-day and inter-individual variability appeared to be high with most patients arbitrarily titrating the dose

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