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Artificial tears for dry eye: A review

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ABSTRACT:
Artificial tears are essential for managing dry eye disease, but they also aid in corneal abrasion and wound healing, managing pain and inflammation, treating conjunctivitis and keratitis, rewetting and removing contact lenses, and eliminating foreign bodies. A systematic review of randomized controlled trials (PROSPERO registration CRD42022369619) aimed at evaluating the effectiveness of artificial tears in individuals with dry eye to guide prescribing decisions, utilizing Web of Science, PubMed, and Medline databases, revealed 64 pertinent articles. There is strong evidence that artificial tears alleviate symptoms of dry eye disease within a month of consistent use, applied roughly four times daily, although signs typically require several months to show improvement. Not every patient with dry eye disease finds relief from artificial tears, so if there's no improvement after a month, alternative treatments should be explored. Combination formulations provide greater effectiveness compared to artificial tears with a single active ingredient. Polyethylene glycol-based artificial tears are superior to those with carboxymethylcellulose/ carmellose sodium and hydroxypropyl methylcellulose. Individuals diagnosed with evaporative dry eye disease gain advantages from using liposome-based artificial tears, particularly those with higher concentrations. The available data is restricted due to the varying definitions of dry eye disease used in published studies, along with the differing severity of the disease evaluated and the infrequency of measuring compliance with artificial tears.

Keywords: artificial tears, dry eye, comfort, contact lenses

I. INTRODUCTION :

Artificial tear drops are primarily linked to the treatment of dry eye disease (DED). Artificial tears are generally part of the primary treatment options for dry eye since they are simple to apply, widely available in various formulations, and have a minimal risk profile.Most artificial tear products are shown to be effective in alleviating the symptoms and signs of dry eye disease (DED); however, the Tear Film and Ocular Surface Society (TFOS) dry eye workshop conducted in 2017 (DEWS II) found that there have been relatively few high-quality randomized controlled trials assessing different formulations against one another. Additionally, there are limited clinical trials that have investigated the effectiveness of various artificial tear products and tried to link this with patient characteristics to assist with management choices for individuals..*3 This situation leaves both doctors and patients confronted with a confusing selection of diverse products with differing ingredients and little to no clear guidance on which is the most effective. Professionals frequently encounter the question, “what is the most effective drop for dry eye,” yet they lack scientific evidence to support their response. Furthermore, additional factors that affect the decisions of both practitioners and patients include:

International Journal of Pharmaceutical Research and Applications
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Consequently, patients might encounter a trial-and-error method for choosing products, leading to increasing expenses and growing frustration along the way. Patients who are very price sensitive will feel this even more acutely, as over-the-counter products are no longer readily accessible through National Health Service (NHS) subsidized prescriptions in the UK. A recent study12 examining the experience of dry eye management across four continents revealed that, on average, dry eye disease (DED) still moderately affected an individual's quality of life (median impact 3/10). Fewer than half of the individuals in any nation had consulted with an eye or healthcare professional regarding their dry eye issues. Approximately half had attempted dry eye treatment, with artificial tears being the most frequently used option, followed by warm compresses, and both treatments were deemed reasonably effective.

1. Formulation :

Most artificial tear formulations are water-based and feature viscosity-boosting agents like carbomer 940, carboxymethyl cellulose (CMC), dextran, hyaluronic acid, sodium hyaluronate (which has a lower molecular weight), hydroxypropyl guar (HP-guar), hydroxypropyl methylcellulose (HPMC, or hypromellose), polyvinyl alcohol, polyvinylpyrrolidone, and polyethylene glycol, which help with lubrication and extend retention time on the eye.1 Additional components might include osmotic agents, osmoprotectants, antioxidants, preservatives, and inactive ingredients such as pH buffers, excipients, and electrolytes.1 Aqueous-based artificial tears primarily address the muco-aqueous layer of the tear film but have been shown to alleviate dry eye symptoms across all subtypes of DED.2

In recent years, lipid-based drops have gained popularity and become more accessible, targeting the superficial tear lipid layer [13,14] as the focus on meibomian gland dysfunction and its contribution to evaporative dry eye grows.1 Randomised controlled trials have shown that lipid-based drops are more efficient in treating DED classified as evaporative.[3,4]These products can be found as nano-emulsion drops or liposomal sprays, which are used on the closed eye and may be more suitable for individuals who find it difficult to instill drops, such as those with diminished manual dexterity or hand tremors. A fully anhydrous drop made entirely of lipid (perfluorohexyloctane) is now accessible, and it also offers the advantage of being free from preservatives

2. Preservation :

Multidose eye drops, such as artificial and medicated topical ocular solutions, often include preservatives to ensure sterility and extend shelf life; however, they are also known to cause toxicity. Benzalkonium chloride, typically present in multidose drops, can have toxic, proinflammatory, and detergent effects, potentially causing or worsening DED.[16]This has led to a shift towards preservative-free and unit dose formulations because of the potential for toxic and allergic reactions, particularly when frequent usage is necessary. Recent formulations might include less harmful preservatives like polyquaternium, or “disappearing” preservatives such as sodium perborate and purite, or utilize specially crafted bottles that stop microorganisms from entering.[17]It is advised to use preservative-free solutions for all forms of dry eye, particularly for severe dry eye or sensitive persons, with further information available in the TFOS DEWS II iatrogenic report.[6]

3. Ideal properties :

It is essential for artificial tear drops to mimic the behavior of natural tears. One facet of this is the physical characteristic of rheology, which pertains to how fluids and soft solids move. The viscosity of human tears is elevated between blinks but decreases during each blink cycle to safeguard the ocular surface from damage caused by fluid turbulence. Thus, they do not exhibit Newtonian behaviors and are characterized as possessing non-Newtonian properties. Hyaluronic acid has been extensively researched and has demonstrated these non-Newtonian shear-thinning characteristics,[18]making it more similar to the tear film and therefore appropriate for artificial tears.[19]A prevalent component of artificial tears, hyaluronic acid is a naturally occurring glycosaminoglycan, present in and around body cells and tissues, such as in synovial fluid, as well as vitreous and aqueous humour.[20] Its application in ophthalmology was initially explored by Andre Balazs in the late 1960s[,21] with Polack and McNiece22 being the first to document its use for dry eye. Hyaluronic acid is soluble in water and can attract large amounts of water relative to its weight, yet its physical characteristics differ based on its molecular weight. Evidence indicates that high molecular weight hyaluronic acid (HMWHA)

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is more effective in treating dry eye disease (DED) than its low molecular weight version. Additionally, HMWHA has demonstrated protective effects against corneal cell apoptosis caused by benzalkonium chloride toxicity, ultraviolet radiation, and chemical burns, while also acting as an anti-inflammatory agent and helping to alleviate pain sensation.

4. Artificial tears for dry eye disease:

Numerous systematic reviews2,[29–31] have been carried out in the last ten years, concluding that artificial tears provide a safe and effective treatment for DED. A meta-analysis found that the efficacy of sodium hyaluronate was consistent regardless of its formulation30, while another [32] indicated that CMC seemed superior to hyaluronic acid for treating DED, but these findings lacked statistical significance. Two recent reviews5,[33] found that although hyaluronic acid was effective in alleviating the symptoms of DED, the optimal drop frequency and formulation (includingconcentration and molecular weight) for varying ages and severities had not yet been explored.So far, there has not been an evaluation of research that compared various artificial tears to determine if specific formulations are more effective. Consequently, to gain a clearer insight into the effectiveness of various artificial tears for treating dry eye, a search was conducted in the Web of Sciences databases (Clarivate Analytics, Philadelphia, USA), which encompasses the Science Citation Index Expanded featuring more than 9200 of the globe's most influential journals from 1900 to today, in addition to PubMed (including MEDLINE) since its beginning. The systematic review was registered in advance on PROSPERO (CRD42022369619) and was carried out according to the guidelines set forth by PRISMA (2020). A search using “artificial tear*” AND “randomi?ed” yielded 481 unique results, which were independently reviewed by two researchers (DB and DS) and confirmed by a third (JSW). Studies could be accepted if they were presented as full papers (not in the form of abstracts or book chapters), compared multiple artificial tears against one another (rather than just with a placebo), and included randomisation to prevent bias. As a result, 64 papers were accepted and the full texts examined for the key elements, which were organized in a spreadsheet and summarized.

All studies are prospective (as anticipated) and include parallel groups (unless indicated differently) of dry eye patients (diagnosed using National Eye Institute, arbitrary or the recent TFOS DEWS II criteria). Nonetheless, fewer than half (20 of 42) are listed in a clinical trials database, and even the ones that are have significant risk of bias traits,35 thus the reliability of the outcome is typically low. The absence of a clear severity classification has been recognized as a factor affecting the comparison of the efficacy of existing artificial tears.31 However, earlier efforts to create a severity matrix table in TFOS DEWS I36 resulted in varying severity assessments for patients depending on the tests used, leading to its discontinuation in TFOS DEWS II;[37] for a dry eye patient, severity is determined by symptoms, whereas, for a cataract surgeon, it is more commonly assessed through signs on the ocular surface. Although the aim of several reviewed studies is to show non-inferiority relative to a standard treatment, some lack sufficient power (refer to TFOS sample size recommendations)[37] and/or include both eyes without considering the correlation between the two eyes38 of a participant.[39–43] In the majority of studies, fluorescein sodium is employed for evaluating corneal staining (although an appropriate blue light peaking around 395nm [not cobalt blue, which peaks at ~450nm] and yellow filter with a cutoff near 500nm is frequently not mentioned).[44] Most studies utilize lissamine green for conjunctival staining , which is the suggested approach,[37] but few specify the brand that can significantly influence the staining results.[45] Certain studies[46,47]report discrepancies even when they fail to satisfy the standard criterion of $p < 0.05$, thus any "difference" should be regarded as noise in the dataset. Although numerous studies evaluating artificial tears are initiated by manufacturers

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Based on the studies compiled so far (noting that the effects may vary due to dry eye severity, complete artificial tear formulation, and patient demographics), direct comparisons among artificial tears suggest that:

- Combination formulations outperform artificial tears with a single active ingredient.
- The merger of CMC and hyaluronic acid proves to be more effective than using either one alone.[48,49]
- Hyaluronic acid50 and sodium hyaluronate[51]gain advantages from incorporating trehalose.
- The inclusion of glycerine improves CMC[.52]
- CoQ10 improves the potency of hyaluronic acid.[53]
- More recent iterations of Systane (Complete and Balance) surpass previous versions with reduced complexity (Ultra).[54,55]
- Certain studies indicate that sodium hyaluronate might be more effective than CMC40 and carbomers,[56]whereas others observe no difference,[57,58] and the ideal percentage remains unclear.[59,60]
- PEG-based artificial tears are more effective than those with CMC[61–65]and HPMC.[66,67]
- Cationic formulations outperform sodium hyaluronate (for objective signs)68 and polyvinyl alcohol.[69]
- Artificial tears with hyaluronic acid may be superior to those with HPMC[,70] but inferior to those containing CMC.[39]
- Artificial tears containing carbomer may be more effective compared to those made with PVA71 or CMC[72]or cellulose/mineral oils[73], but they could be less[56,74] or equally[43]effective as sodium hyaluronate.
- Many studies suggest using it four times a day, but actual reported or measured usage is typically lower than the recommended amount.[42]
- Sustained adherence is essential to enhance ocular surface indicators rather than merely addressing symptoms, and symptoms show improvement with four times daily dosing compared to "as needed" administration.
- An increase in liposomal concentration enhances efficacy.[76,77]
- Reduced osmolarity in eye drops enhances the efficiency of an artificial tear drop.[46]
- A higher concentration (viscosity) of CMC is more successful in minimizing corneal and conjunctival staining, yet it resulted in more reports of visual disturbances[.78]
- Although drops aimed at specific layers of the tear film appear similarly efficient, studies have demonstrated that one can predict the most effective drop for a person based on their baseline classification; phospholipid-containing drops are more beneficial for individuals with evaporative dry eye, while osmoprotectants help those experiencing high tear film osmolarity.
- Artificial tears might not be helpful for nearly one-third of patients, yet this can

These results can guide clinical practice for dry eye; to summarize: non-preserved or softly preserved artificial tears are suitable for prescribing to patients, irrespective of their DED severity; individuals with evaporative dry eye should be given artificial tears with a high liposome concentration; a compliant usage of four times a day for one month is suggested to assess if an artificial tear can effectively alleviate the patients' symptoms over time; improvement signs of ocular surface disease usually take up to four months to manifest, necessitating patience; artificial tears containing multiple active components (particularly with PEG) appear to outperform simpler previous generation drops; the ability to utilize various types of artificial tear bottles or sprays differs and should be considered when making prescriptions. Although the effectiveness of artificial tears is well recognized for treating DED, [71]their application in asymptomatic ocular surface disease to enhance post-surgical symptoms and mitigate refractive 'surprises' from inadequate ocular biometry80 is not as well documented. The information assessed in this study is constrained by the differing definitions of dry eye disease in published research, the variability in disease severity evaluated, and the infrequent measurement of adherence to artificial tears.

5. Other therapeutic function of artificial tears :

In addition to serving as a management option for dry eye disease and the ocular surface, artificial tears can be employed for various therapeutic purposes, including the treatment of anterior eye trauma, infections, inflammation,[63] and diseases, along with managing contact lenses.

International Journal of Pharmaceutical Research and Applications
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i. Corneal abrasion and wound healing

Corneal abrasions may result from foreign objects, injury, and trichiasis, leading to discomfort, redness, tearing, and sensitivity to light. Artificial tears enhance the healing of epithelial tissues.81 It is best to use preservative-free drops since they generally promote superior ocular surface health and comfort.[67] The primary treatment for corneal abrasions occurring around the time of surgery is artificial tears, often accompanied by a blend of artificial tears and antibiotic ointment.83 Many artificial tears include hydrogels, which are recognized for activating the epidermal growth factor (EGF) receptor that aids in the repair of corneal epithelial injuries.84.

ii. Pain and inflammation management

Artificial tears are frequently employed in the treatment of eye discomfort and inflammation. In the management of episcleritis, using a combination of cold compresses and artificial tears offers symptomatic relief.[72]No notable differences in signs or symptoms of idiopathic episcleritis have been noted when artificial tears or topical ketorolac (NSAID) are administered. After undergoing photorefractive keratectomy (PRK), using preservative-free artificial tears alleviates postoperative ocular discomfort and enhances visual recovery. Chilled artificial tears have demonstrated the ability to lessen corneal and conjunctival sensitivity, with 4°C being the most soothing temperature.[71] However, Bitton et al. reported no improvement in patient comfort perception when refrigerated Systane Ultra artificial tears were utilized by individuals with mild to moderate dry eye.It's important to recognize that pain complaints may correlate with varying subjective responses, and for certain patients, artificial tears may not effectively ease uncomfortable symptoms.

iii. Conjunctivitis

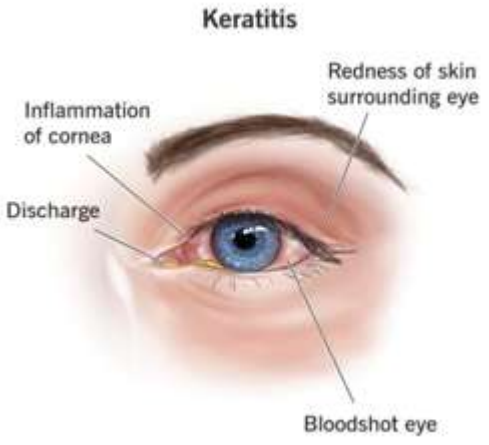
Allergic conjunctivitis leads to eye itching, watery discharge, swelling of eyelids, and conjunctival chemosis. Bilkhu et al subjected 18 participants (with a known allergy to grass pollen) to grass pollen and discovered that artificial tears and cold compresses alleviated the signs of allergic conjunctivitis and offered symptomatic relief.[70] Nonetheless, if symptoms persist, it is advisable to use topical antihistamines and mast cell stabilizer drops for a short duration.

Viral (non-herpetic) conjunctivitis results in redness, irritation, and tearing. Follicles on the palpebral conjunctiva and punctate epithelial lesions on the cornea can also be seen. Research has demonstrated that 0.5% topical ketorolac, 0.45% ketorolac tromethamine, and 1% prednisolone acetate do not provide greater relief of signs or symptoms of viral conjunctivitis than artificial tears.

Bacterial conjunctivitis leads to redness, discomfort, and generates a sticky discharge that results in crusting of the eyelids. Bacterial conjunctivitis often resolves on its own, but using artificial tears and rinsing the eyes promotes comfort and cleanliness. When bacterial conjunctivitis continues for 3–4 days, the use of topical antibiotics is typically suggested.

iv. Keratitis

.Keratitis is a corneal inflammation with various causes such as viral (Herpes Simplex), bacterial (marginal keratitis), fungal, contact-lens related, and unshielded exposure to ultraviolet light (photokeratitis). The use of artificial tears has been advised for dry eye and photokeratitis. In cases of herpetic keratitis,[71] marginal keratitis, fungal keratitis, and keratitis related to contact lenses, artificial tears are recommended (for moisture and symptom relief) in conjunction with further treatments like topical antivirals, topical and/or oral antibiotics, and antifungal medications.



v. Contact lens rewetting and removal

Users of contact lenses often utilize preservative-free artificial tears for eye lubrication, comfort, and rehydrating contact lenses. As wear time increases, contact lenses tend to dry out and fit more snugly. Using artificial tears lessens friction on the cornea and can help ensure safe removal of lenses.[72]

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vi. Foreign bodies removing

Foreign bodies in the cornea may lead to irritation, tearing, blurred sight, and redness. Foreign bodies that are loose can be washed away with normal saline or artificial tears. After the successful extraction of a foreign object, it is recommended to use prophylactic antibiotics, analgesics, and artificial tears.[71][72].

6. Summary :

Artificial tears serve as the cornerstone of managing DED, but they also play a role in corneal abrasion and healing, alleviating pain and inflammation,[71] treating conjunctivitis and keratitis, rewetting and removing contact lenses, and foreign body extraction. An analysis of randomized controlled trials assessing artificial tears found 64 articles. Strong evidence suggests that artificial tears alleviate symptoms of DED within a month of consistent application, around four times daily, but signs typically require several months to show improvement. Not every patient with DED experiences relief from artificial tears, so if there is no improvement after a month, other treatment options should be explored[72]. Combination formulations are superior to artificial tears with a single active ingredient. PEG-based artificial tears are superior to those that include CMC and HPMC. Individuals categorized with evaporative dry eye disease derive advantages from artificial tears containing liposomes, particularly those with elevated concentration.

7. Disclosure :

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