

UNDERSTANDING THE BIOCHEMICAL MECHANISM OF ACTION OF CARBOXYMETHYLCELLULOSE FOR DRY EYE SYNDROME

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ABSTRACT

Dry eye syndrome (DES) is a prevalent condition characterized by insufficient lubrication on the ocular surface, leading to discomfort, visual disturbances, and potential damage to the eye. Carboxymethylcellulose (CMC), a cellulose derivative, is widely used in artificial tear formulations to alleviate the symptoms of DES. This paper explores the biochemical mechanism by which CMC alleviates dry eye symptoms, focusing on its viscoelastic properties, interaction with tear film components, and cellular effects on the ocular surface. There are many different kinds of tear substitutes on the market, but not much research have been done to compare how well they work. A deeper comprehension of the distinct pharmacological and mechanical functions of each component that makes up the various formulations is required. This review discusses carboxymethylcellulose (CMC) as a potential replacement for tears, including viscosity-enhancing agents, electrolytes, osmo-protectants, antioxidants, lipids, surfactants, and preservatives. It also discusses CMC's effects on the ocular surface and offers insights into how specific CMC constituents and their physical and chemical characteristics may aid in the healing of corneal wounds and/or reduce inflammation.

1. INTRODUCTION

Dry eye syndrome (DES) affects millions worldwide, manifesting as a multifactorial disease involving tear film instability and ocular surface inflammation. The TFOS DEWS II report defines DES as a "ocular surface disease, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" and is characterized by a loss of tear film homeostasis and ocular signs. The ocular discomfort, weariness, and visual disruption caused by this disease have a substantial impact on the patients' quality of life [1]. The use of artificial tears is a common therapeutic approach, with Carboxymethylcellulose (CMC) being a key component due to its favourable properties [2]. Understanding the biochemical mechanisms through which CMC exerts its effects can aid in the development of more effective treatments.

However, before we proceed into the biochemical aspect of CMC as an artificial tear, let's take a look at the general properties and applications of CMC. The uses for carboxymethyl cellulose (CMC) are incredibly diverse. It functions as a soil-suspending agent in soaps and detergents. It serves as a thickening, emulsion stabilizer, or water binder in food products like diet foods and ice cream. The textile sector also uses CMC as a coating agent. CMC is utilized in the pulp and paper industry to provide coating colors that enhance the surface qualities of paper and paper board [3]. CMC is added to drilling mud, resin emulsion paints, adhesives, and printing inks, among many other products. Additionally, CMC is used in the formulations of numerous medicinal and cosmetic goods as a viscosity-increasing, suspending, or tablet excipient [4].

What is 'Dry Eyes Syndrome' in human?

Dry eye syndrome, also known as dry eye disease or keratoconjunctivitis sicca, is a common condition where the eyes do not produce enough tears or the tears evaporate too quickly, leading to a lack of proper lubrication [5]. This can cause discomfort and various other symptoms. Here are the common signs and symptoms of dry eyes:

1. **Dryness and Irritation:** A sensation of dryness, grittiness, or scratchiness in the eyes is one of the primary symptoms of dry eye disease.
2. **Redness:** Dry eyes can cause the blood vessels in the conjunctiva to dilate, leading to visible redness.
3. **Burning or Stinging Sensation:** Many people with dry eyes report a burning or stinging feeling.
4. **Itching:** Itching can occur due to the dryness and irritation of the ocular surface.
5. **Foreign Body Sensation:** This feels like something is stuck in the eye, often described as a feeling of sand or grit.
6. **Blurry Vision:** Dryness and unstable tear film can lead to fluctuations in vision, causing intermittent blurring.
7. **Light Sensitivity (Photophobia):** Dry eyes may increase sensitivity to light, causing discomfort in brightly lit environments.
8. **Excessive Tearing (Reflex Tearing):** Ironically, some people with dry eyes experience excessive tearing due to a reflex response from the lacrimal glands to combat the dryness.
9. **Eye Fatigue:** Eyes may feel tired, particularly after prolonged visual tasks such as reading or working on a computer.

10. Difficulty Wearing Contact Lenses: Contact lenses can exacerbate dry eyes, leading to discomfort or reduced wear time.

11. Mucous Discharge: Some people with dry eyes notice a stringy or sticky mucous discharge.

The symptoms of dry eyes could be an indication of a systemic illness, thus early identification could help identify a potentially fatal condition. Patients with dry eye also have a higher chance of problems from popular operations like laser refractive surgery, as well as potentially blinding infections like bacterial keratitis [6]. Recent advancements in the pathophysiology of dry eye illness have led to a better understanding of the condition's multifactorial nature, which is typified by decreased tear production and ocular surface inflammation [7]. Because of this insight, extremely successful therapies have been developed.

What causes 'Dry Eyes Syndrome'?

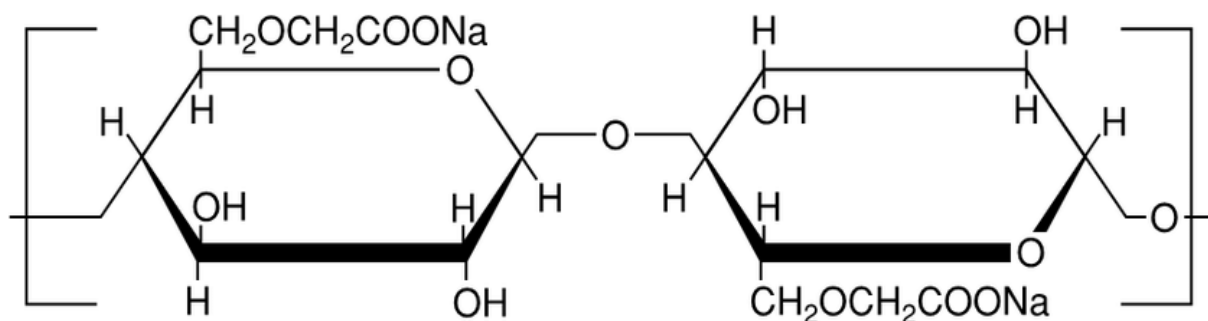
Dry Eye Syndrome (DES), also known as dry eye disease or keratoconjunctivitis sicca, occurs when the eyes don't produce enough tears or when the tears evaporate too quickly, leading to inadequate lubrication and moisture on the eye's surface [8]. This condition can result from various factors, often interconnected. Here are some common causes of Dry Eye Syndrome:

1. **Aging:** As people age, tear production tends to decrease. This is why dry eyes are more common in older adults, particularly those over 50.
2. **Environmental Factors:** Conditions like dry or windy weather, high altitudes, air conditioning, or heating can increase tear evaporation, contributing to dry eyes.
3. **Medication:** Certain medications can reduce tear production or change tear composition, leading to dry eyes. These include antihistamines, decongestants, antidepressants, diuretics, beta-blockers, and some birth control pills [9].
4. **Medical Conditions:** Some diseases and syndromes are associated with dry eyes, such as:
 - **Autoimmune Diseases:** Conditions like Sjögren's syndrome, rheumatoid arthritis, lupus, and thyroid disorders can affect tear production and composition.
 - **Diabetes:** Can alter tear production.
 - **Neurological Disorders:** Conditions affecting nerve function in the eyes can impact tear production.
5. **Hormonal Changes:** Changes in hormone levels, particularly in women due to menopause, pregnancy, or the use of contraceptives, can lead to decreased tear production and dry eyes [10].
6. **Meibomian Gland Dysfunction (MGD):** The meibomian glands in the eyelids produce the lipid (oily) layer of the tear film. Dysfunction or blockage of these glands can result in a quicker evaporation of tears.
7. **Contact Lens Use:** Wearing contact lenses can interfere with tear production or distribution, contributing to dry eyes.
8. **Eye Surgeries:** Certain eye surgeries like LASIK or cataract surgery can affect tear production or the sensitivity of nerves in the cornea, potentially leading to dry eyes [11].
9. **Lifestyle and Screen Use:** Extended screen use (computers, smartphones, TVs) can reduce blinking rates, contributing to tear evaporation and dry eyes.
10. **Infrequent or Incomplete Blinking:** Blinking is essential for spreading tears across the eye surface. Reduced blinking, often due to prolonged focus, can contribute to dry eyes.

Treatment for dry eye syndrome should not be started until a thorough evaluation has been completed, as there are numerous possible explanations for this condition. A thorough medical history should be taken, paying special emphasis to conditions involving the connective tissues, diabetes, thyroid illness, and contact lens usage. Determining the aetiology of dry eye condition also requires considering previous ocular treatments, such as laser refractive surgery. Examining the patient's medication history is crucial because several drugs have the potential to impact tear production. Slit lamp bio-microscopy should be part of a thorough clinical examination to assess the condition of the ocular surface and identify any associated blepharitis, meibomian seborrhoea, or malfunctioning meibomian glands [12].

Composition of Artificial Tears

The aqueous, mucin, and lipid components of genuine tears are all replicated in artificial tears by formulation. Water, electrolytes, and polymers like hyaluronic acid (HA), carboxymethylcellulose (CMC), and hydroxypropyl methylcellulose (HPMC) are frequently found in them. Lipids are also included in some formulations to treat the evaporative aspect of DES [13]. There are choices without preservatives to reduce the possibility of toxicity and allergic responses.



Mechanisms of Action

1. Hydration and Lubrication

The main way that artificial tears work is by hydrating and lubricating the surface of the eyes. Polymers such as CMC and HPMC make the fluid more viscous, which extends the time the tear film remains on the eye and improves its stability [14]. Because of its strong ability to bind water, hyaluronic acid provides excellent hydration and viscoelasticity, which aids in wound healing and lessens blinking friction [15].

2. Stabilizing Tear Film

By restoring the aqueous and mucin layers of the tear film, artificial tears aid in its stabilization. Mucin-mimetic substances, such as CMC, work in concert with natural mucins to enhance the durability and spreadability of tear films [16]. Formulations with lipids decrease tear evaporation by enhancing the lipid layer, which is important for meibomian sufferers [17].

3. Protection of Ocular Surfaces

Artificial tears protect the surface of the eye from mechanical stress and environmental irritants by covering the corneal epithelium in a protective layer. According to Bron et al. [14], this barrier of protection promotes the health and homeostasis of epithelial cells by lowering inflammation and desiccation.

Biochemical Properties of Carboxymethylcellulose

Carboxymethylcellulose is a water-soluble anionic polymer derived from cellulose. It is characterized by its high molecular weight and the presence of carboxymethyl groups that confer unique physicochemical properties. These properties include high viscosity, bio adhesiveness, and the ability to form hydrogen bonds with mucins and other components of the tear film [18].

Clinical Performance

Artificial tears are effective in lessening the symptoms of DES and enhancing the health of the ocular surface, according to clinical research. For example, a study by Schiffman et al. demonstrated that CMC-based artificial tears significantly improved tear film integrity and relieved symptoms [19,20]. A different study [13] demonstrated the advantages of HA-containing drops in improving ocular surface staining scores and tear break-up time (TBUT).

Viscoelastic Properties and Tear Film Stability

The viscoelastic properties of CMC are crucial for its function as a lubricant. These properties allow CMC to mimic the natural tear film, providing both cushioning and prolonged retention on the ocular surface. The high viscosity of CMC solutions increases the residence time of artificial tears, reducing the evaporation rate and enhancing tear film stability. Additionally, CMC forms a protective layer over the corneal epithelium, reducing friction and mechanical stress during blinking [21].

Interaction with Tear Film Components

CMC interacts with various components of the tear film, particularly mucins, which are glycoproteins responsible for maintaining tear film integrity. The anionic nature of CMC allows it to form electrostatic interactions with the positively charged regions of mucins, enhancing mucin spreading and promoting a more stable and uniform tear film. This interaction not only improves tear film stability but also helps in replenishing the depleted mucin layer in patients with DES [17].

Cellular Effects on the Ocular Surface

At the cellular level, CMC has been shown to have protective effects on the corneal and conjunctival epithelia. CMC forms a hydrated matrix that shields epithelial cells from desiccation and environmental insults. Furthermore, CMC has anti-inflammatory properties, reducing the release of pro-inflammatory cytokines and mitigating the inflammatory

response associated with DES. Studies have demonstrated that CMC can modulate cell signalling pathways involved in inflammation and apoptosis, thereby promoting epithelial cell survival and homeostasis [22].

Shear Thinning Behaviour

CMC solutions exhibit shear thinning behaviour, which means that their viscosity decreases with increasing shear rate. This property is advantageous in many applications, such as in eye drops or food products, where a high viscosity is needed to maintain stability at rest, but a lower viscosity is preferred during application or consumption for ease of use [23].

2. CONCLUSION

Carboxymethylcellulose is an effective therapeutic agent for dry eye syndrome, owing to its unique biochemical properties. Its viscoelastic nature, ability to interact with tear film components, and protective effects on ocular surface cells collectively contribute to its efficacy in alleviating dry eye symptoms. With its high viscosity, CMC helps artificial tears stay on the surface of the eyes longer, providing longer-lasting relief from dryness and irritation. When blinking, the viscous nature of CMC solutions lessens friction between the eyelid and the cornea, relieving discomfort. Through its interactions with mucins, CMC enhances the tear film's stability and spreadability. The health and comfort of the ocular surface depend on the formation of a more consistent and stable tear film, which is facilitated by this interaction. Because of its hydrophilic (attractiveness to water) qualities, CMC may hold onto moisture, keeping the surface of the eye continuously hydrated. This is especially helpful in reducing the dryness-related symptoms linked to DES. Over the corneal epithelium, CMC creates a barrier to protect it from outside stimuli. Further research into the molecular interactions and long-term effects of CMC will continue to enhance our understanding and treatment of this condition.

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