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Bringing comfort to the masses: A novel evaluation of comfort agent solution properties

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ABSTRACT

Ocular comfort agents are molecules that relieve ocular discomfort by augmenting characteristics of the tear film to stabilize and retain tear volume and lubricate the ocular surface. While a number of clinical comparisons between ocular comfort agent solutions are available, very little work has been done correlating the properties of specific comfort agents (species, molecular weight, and water retention) and solution properties (concentration, viscosity, zero shear viscosity, and surface tension) to the performance and effectiveness of comfort agent solutions. In this work, comfort-promoting properties related strongly to comfort agent concentration and molecular weight, the first objective demonstration of this relationship across diverse comfort agent species and molecular weights. The comfort agents with the greatest comfort property contributions (independent of specific molecular weight and concentration considerations) were hyaluronic acid (HA), hydroxypropyl methylcellulose (HPMC), and carboxymethylcellulose (CMC), respectively. The observed, empirical relationships between comfort property contribution and comfort agent species, solution properties, comfort agent molecular weight, and solution concentration was used to develop novel comfort agent index values. The comfort agent index values provided much insight and understanding into the results of experimental studies and/or clinical trials and offer potential resolution to numerous conflicting reports within the literature by accounting for the difference in comfort agent performance due to molecular weight and concentration of comfort agents. The index values provide the first objective, experimental validation and explanation of numerous general trends suggested by clinical data.

1. Introduction

Relief of ocular discomfort and the production of high comfort ocular solutions, materials, and devices has become one of the greatest driving forces within the field. Comfort agents are used extensively within topical eye drop formulations [1–13]. Comfort agents promote comfort through many different mechanisms of action [14–16], such as retaining tear volume by reducing drainage rates [17], stabilizing the tear film [18], changing tear film surface tension [19–21], preventing tear evaporation [15], and altering tear fluid viscosity [19,20,22,23]. In addition, comfort agents have been incorporated into a variety of ocular devices, such as contact lenses [24–26,36–41,43,97–101]. There is a significant need for contact lenses that have optimal material characteristics but, at the same time, possess an extended duration of comfort. Contact lens induced dry eye (CLIDE) and contact lens associated discomfort (CLAD) complaints lead to decreased contact lens use and patient dissatisfaction with contact lenses [27–30]. Incorporating comfort agents into contact lenses prevents lens dehydration [31–34], reduces protein adhesion rates [35–40], maintains surface wettability and lubrication [37,41], decreases surface friction and tension [42–44], and has other effects [44].

It has been well documented that frequent application of comfort agent-containing eye drops can greatly increase the level of comfort perceived by consumers [15,16,23,41,45–61], though little work has been conducted to isolate the effects of comfort agent species, molecular weight, percent concentration, and dosage on the efficacy of comfort agents. The purpose of this paper is to relate properties of comfort agent species and solution properties of common comfort agents to molecular weight and concentration. These experiments are needed within the field to, first, allow stringent objective comparative analysis of comfort agents, and second, to use this understanding to identify the most effective comfort agents in the development of highly comfortable formulations and devices.

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Table 1
Advantages of incorporating comfort agents into various topical formulations and ocular devices.

Type	Product	Potential advantage	Potential disadvantage
Topical	Eye drops Artificial tears	Retains tear volume Increases/decreases viscosity Lubricates the eye	Decreased residence time compared to ointment Applied frequently
	Ointments	Prevents excess evaporation Maintains tear film	Increased invasiveness to apply compared to eye drops Reduced vision (temporarily) and aesthetics Increased discomfort due to viscosity or roughness of coating
Devices	Contact lenses	Reduces protein adhesion Maintains lens wettability Lubricates lens surface Refreshes lens surface Releases comfort agent into the tear fluid which leads to same advantages of eye drops without disadvantages	Must be optically clear Loading is constrained by lens thickness and optical clarity
	Punctual plugs	Increased tolerance of plug installation Does not need to be optically clear	Plug must be applied by professional May be expelled without patient knowledge Limited loading due to plug volume Limited release due to decreased surface area and location
	Inserts	Releases comfort agent to the tear fluid which leads to same advantages of eye drops without disadvantages Does not need to be optically clear Versatility in design shape or thickness	Difficult to apply May be expelled without patient knowledge Limited release due to decreased surface area and location

There are many difficulties in defining and differentiating comfort agents. For instance, a number of terms are used to describe them, such as lubricating agents, re-wetting agents, demulcents and mucoprotective agents. While there is no universally agreed upon definition of comfort or comfort agents within the field, comfort agents augment characteristics of the tear film (i.e., increase stability and volume of the film). It is important to note that "comfort agent" does not refer to drugs or molecules that relieve discomfort through pharmacological action, but through material and solution properties that prevent disruption of the tear film, prevent loss of tear volume, and/or reduce stress on the corneal epithelium, specifically to alleviate ocular discomfort. The strength of these properties can be highly variable among different comfort agent species, and certain comfort agents provide comfort through multiple properties while others are limited to one property and are often categorized according to the primary mechanism of action. Lubricating agents primarily reduce the shear stress of eyelid movement on the ocular surface. Re-wetting agents primarily restore or retain tear fluid volume to reduce discomfort. Demulcing agents primarily stabilize fluid films that can act as a protective barrier. A brief summary of the advantages of incorporating comfort agents into various topical formulations and ocular devices is provided in Table 1.

There are two broad classes of comfort agents: polysaccharide comfort agents and acrylic comfort agents. Polysaccharide comfort agents are typically macromolecules composed of one or more types of monosaccharide. Most often, polysaccharide comfort agents are typically linear, hydrophilic, and possess high molecular weight. Substitution along the polymer backbone is common and can affect the overall conformation of the macromolecule, particularly at high degrees of substitution. These substitutions can be branches, alkyl groups, functional groups, or even salt complexes. In solution, polysaccharides have high hydrodynamic volume and a stiff, rod-like conformation at low molecular weight and adapt a Gaussian coil conformation at higher molecular weight [62–69]. Solution viscosity of polysaccharide comfort agents is typically high and pseudoplastic in behavior [70]. However, highly diverse and varied properties can be achieved by controlling monosaccharide composition and morphology within the polysaccharide architecture. In general, polysaccharides all have high water affinity and high rheological-modifying properties. These molecules act as thickeners but demonstrate thixotropic, shear-thinning behavior and possess bio-adhesive properties [70]. These properties vary with changes in molecular weights, concentration, and, in particular, comfort agent species. Comfort agents used in the salt form are referred to as polyelectrolytes, and charged polysaccharides are known as polyelectrolyte polysaccharides.

Acrylic comfort agents are linear chains composed of carbon–carbon backbones with regular repeat units, often including at least one functional group. Acrylic comfort agents can be used as polyelectrolytes or in the neutral state. This category also includes polyacids, which are used less often than other agents but have slightly increased water retention properties when compared to neutral acrylic agents.

Various comfort agents have been tested within clinical trials and are on the market today as topical eye drop formulations. Commonly used comfort agents in over-the-counter (OTC) topical eye drops are presented and described in Table 2 [1–13]. Studies comparing different commercial brands often neglect molecular weight and concentration and compare different molecular species as the only significant variable. The conclusions of clinical trials are often contradictory in the comparison of comfort agent effectiveness as polymeric properties are strongly dependent on molecular weight and solution properties vary dramatically with concentration. One example is the investigation of minimum effective concentration of hyaluronic acid (HA) by several independent studies. Improvements in corneal tissue staining and other measurements were seen in 24 patients after 0.1% HA eye drop solutions were applied, indicating that 0.1% HA is an effective dose [71]. However, an evaluation of 0%, 0.1%, and 0.2% HA topical solutions found no effect with the 0.1% HA solution and concluded that 0.2% was the minimum effective concentration [54]. A more detailed study of 104 patients indicated that 0.1% HA solution was effective in relieving comfort and found