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Improving Ophthalmic Tear Replacement Therapies: A Bioengineering Approach: Mini Review

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Introduction

Dry eye is a troubling and widespread condition affecting between 5 and 35% of humans globally [1,2] and between 0.5 and 35% of dogs [3]. Topical cyclosporine or tacrolimus, used as lacrimogenic agents, have improved the treatment of dry eye in people and animals substantially [3,4] but topical tear improvement and replacement still plays an important role in the alleviation of the pathological changes and ocular signs and symptoms seen in cases of dry eye. The problem with such topical lacrimomimetic therapy is the frequency with which tear replacement drops still have to be applied resulting in poor compliance by human patients or owners of affected dogs [5]. Topical therapies range from those such as Lacri-lube containing lanolin derived from the sebaceous glands of wool-bearing animals such as sheep and comprised predominantly of long chain waxy esters, through carboxy methylcellulose or hydroxy propylmethyl cellulose (HPMC) [6] through polyvinyl alcohol (PVA) [7] to carbomer-based medications and hyaluronic acid (HA) in various formulations [8-10]. We have recently shown a cross-linked HA polymer hydrogel to have significantly better efficacy than regular HA in a spontaneous canine model of dry eye both in an open-label [11] (Figure 1)and masked controlled study [12]. Here the structure and function of the tear film is discussed together with the development and beneficial effects of this novel topical liquid-gel formulation.

The Normal Tear Film

Developing an optimised tear replacement therapy requires a knowledge of the normal tear film. Previously the tear film was presumed to be comprised of three layers, an inner mucin layer, a middle aqueous layer and an outer lipid layer. More recently studies have shown that such a simple trilaminar structure is not fully representative of the tear film. There are mucins which are attached to the outer surface of the corneal epithelium and mucins which are free in the tear film so the boundary between the mucin layer and aqueous layer is much more complex than previously thought. Epithelial cells of the ocular surface produce high molecular weight heavily glycosylated membrane-bound mucins (MUC1, MUC4, and MUC16) which form a hydrophilic barrier, the glycocalyx, key in lubrication and protection of the eye [13]. Mucins are not only attached to the ocular surface but secretory mucins MUC7 and the gel-forming MUC5AC are also liberated into the tear film [14]. The glycosylation of the mucins allows the glycocalyx to reduce friction during blinking and enables the tearfilmto maintain wetting of the eye and stay in place. The outer lipid layer originates predominantly from the Meibomian glands which empty their products at the lid margin. This tear film lipid layer only comprises 0.3% of the tear film but it is a highly complex mix of lipids vital in spread and stabilization of the tear film [15].

With the eye open, the tear film needs to have a high viscosity to resist tear film breakup. But during blinking the tear film must be of a low viscosity to avoid damage to the epithelial cells of the ocular surface [16]. As the tear film flows therefore, it exhibits non-Newtonian rheology with so-called shear-thinning where the viscosity falls as the shear rate increases. The problem is that while the mix of mucins, lipids and aqueous secretion allows such a complex flow behavior, modeling this in an artificial tear replacement is difficult. Tear fluid with its lipid component removed exhibits Newtonian flow characteristics and it is only with the reconstitution of lipids that the non-Newtonian nature is restored [14]. This does not depend on the lipid bilayer on the tear film surface nor in free lipids within the tear film however, but rather the protein tear lipocalin (TL) with its ability to bind hydrophobic lipids [17]. Apo-TL shows classic shear-thinning behavior with a viscosity reaching 18mPa s at its lowest shear rate reducing to 0.92 mPa s at its highest shear rate of 130s-1.

Rheology of tear replacements

Long chain molecules in which there are high levels of intra molecular interactions give flow characteristics more similar to those of the normal tear film than simple small molecule topical medications [18]. Carbomers are polyacrylic acid polymers, available as linear, branched or cross-linked molecules with the acidic carboxyl groups partially dissociating in water to produce

a flexible coil. Different molecules behave in varying manners with those having long alkyl chains acting more elastically and those with shorter ones being less elastic, these having different muco adhesive indices [19-21]. Older tear replacement eye drops such as those based on carboxy methyl cellulose, polyvinyl alcohol have the disadvantage that, although they are long-chain molecules, there is limited inter-chain interaction. Carbomers can be covalently cross-linked substantially changing their rheological properties [19] and cross-linked hyaluronic acid gels have been used as agents for tissue reconstruction, drug delivery, more recently as very safe and effective tear substitutes [22,23] (Figure 1).

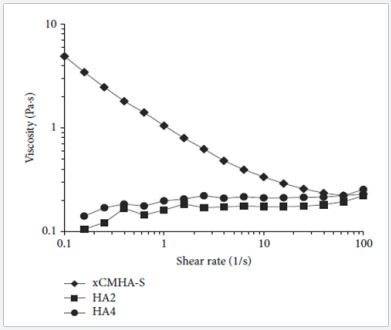

Figure 1: Markedly reduced viscosity of the cross-linked HA product at high sheer rates shows non-Newtonian flow dynamics reproduced.

Development of a novel cross-linked hyaluronic acid hydrogel, CMHA-S

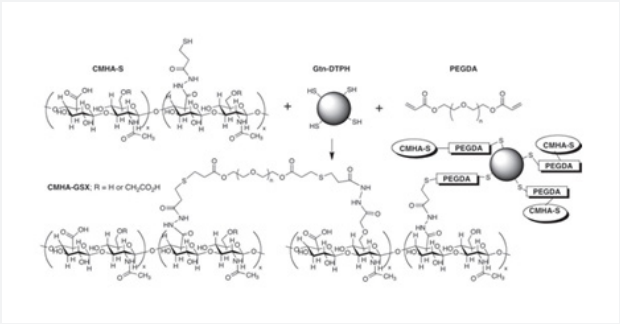

Figure 2: The chemistry behind formation of a cross-linked hyaluronic acid polymer acting as a tear replacement and corneal repair gel.

Researchers at the University of Utah developed a new disulphide cross-linking technique which allowed them to prepare a hyaluronic acid hydrogel from thiolated hyaluoronic acid by synthesing dithiobis propanoic dihydrazide and diothiobidbutyric dihydrazide and coupling them to hyaluronic acid through a carbodiimide intermediate giving the compound shown in Figure 2, reducing the disulphide bonds thus formed using dithioreitol and purifying with exhaustive dialysis [22,23]. This cross linked thiolated carboxy methylated hyaluronic acid is referred to as CMHA-S. Differential oxidation can modify the degree of disulphide cross-linking and thus the viscosity of the gel [22].Rheological studies show the CMHA-S to behave in non-Newtonian manner as shown in the graph of shear rate and viscosity in figure 2 where the viscosity reduces dramatically with increasing shear rate. Previous work has shown that the CMHA-S accelerated healing and re-epithelization of experimentally induced corneal ulcers [24] and recent work has extended this work showing similar effects in spontaneous ulceration of canine and feline corneas [25]. As noted above we showed the CMHA-S to have great benefits in cases of dry eye in canine patients in our hospital [11,12]. The CMHA-S has great potential for use in cases of dry eye and those with corneal ulceration both in both domestic pet species and in human patients, where a tremendous unmet need exists. CMHA-S has recently demonstrated positive data in clinical studies for accelerating corneal epithelial defect closure post refractive surgery in humans, again confirming the safety and effectiveness of this product.

Conclusion

While the tear film may seem a simple structure, it is in effect a highly complex molecular mix behaving such that it is retained on the ocular surface with a relatively high viscosity, but once moved by the eyelid margin during blinking has a low viscosity. Emulating this non-Newtonian fluid behaviour in artificial tear formations is a difficult task, but recent advances with cross-linked hyaluronic acid moieties, such as the CMHA-S, have made significant advances in optimizing tear replacement therapies which can have a benefit in protecting and re-epithelizing an injured cornea.

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