

SYSTANE® HYDRATION PF's Dual-Polymer Technology: Hydroxypropyl-Guar and Sodium Hyaluronate

Lyndon Jones, PhD, FCAHS, FCOptom, FAAO¹

William Ngo, OD, PhD, FAAO²

Thao Yeh, OD, PhD, MPH, FAAO³

**1. Professor / Director / University Research Chair, Centre for
Ocular Research & Education, School of Optometry & Vision
Science, University of Waterloo, Ontario, Canada**

**2. Head of Biosciences, Centre for Ocular Research & Education,
School of Optometry & Vision Science, University of Waterloo,
Ontario, Canada**

3. Alcon Medical Affairs, North America, Fort Worth, TX

Key Messages

- Artificial tears are designed to lubricate the ocular surface by mimicking the natural tears through the use of various viscosity-enhancing agents, including but not limited to hydroxypropyl-guar (HP-guar) and sodium hyaluronate (HA).
- SYSTANE® HYDRATION PF is a new unit-dose, preservative-free artificial tear containing dual demulcents (propylene glycol and propylene glycol) and a unique combination of both HP-guar and HA polymers to leverage the water-retentive and viscoelastic properties of the HA, and the mucoadhesive properties of the HP-guar, to enhance ocular surface residence time and spread of demulcents in the formulation.
- The dual-demulcent, dual-polymer artificial tear (SYSTANE® HYDRATION PF) provides statistically significantly improved protection against desiccation through increased surface retention time compared to single-polymer (HP-guar or HA) formulations, and it also reduces surface friction and maintains lubricity to a greater extent than the HA single-polymer formulation.

Introduction

Artificial tears are designed to lubricate the ocular surface and relieve symptoms of dry eye by replacing or supplementing the natural tears, which have a unique viscoelastic property. Natural tears are viscous enough to prevent quick draining and evaporation but fluid enough such that, with a blink, they spread to lubricate the entire ocular surface. Artificial tears try to model this behavior. To mimic the properties of the natural tears, artificial tears contain a variety of viscosity-enhancing agents, with the aim of improving lubrication and prolonging retention of the demulcents on the ocular surface. The viscosity-enhancing agents used in artificial tears may include the FDA-approved active ingredients carboxymethyl cellulose (CMC), dextran, hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and polyethylene glycol (PEG). Other possible viscosity-enhancing agents include carbomer 940 (polyacrylic acid), hyaluronic acid (HA), hydroxypropyl-guar (HP-guar), and polyvinylpyrrolidone (PVP), all of which are inactive ingredients based on the FDA monograph.¹

The SYSTANE® family's core technology consists of the demulcent propylene glycol (PG), the viscosity-enhancing agent HP-guar, borate, and sorbitol (Table 1).² Each SYSTANE® product line targets a specific type of dry eye through the addition of demulcents, oils, and/or viscosity-enhancing agents.

SYSTANE® HYDRATION PF is the most recent addition to the SYSTANE® portfolio. It is a unit-dose preservative-free artificial tear formulated with the SYSTANE® core technology and the key additions of the PEG 400 (active ingredient) and sodium hyaluronate (also known as hyaluronic acid, or HA), as well as the removal of ingredients that act as preservatives. SYSTANE® HYDRATION PF is ideal for moderate-to-severe dry eye patients who have a sensitivity to preservatives, who concurrently use other preserved eye drops, or require ocular lubrication more than 4-6 times per day. Below, we discuss the chemistry and clinical findings for HP-guar and HA, as well as the benefits from combining the two polymers.

		Preserved			Preservative-free	
		SYSTANE® ULTRA	SYSTANE® BALANCE	SYSTANE® COMPLETE	SYSTANE® ULTRA PF	SYSTANE® HYDRATION PF
Active ingredients	Propylene glycol	✓	✓	✓	✓	✓
	Polyethylene glycol 400	✓	x	x	✓	✓
Inactive ingredients	HP-Guar	✓	✓	✓ (3x concentration of BALANCE)	✓	✓
	Boric Acid	✓	✓	✓	✓	✓
	Sorbitol	✓	✓	✓	✓	✓
	Purified Water	✓	✓	✓	✓	✓
	Mineral oil	x	✓	✓	x	x
	Sodium Hyaluronate	x	x	x	x	✓
	Sodium Borate	x	x	x	x	✓
	Aminomethylpropanol	✓	x	x	✓	✓
	Potassium Chloride	✓	x	x	✓	✓
	Sodium Chloride	✓	x	x	✓	✓
	Polyquad® (preservative)	✓	✓	✓	x	x
	EDTA	x	✓	✓	x	x
	Dimyristoyl Phosphatidylglycerol	x	✓	✓	x	x
	Polyoxyl 40 Stearate	x	✓	✓	x	x
	Sorbitan Tristearate	x	✓	✓	x	x
Product type		Solution	Emulsion	Nanoemulsion	Solution	Solution

Table 1: SYSTANE® products and their ingredients.

Hydroxypropyl-Guar (HP-Guar, Inactive Ingredient)

Guar gum is a high molecular weight, natural polysaccharide derived from the guar bean (*Cyamopsis tetragonoloba*).³ Its ability to form a viscous solution at low concentration makes it an attractive option as a thickening and viscosity agent in a wide range of industrial products.³ For ophthalmic use, HP-guar is used in a rigid gas permeable contact lens solution and in SYSTANE® artificial tears.

Chemistry and Properties

Like guar gum, HP-guar is a polysaccharide composing of a linear backbone of mannose units and side chains consisting of galactose units, with a 2:1 ratio of mannose:galactose. However, HP-guar is a chemically-modified guar designed to improve heat stability of guar, with minimal effect on the cross-linking potential with metal ions, including tetra-hydroxyborate (Figure 1).³ A borate anion condenses onto one galactose unit, converting nonionic HP-guar into an anionic HP-guar (Figure 1, top). Through this mechanism, the borate can crosslink two separate HP-guar segments and increases solution viscosity, giving rise to gels (Figure 1, bottom).⁴ This HP-guar/borate interaction transforms a low-viscosity liquid to a shear-thinning gel, and occurs between pH 7 and 8.⁵ Functionally, HP-guar acts as a gelling agent and mimics the mucin layer of the tear film.⁶ It has been shown to have good lubricity by demonstrating excellent drag reduction.⁵

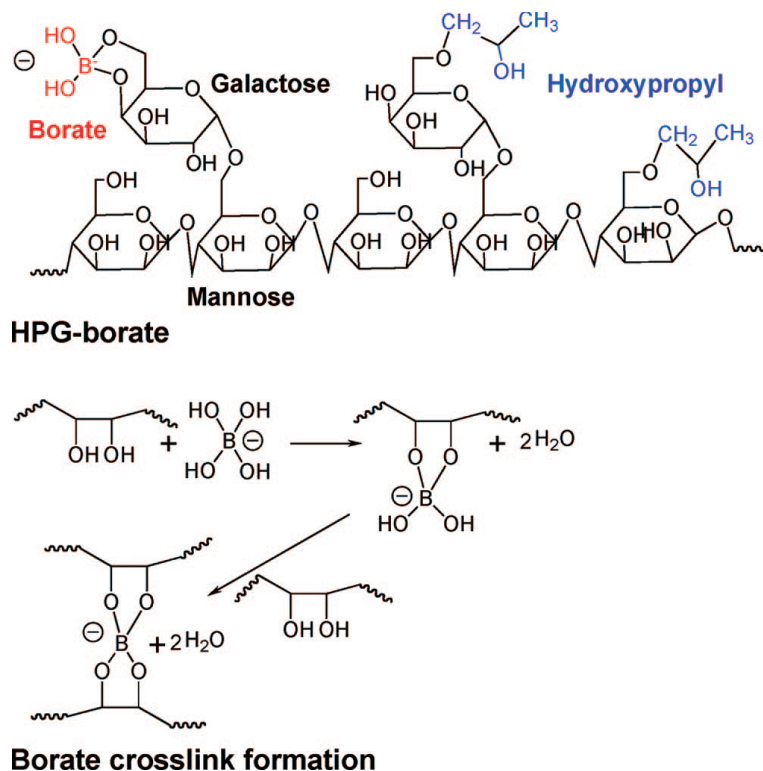


Figure 1: Hydroxypropyl guar (HP-guar) is a linear polymannose with pendant galactose sugars on alternating mannose units.⁴

Mechanism of Action


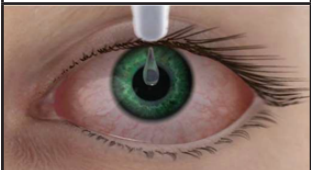
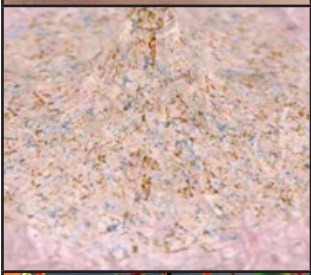
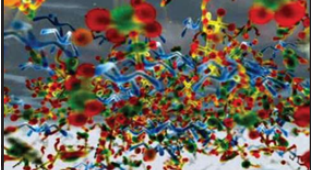
	<p>In the bottle, the pH is approximately 7.9 and sorbitol/borate/HP-guar complexes are in a state of dynamic equilibrium, whereby sorbitol competes with borate to form complexes with HP-guar.²</p>
	<p>When a drop is instilled, the pressure exerted on the bottle to extract the drop reduces gel viscosity.²</p>
	<p>Upon instillation, the following ocular surface characteristics fortify the borate/HP-guar crosslinks:</p> <ul style="list-style-type: none"> • Change in physiological pH (normal: 7.5, dry eye: 7.8)³, and • Presence of natural divalent ions in the tear film (e.g., calcium, zinc, and magnesium) that weaken sorbitol/HP-guar interactions, thereby increasing the borate/HP-guar complexes.²
	<p>The increased density of the borate/HP-guar crosslinks results in a matrix that prolongs the retention time of the demulcents on the ocular surface.</p>

Figure 2: Mechanism of action for SYSTANE® artificial tears.

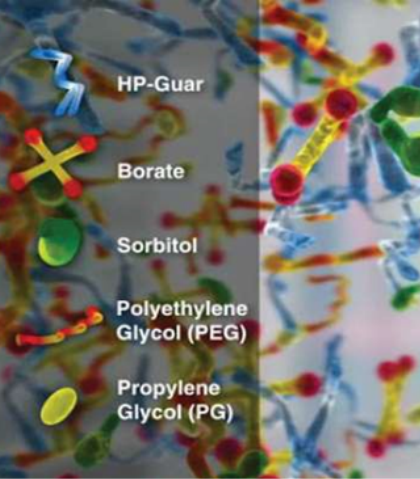
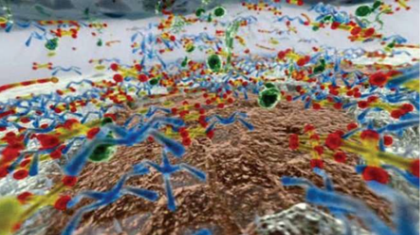
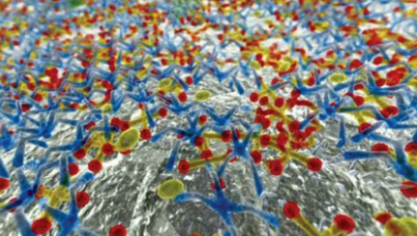
SYSTANE® Technology*	SYSTANE® Function	
	 <p data-bbox="540 451 911 583">A tightly structured protective matrix is formed over the hydrophobic, damaged areas of the ocular surface³</p>	 <p data-bbox="963 420 1300 619">This highly structured protective matrix enhances retention of the active demulcents to allow long-lasting lubrication and surface protection</p>
(a)	(b)	(c)

Figure 3: (a) The interplay between HP-guar, borate, and sorbitol control the density of cross-linking. (b) When mixed with the tears, a polymer network forms and binds to areas of compromised glycocalyx integrity, (c) ultimately spreading and prolonging the exposure of the active ingredients (in this example, demulcents PG and PEG) to the ocular surface.

*PEG is included in SYSTANE® ULTRA and HYDRATION (not BALANCE or COMPLETE).

Sodium Hyaluronate (Inactive Ingredient)

Sodium hyaluronate (HA) is a naturally-occurring, biocompatible polysaccharide with unique viscoelastic and hygroscopic (water absorptive) properties, enabling it to serve many critical roles in the human body. It can be found in the extracellular matrix of connective tissue in the skin, umbilical cord, and synovial fluid.⁷ In the eye, HA can be found in the vitreous, lacrimal gland, corneal epithelium, conjunctiva, and the human tear fluid.⁷⁻¹⁰ In surgical procedures, HA has been used to replace the vitreous, protect the corneal endothelium from mechanical trauma during cataract extraction, and spread over the surface of the lens and iris before suturing the graft during keratoplasty to provide better graft transparency.¹¹

Chemistry and Physicochemical Properties

The hydrophilic HA molecule is made of repetitive units of D-glucuronic acid and N-acetyl-glucosamine (Figure 4, left).¹²

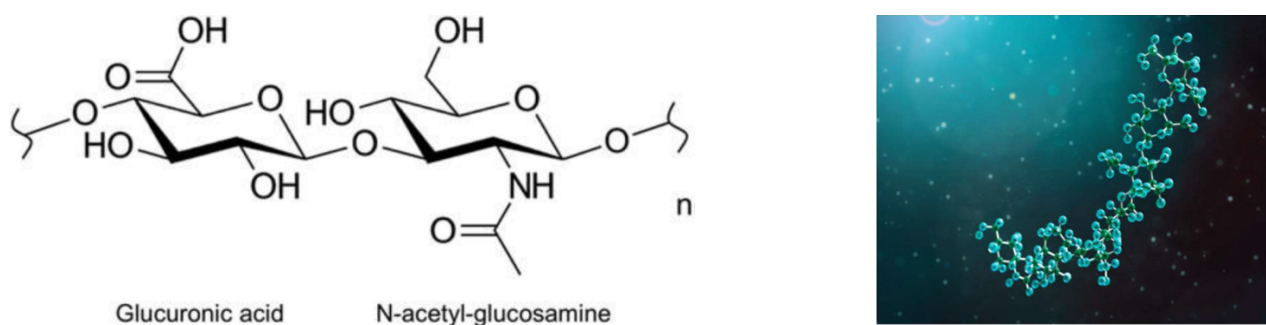


Figure 4: The repeating unit (left) and cartoon depiction (right) of sodium hyaluronan (HA).

The molecular structure of HA gives it some very unique properties.

Hydration: The random coil structure of HA (Figure 4, right) is believed to allow HA to hold up to 1,000 times its weight in water, giving HA its hygroscopic property.¹³

Viscoelasticity: Like natural tears, HA-containing solutions are non-Newtonian in nature and actively change their viscosity based on the presence of shear force.¹² When the eye is open, HA maintains a higher viscosity that allows it to be retained on the ocular surface. During a blink, when shear force is applied, the viscosity of HA decreases and permits it to spread across the ocular surface.^{14,15} This unique property increases tear film stability and adherence to the corneal epithelium, while also reducing friction during blinking.^{6,16}

The hygroscopic and viscoelastic properties of HA, as well as its tolerability, make it well-suited for use in artificial tears and other ophthalmic products because they enhance the retention of demulcents, thereby improving hydration.¹⁷

Dual-Polymer (HA/HP-guar) Lubricant

SYSTANE® HYDRATION PF combines the unique properties of both HP-guar and HA to enhance retention and spread of the demulcents, PG and PEG 400 (Figure 5).¹⁶ Below is a summary of a pre-clinical study that evaluates the potential benefits of this unique combination.

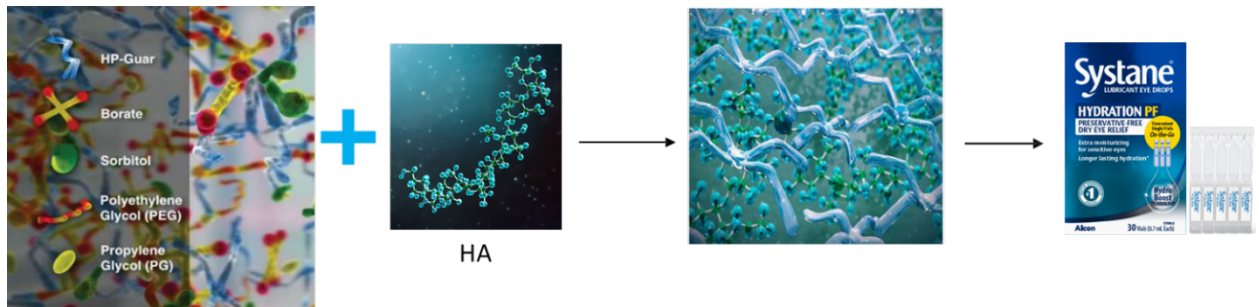


Figure 5: SYSTANE® HYDRATION PF combines HP-guar and sodium hyaluronan (HA).

A Pre-Clinical Study

Effects of a Hyaluronic Acid/Hydroxypropyl Guar Artificial Tear Solution on Protection, Recovery, and Lubricity in Models of Corneal Epithelium¹⁶

Rangarajan, R., et al. Journal of ocular pharmacology and therapeutics: the official journal of the Association for Ocular Pharmacology and Therapeutics, 2015. 31(8): p. 491-497.

This in vitro study compared a dual-demulcent (PG, PEG 400), dual-polymer (HA, GP-guar) formulation (SYSTANE® HYDRATION) to similar single-polymer formulations containing either HP-guar or HA, and to a control (media). The single polymer formulations contained the same dual-demulcents and inactive ingredients as SYSTANE® HYDRATION, but without either the HA (HP-guar formulation) or HP-guar (HA formulation). Each formulation was assessed for efficacy based on the following properties: (1) protection against desiccation, (2) protection from surfactant insult, and (3) surface and sustained lubricity.

Desiccation Protection

Cultured human corneal epithelial cells were grown to confluence and then treated with test formulations. Protection against desiccation was assessed after removing test formulations and exposing cells to air in 45% humidity for 30 minutes. Formulation retention was assessed by rinsing cells with media five times before exposing them to desiccation. Using cell viability assays, protection and retention was calculated as percent viability relative to an undesiccated control.

The study found that the dual-polymer (HP-guar/HA) formulation was associated with significantly greater cell viability than the individual single polymer formulations (HP-guar/HA: 53.6%, HP-guar: 36.5%, HA: 25.0%). After rinsing away the formulations and desiccating the cells, the HP-guar/HA formulation still yielded significantly greater cell viability than the two individual single polymer formulations (HP-guar/HA: 44.4%, HP-guar: 29.8%, HA: 21.5%). These results demonstrate that the dual polymer (HP-guar/HA) formulation confers greater desiccating resistance, possibly through hydration and enhanced retention (Figure 6). In both cases, the media control with no added formulations resulted in minimal cell viability.

* $P < 0.05$ vs control, HP-guar, and HA

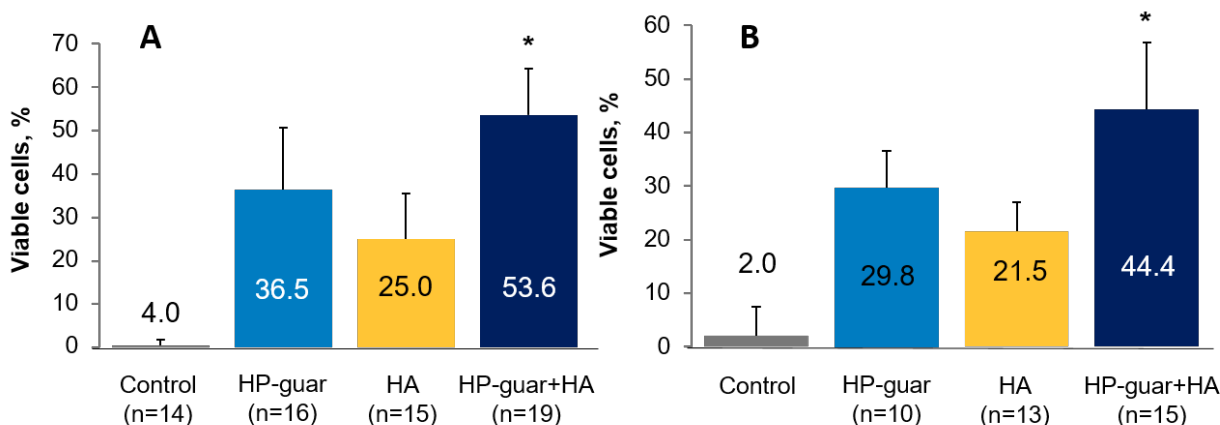


Figure 6: Protection against desiccation (A) immediately after treatment (i.e., hydration) and (B) after the formulation was rinsed away (i.e., retention of effect).

Protection Against Surfactant Insult

Immortalized human corneal-limbal epithelial cells were grown to confluence and treated with each of the formulations. The cells were then exposed to a surfactant-based insult. The ability of the formulations to protect the cells from the surfactant insult was assessed by quantifying cell membrane fluorescein permeability, transepithelial electrical resistance (TEER), and with a live/dead cell viability assay. After the insult, the cells associated with the HP-guar/HA formulation exhibited greater cell membrane barrier function (least fluorescein permeated through the cells, and greatest TEER) than those associated with the single-polymer formulations (Figures 7 and 8). Consistent with these findings, the group with the greatest number of cells still viable after the insult belonged were those treated with HP-guar/HA (Figure 9). In all cases, the cells in the media control group was unable to maintain membrane barrier function and viability after the surfactant insult.

* $P < 0.05$ vs control, HP-guar, and HA

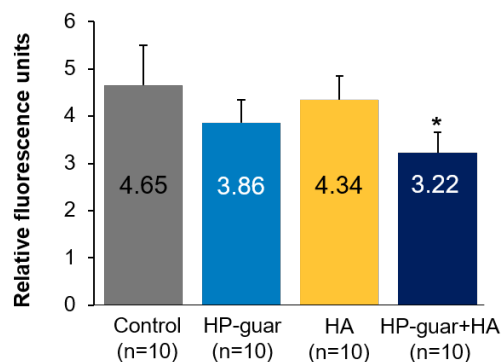


Figure 7: Barrier sodium fluorescein permeability after 4 hours of recovery show that only the dual-polymer (HP-guar/HA) formulation had significantly less NaF permeability relative to the control.

* $P < 0.05$ vs control, HP-guar, and HA

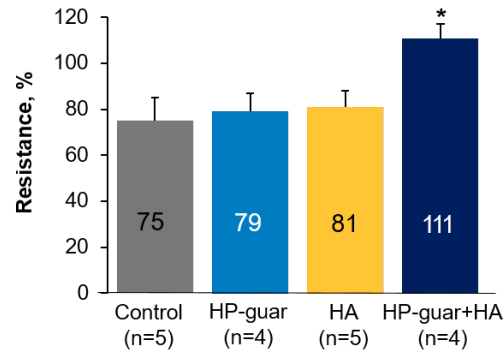


Figure 8: TEER was significantly greater with the dual polymer (HP-guar/HA) formulation compared to the single-polymer (HP-guar and HA) formulations and control.

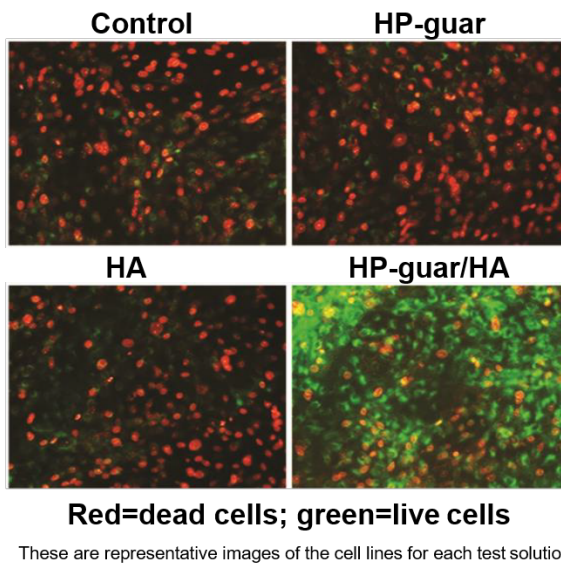


Figure 9: After surfactant exposure, a greater number of viable cells were observed with dual-polymer (HP-guar/HA) formulation compared with media controls and each of the single-polymer (HP-guar and HA) formulations.

Lubricity

Finally, to test surface lubrication, a tribological apparatus was used to quantify the surface friction of pericardium tissue associated with each of the test formulations. Saline was used as a control. The coefficient of friction was measured at baseline, and at 1 and 2 minutes after treatment with 50 μ L of the test formulations. The test formulations were then removed and the pericardium tissues were blotted dry. To test the retention of the formulations, saline (50 μ L) was added and the coefficient of friction was measured again for 6 times at 1-minute intervals.

The key findings were that (1) the hydrodynamic friction on the pericardial tissue was reduced significantly after the application of HP-guar, HA, or HP-guar/HA test formulations compared with saline, (2) the dual polymer (HP-guar/HA) formulation was associated with significantly lower friction than the HA formulation, and (3) significant differences in friction were evident 1 min after instillation and 1 min after tissue surfaces were blotted and rinsed with saline (Figure 10).

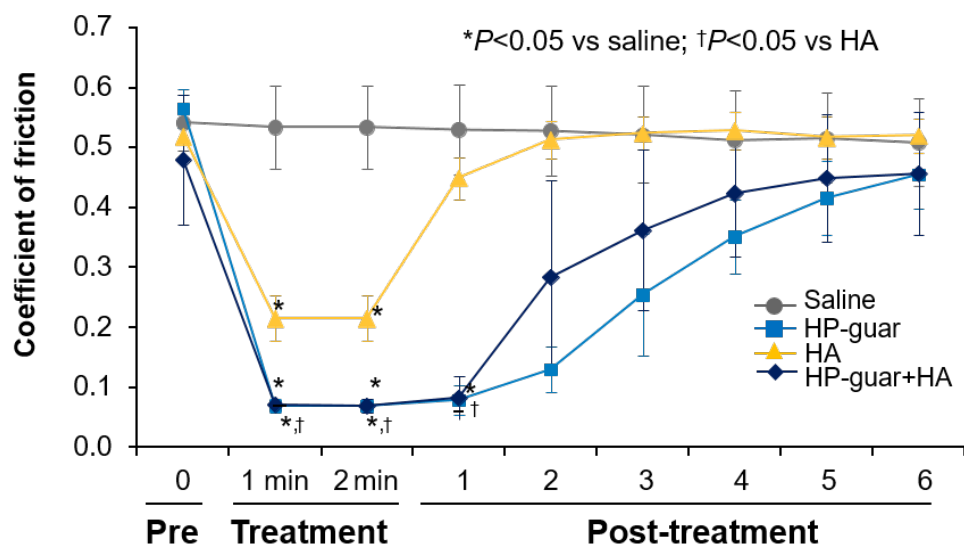


Figure 10: The coefficient of friction for the test formulations: saline (Control), HP-guar, HA, and HP-guar+HA.

Conclusions

The newest addition to the SYSTANE® family of artificial tears, SYSTANE® HYDRATION PF, combines the core SYSTANE® technology (PG demulcent and inactive HP-guar) with the demulcent PEG 400 and HA into a single preservative-free formulation. The dual-demulcent (PG and PEG 400), dual polymer (HP-guar and inactive HA) artificial tear leverages the hygroscopic and viscoelastic properties of HA, and the mucoadhesive properties of HP-guar. These properties extend ocular surface residence time, enhance spread of demulcents, in addition to providing enhanced lubricity and increased protection against desiccation and surfactant insult, as shown in an *in vitro* study.

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