White Paper

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Evolution of Systane® Artificial Tears

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Key Messages

- Artificial tears aim to replicate the natural tears' composition and physical properties.
- As the understanding of the pathophysiology of dry eye has expanded over the last two decades, artificial tears have transformed from simple saline aqueous lubricant formulations to more advanced mixtures to target the etiology of dry eye disease. Formulations to provide relief via unique gelling chemistry and eye supplementation with demulcents, phospholipids, mucomimetic polymers and oils coupled to innovative packaging have paved the way for novel preserved and preservative-free formulations.
- The evolution of the Systane® artificial tears offers some of the most technologically advanced and robust formulations, including preservative-free options, for all major forms of dry eye.

Introduction

Dry eye disease (DED) is characterized clinically by reduced tear volume, tear film instability, and increased rate of tear evaporation.[1] The lacrimal functional unit (LFU), which consists of the lacrimal glands, ocular surface (cornea, conjunctiva and meibomian glands) and lids, and the sensory and motor nerves that connect them, controls the balance of lipids, proteins, mucins, and electrolytes in the tear film. In DED, the LFU is compromised, which can lead to tear hyperosomolarity, ocular surface inflammation and damage, and symptoms of dryness and irritation.[2]

Artificial tears are traditionally considered the mainstay therapy for DED, offering palliative care throughout all stages of DED.[3] Although artificial tears do not contain the biologically active components of natural tears, their ingredients and biophysical properties supplement the human tear film to provide long-lasting symptom relief. The key components of artificial tears and how Systane® products have evolved to optimize relief for the full spectrum of dry eye patients are discussed below.

Artificial Tear Targets and Formulations

The natural tear film consists of aqueous, mucins, lipids, proteins, and electrolytes that all work together to hydrate, protect, and stabilize the ocular surface.[1] Furthermore, the viscoelasticity of natural tears allows it to spread well across the ocular surface with the shear force of a blink.[1, 4] Artificial tears aim to mimic these characteristics by providing moisture, lipids, and / or electrolytes using a viscoelastic vehicle for increasing retention and optimizing ocular surface coverage.

In the United States (US), over-the-counter (OTC) artificial tears are marketed under the Food and Drug Administration (FDA) Ophthalmic Final Monograph.[5] The monograph specifies permitted active ingredients, combinations of active ingredients and their concentrations.[5] However, the monograph does not specify which excipients or ingredients can be added to the products and solution parameters can vary widely.[5] Therefore, inactive ingredients can be a key differentiator between artificial tear brands. Common inactive ingredients include buffers, viscosity-enhancing agents, phospholipids, osmotic agents, and preservatives.[3] Buffers stabilize the pH of solutions at the specific target for ocular pH needs.[3] Viscosity-enhancing agents can benefit the dry eye ocular surface through various mechanisms, such as increasing tear film thickness, protecting against desiccation, and promoting tear retention at the ocular surface.[3] Phospholipids are found in the natural tear film and can help replenish the tear lipid layer in patients with lipid deficiency.[3, 6] Osmotic agents, including electrolytes and organic osmolytes, can balance the osmotic pressure on the ocular surface to prevent or protect tissues from hyperosmotic stress.[3] Finally, preservatives are added to multi-dose bottles to prevent microbial growth due to potential repeated exposure of the tip to contaminated surfaces.[3]

Systane

Systane artificial tears have almost two decades of history (Figure 1). The artificial tear portfolio consists of non-lipid-based and lipid-based formulations, and preservative-free formulations are available for the non-lipid-based products. The Systane product landscape and evolution of the platform technology into non-lipid and lipid-based formulations are discussed below.

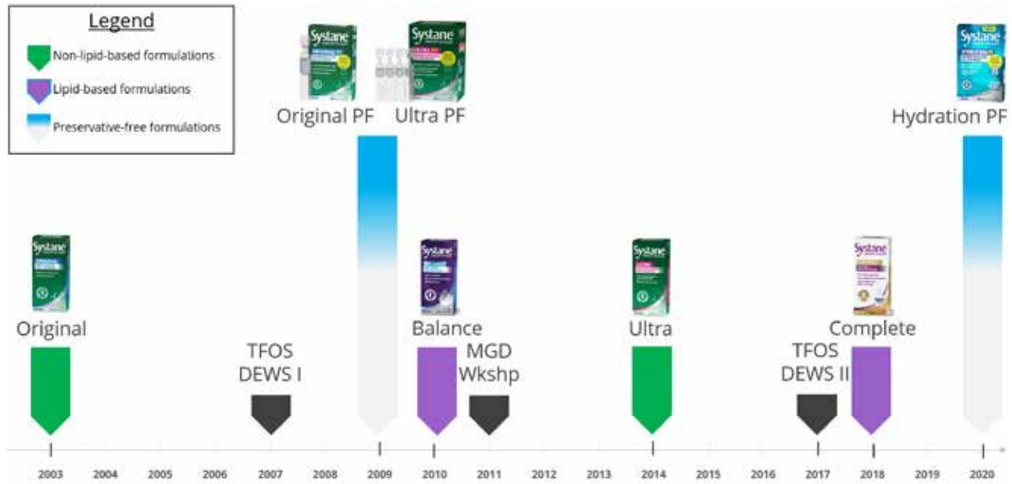

Figure 1: Systane artificial tears timeline.

Systane Foundation: Propylene Glycol + Hydroxypropyl Guar (HPGuar) / Borate Gelling Technology

Systane artificial tears contain the demulcent(s) propylene glycol (PG) alone or combined with polyethylene glycol (PEG). They are combined with Systane's unique hydroxypropyl guar (HPGuar) / borate gelling technology (Figure 2), which helps soothe irritated areas of the ocular surface epithelium by targeting and protecting mucus membranes with its oily or mucilaginous consistency. HPGuar is a high molecular weight water loving polymer with chemistry along the polymer backbone to generate a high viscosity gel when placed in the eye.[7] The HPGuar (structure shown in Figure 2) is a hydroxypropyl derivative of guar.[7] The hydroxypropyl groups block the intermolecular hydrogen bonding so that the solubility of guar is increased and can bind preferentially to hydrophobic regions via the hydroxypropyl groups to damaged areas of the glycocalyx surface.[7] Borate is a buffer and, in Systane formulations, the borate ions can bind with cis-diols of the HPGuar to form covalent bonds and crosslink the polymers to form viscoelastic gels.[8] The HPGuar viscosity-enhancing polymer in combination with demulcents forms a hydrated scaffold on the ocular surface to protect and resist desorption for long term protection. The *in situ* crosslinking generated with HPGuar and borate is unique in that is works with the ocular pH of the tear film. The generated gel serves to act like an ocular shield and is facilitated by the physiological pH of the ocular surface tear film to help retain the demulcent(s) on the ocular surface.[9] In concert with the retained demulcent(s), the gel mixture spreads across the ocular surface to provide lubrication and increased ocular comfort during the blink.

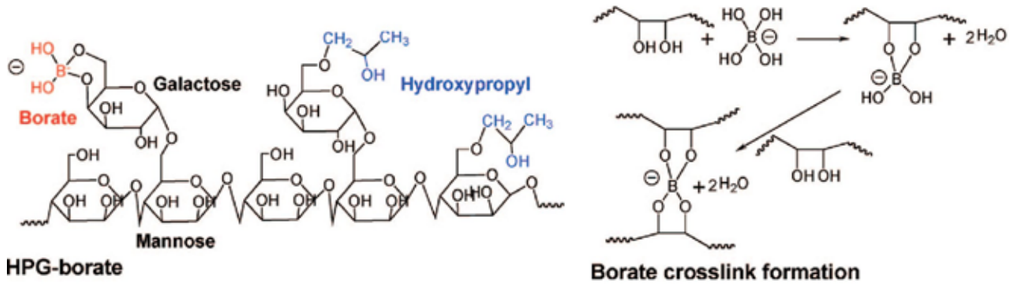

Figure 2: Hydroxypropyl guar is a linear polymannose with pendant galactose sugars on alternating mannose units. HPG=hydroxypropyl guar.

Non-Lipid-Based Formulas

Systane ORIGINAL was the first of several generations of Systane ocular lubricants (Figure 3). The artificial tear formulation consists of two demulcents (PG and PEG), Systane gelling technology (HPGuar and borate), electrolytes (calcium, potassium, magnesium, sodium, and zinc chloride), and the preservative POLYQUAD® (Polyquaternium-1 0.001%) (Table 1).

Figure 3: Systane non-lipid-based formulations.

Opportunities to enhance the gelling technology led to the development of Systane ULTRA. The addition of sorbitol and the removal of multivalent electrolytes (calcium, magnesium, and zinc chloride) are the key differences from its predecessor. By competing with borate to bind to HPGuar, sorbitol reduces the in-bottle gel formation, and hence viscosity.[10] Once on the ocular surface, the dilution of sorbitol and the physiological pH of the dry eye tear film promote the HPGuar / borate crosslinking to improve in situ viscoelasticity.[10] HPGuar, borate, and sorbitol form the Systane Advanced Gel Technology, which increases the retention time of the active demulcents on the ocular surface and serves as the standard for all subsequent Systane artificial tear formulations, with the exception of Systane BALANCE.

The most advanced non-lipid-based Systane formulation is Systane HYDRATION, which has the unique combination of the Systane Advanced Gel Technology and sodium hyaluronate, Sodium hyaluronate is the water-soluble salt form of hyaluronic acid, a biocompatible polysaccharide with unique hygroscopic and viscoelastic properties.[11] Its role as a natural lubricant and its water-retaining properties make it well-suited for the ocular surface to help provide enhanced hydration and comfort to dry eye patients.[12]

		Systane ORIGINAL	Systane ULTRA	Systane HYDRATION PF
	ACTIVE INGREDIENTS			
Demulcents	Polyethylene Glycol 400 0.4%	✓	✓	✓
	Propylene Glycol 0.3%	✓	✓	✓
	INACTIVE INGREDIENTS			
Advanced Gel Technology	Hydroxypropyl Guar	✓	✓	✓
	Boric Acid	✓	✓	✓
	Sorbitol		✓	✓
Electrolytes	Potassium Chloride	✓	✓	✓
	Sodium Chloride	✓	✓	✓
	Calcium Chloride	✓		
	Magnesium Chloride	✓		
	Zinc Chloride	✓		
Humectant	Sodium Hyaluronate			✓
Buffer	Aminomethylpropanol		✓	✓
	Sodium Borate			✓
Vehicle	Purified Water	✓	✓	✓
Preservative	Polyquaternium-1	*	*	**

*Polyquaternium-1 only present in preserved formulations. **No preserved formulation available in US.

Table 1: Systane non-lipid-based formulations.

All non-lipid-based Systane artificial tears are available as preservative-free formulations in single-use, unit-dose vials (Figure 1). The formulations available for unit-dose do not contain the preservative POLYQUAD® and are ideal for severe dry eye patients who require frequent daily dosing of artificial tears and who are using preserved prescription ophthalmic medications for conditions such as glaucoma, and during refractive and cataract perioperative management.

Lipid-Based Formulas

While the non-lipid-based formulations deliver much needed relief to patients suffering from ocular surface discomfort, it is estimated that the majority of dry eye patients have evaporative dry eye, a condition in which insufficient lipid production or irregular lipid composition compromise the integrity of the tear film.[13] Systane's lipid-based formulations address the needs of this population.

Systane BALANCE was the first formulation to combine a demulcent (PG), an emollient (mineral oil), an anionic polar phospholipid (dimyristol phosphatidylglycerol (DMPG)), emulsifying agents (polyoxyl 40 stearate and sorbitan tristearate), and a modified HPGuar / borate gelling technology (Table 2).[6] It was designed to soothe and lubricate the irritated ocular surface with PG, provide protection against desiccation with the mineral oil, and supplement the tear lipid layer with DMPG to help reduce the rate of tear evaporation. The emulsifying agents help to reduce the surface tension to promote the spread on the ocular surface. One limitation of this formulation was the reduced HPGuar concentration, which was less than one-third of the non-lipid-based formulations.

The most advanced lipid-based formulation in the portfolio is the nanoemulsion Systane COMPLETE. The formulation was developed with improved oil-phase processing to reduce lipid droplet size (<100 nm), which also allowed for a 3-fold higher concentration of HPGuar compared to Systane BALANCE. The higher HPGuar concentration matches the Advanced Gel Technology contained in all non-lipid-based Systane formulations to improve the retention and spread of the demulcents and to enhance lubrication during the blink.

Figure 4: Systane lipid-based formulations. (*Less than one-third of HPGuar concentration contained in all non-lipid-based Systane formulations).

		Systane BALANCE	Systane COMPLETE
	ACTIVE INGREDIENTS		
Demulcent	Propylene Glycol 0.6%	✓	✓
	INACTIVE INGREDIENTS		
Advanced Gel Technology	Hydroxypropyl Guar	✓*	✓
	Boric Acid	✓	✓
	Sorbitol	✓	✓
Lipitech™ System	Dimyristoyl Phosphatidylglycerol	✓	✓
	Mineral Oil	✓	✓
Emulsifiers	Polyoxyl 40 Stearate	✓	✓
	Sorbitan Tristearate	✓	✓
Chelating Agent	Edetate Disodium	✓	✓
Vehicle	Purified Water	✓	✓
Preservative	Polyquaternium-1	✓	✓

*Hydroxypropyl guar concentration in BALANCE is one-third contained in COMPLETE.

Table 2: Ingredients for Systane lipid-based formulations.

Study Highlights for Systane HYDRATION and COMPLETE

Systane HYDRATION Pre-Clinical Study Results

A preclinical in vitro study compared the effects of four test solutions (vehicle, Systane HYDRATION, HYDRATION without sodium hyaluronate (HPGuar), and HYDRATION without HPGuar (HA)) and found that Systane HYDRATION provided better protection against desiccation and surfactant insult compared to the control and the HA single-polymer formulation (Figure 5).[14]

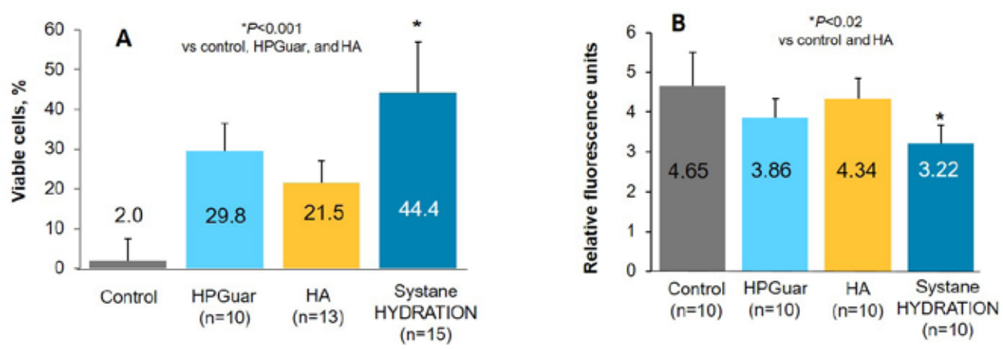

Figure 5: (A) Percentage of viable immortalized human corneal epithelial cells after exposure & removal of test solutions and desiccation, and (B) Relative fluorescence units of immortalized human corneal-limbal epithelial cells 4 hours after surfactant exposure for each test solution.

Systane COMPLETE Clinical Study Results

In a Systane COMPLETE phase IV, open-label, single-arm, interventional, multicenter study, 134 adult participants (mean age: 56.6 years; female: 75.4%) with DED – subtyped into aqueous deficient, evaporative, and mixed dry eye – were asked to instill one drop in each eye twice daily to assess the efficacy of Systane COMPLETE.[15] After 14 days of use, tear film breakup time and ocular discomfort visual analog score (VAS) improved from baseline for the overall cohort and for all subgroups (Figures 6 and 7, respectively).[15] The improvement was both statistically significant and clinically relevant. Adverse events (AEs) were reported in 9 (6.7%) participants, but no serious AEs were reported during the study.[15]

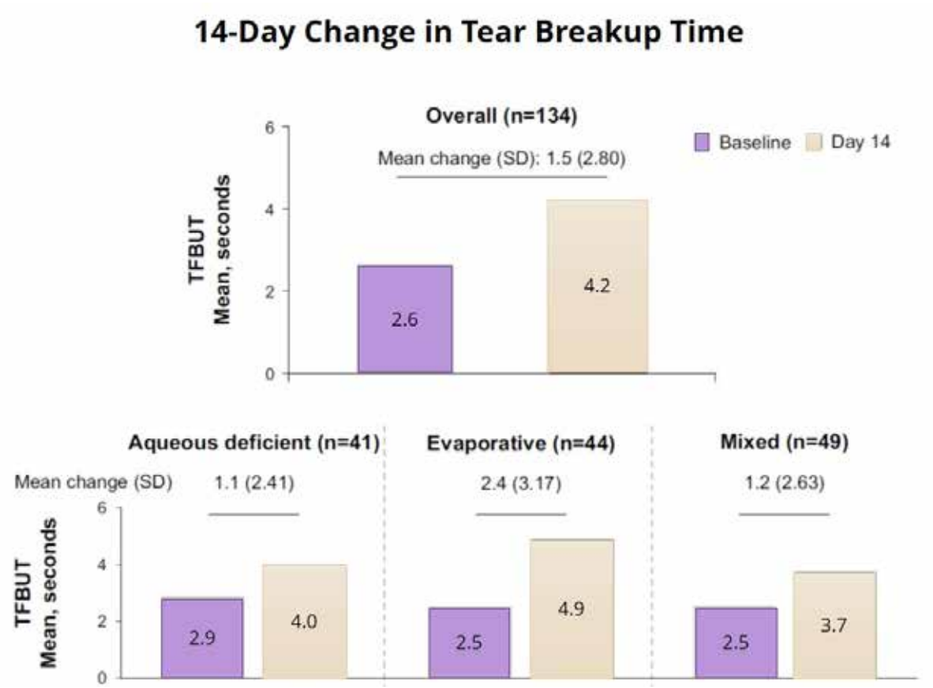

Figure 6: Change from baseline in TFBUT up to Day 14 in the overall cohort and dry eye subtypes (full analysis set). TFBUT=Tear breakup time with fluorescein.

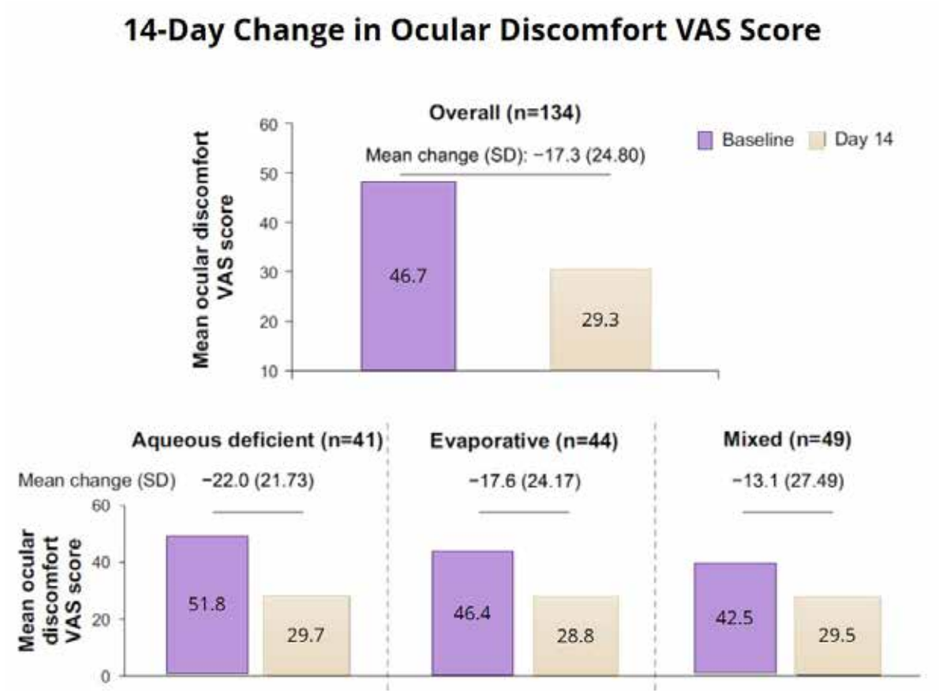

Figure 7: Change from baseline in ocular discomfort VAS score at Day 14 in the overall cohort and dry eye subtypes (full analysis set. VAS=Visual Analog Score.

Conclusion

Over nearly two decades, the Systane family of artificial tears has evolved to meet the specific needs of dry eye patients. As the science and technology developed, so did the Systane formulation and delivery systems to address the complexities of aqueous-deficiency, evaporative dry eye (including meibomian gland dysfunction (MGD)), and ocular surface sensitivities to preservatives. Today, Systane HYDRATION and Systane COMPLETE represent the latest innovations in the portfolio for aqueous-deficient and all major types of dry eye (e.g., aqueous-deficient, evaporative dry eye / MGD), respectively. Furthermore, the preservative-free formulation in unit-dose vials are particularly beneficial for severe dry eye patients who require frequent daily dosing of artificial tears and who are using preserved prescription ophthalmic medications for conditions such as glaucoma, and during refractive and cataract perioperative management.

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