Dry Eye Syndrome: A Review & Novel Formulation Approach

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Introduction

Dry eye symptoms are one of the leading causes of visits to ophthalmologists, and 30% of patients seen by ophthalmologists describe symptoms consistent with dry eye syndrome.[1-3] Up to 50 million people in the US have some form of dry eye disease, and the prevalence of dry eye syndrome is increasing.[4,5] Reasons for this rise include an aging population and related hormonal changes associated with aging in females, increased numbers of people undergoing cataract and refractive surgical procedures that are associated with post-operative dry eye, steady growth in contact lens use that can cause and exacerbate dry eye, and an increase in screen-related visually demanding tasks.[4,5] The pharmaceutical market size for dry eye has been similarly growing. Recent reports suggest a greater than 6% year-over-year growth rate, with an estimate of $1.6 billion based on global sales estimates. Therapies for dry eye disease are facing a resurgence of interest following a brief lull in venture investment that was seen after several prescription products failed to meet the demanding Phase III primary endpoints required by the FDA for a new drug approval.

Dry eye symptoms consist of ocular irritation, visual blurring, grittiness, burning, stinging, and reflexive tearing to name a few. These symptoms are associated with clinical findings, including tear film instability, rapid tear film break-up time, fluctuating visual acuity, corneal surface irregularities, staining of the cornea when vital dyes are introduced into the eye upon examination, and tear hyperosmolarity.[6] The pathophysiology behind dry eye is not completely understood, but it is a multifactorial disease. The tear film is a complex fluid that contains water, salts, mucins, proteins, and lipids. When the quality of the tears diminishes and the epithelial surface of the eye becomes less hydrophilic,

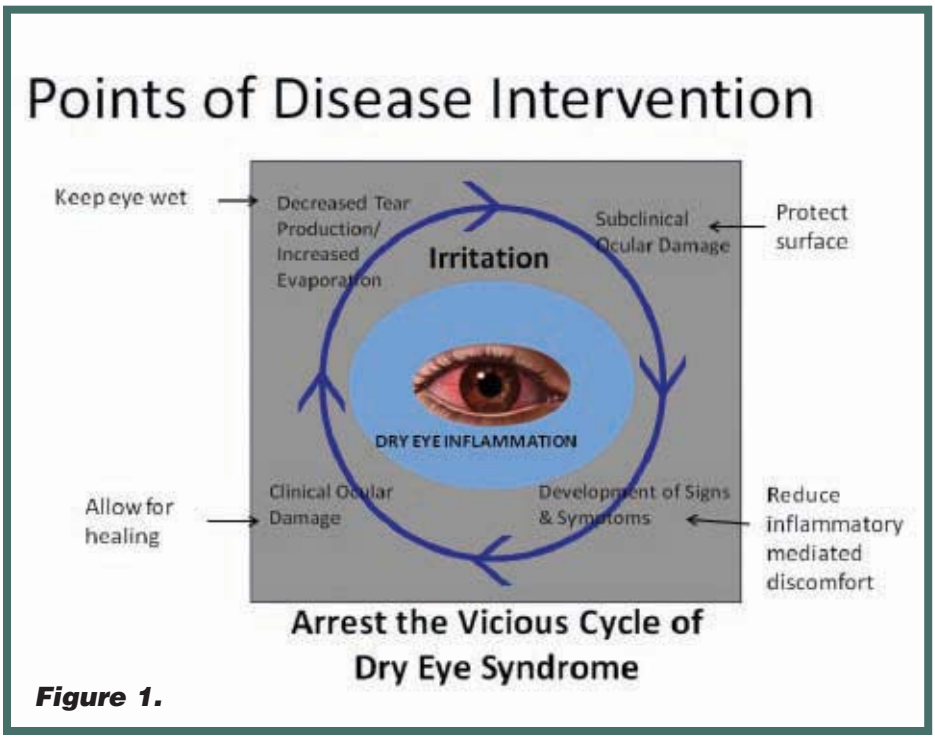

Figure 1.

dry eye symptoms develop.

There is wide agreement in the literature and among experts that tear film instability is a critical aspect of dry eye disease and is the ultimate result following the multiple different pathologic processes implicated in dry eye. Tear film instability is associated with a lack of uniform and long-lasting tear film coverage on the surface of the eye. The surface of the eye should be kept wet at all times, both for optimal vision and for maintenance of external eye health. Tear film instability leads to faster tear break-up times and surface desiccation as well as to the signs and symptoms of the disease.

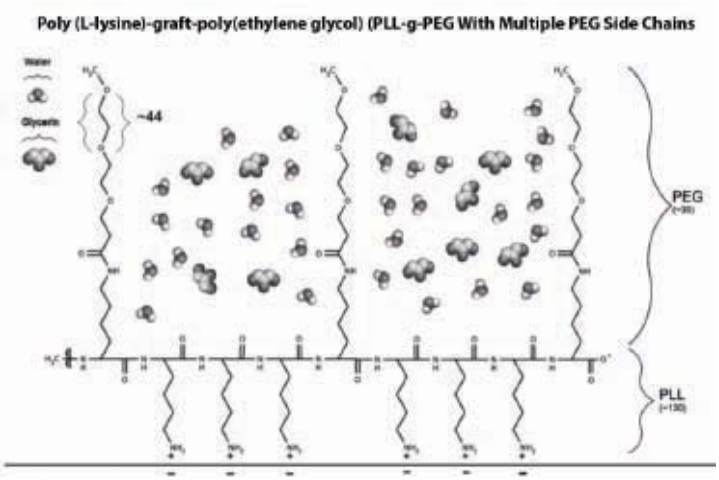

Figure 2.

Current Therapies for Dry Eye

Dry eye is broken down into two major diagnostic categories: aqueous deficiency and evaporative. Regardless of the diagnostic category, the symptoms and clinical findings are similar. A reasonable simplification of the common end-stage pathway yields a vicious cycle of tear instability, surface damage, inflammation, continued tear instability, and complaints of irritation. The diagram in Figure 1 describes this sequence of events and also identifies points of disease intervention.

The mainstay of therapy for dry eye is over-the-counter (OTC) artificial tears. Artificial tears effectively moisten the surface of the eye, and these products account for 60% of the pharmaceutical dry eye market. All OTC artificial tears in the US include an active agent from the FDA Monograph for OTC Ophthalmic Drug Products. A commonly known and safe demulcent, such as polyethylene glycol, propylene glycol, carboxymethylcellulose, hypromellose, or glycerin (alone or in combination, at or below a low single digit weight/weight (w/w) percent) is the active ingredient in an OTC artificial tear. Drug product excipients include water, salts, preservatives, and other polymers. Manufacturers are continually adjusting inactive components to improve the performance of artificial tear drug products. For example, Alcon/Novartis includes guar gum and boric acid in their Systane® family of products to create a gelling matrix when the eye drop is exposed to physiologic (or near physiologic) pH. The Systane franchise has become a market leader and significant source of revenue (over $300 million based on annual report analysis) for Novartis. Although Systane does show superiority over competitors with regard to certain metrics of analysis, such as prolongation of tear film break-up time, current artificial tear products including Systane provide only temporary relief and are quickly washed out of the eye. A careful review of the literature suggests very few, if any, commercial products have a duration of activity longer than 1 hour.[7-11] Most of the products lose effectiveness at 20 minutes unless they are very viscous.[9-12] However, viscous products are poorly tolerated because they interfere with vision. There is a significant opportunity, described in greater detail further, for developing better and longer-acting artificial tears through advances in formulation and excipient

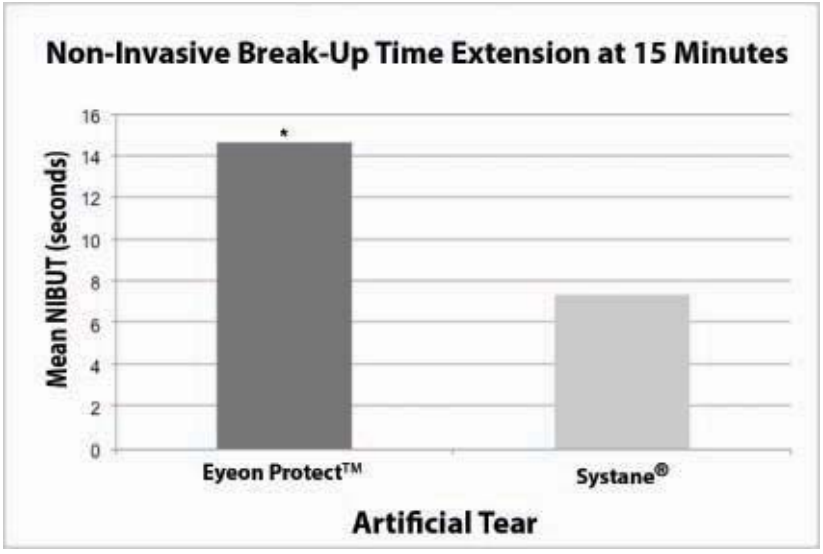

Figure 3.

* p = 0.05; n = 16

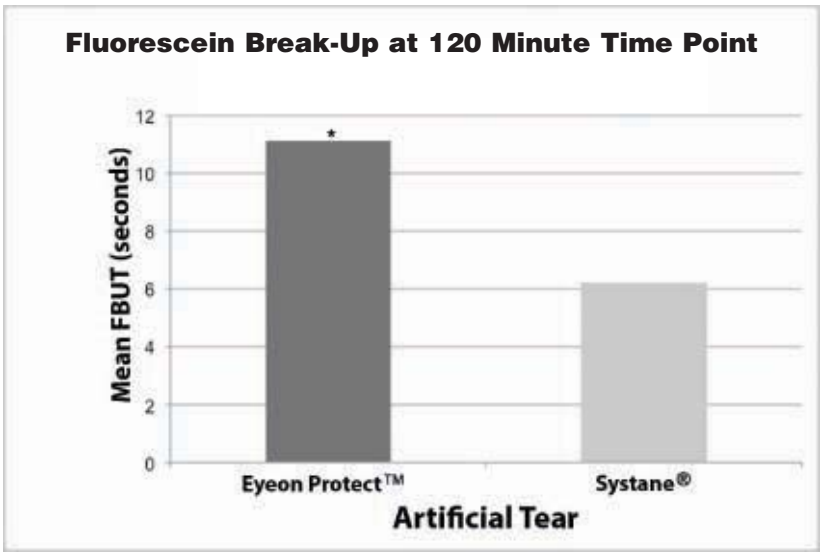

Figure 4. * p = 0.12; n = 16

chemistry. Indeed, the pathology associated with dry eye should respond very well to better and longer-lasting artificial tear products. Disease may eventually be effectively managed with superior-performing OTC artificial tears, thereby cutting significantly into the anticipated growth in the dry eye prescription product market.

The only prescription product currently approved in the US is Restasis®, which is an ophthalmic emulsion formulated with mineral oil to solubilize the cyclosporine active, which is included at the low w/w concentration of 0.05%. Despite its marginal efficacy (it showed statistical benefit over control in only one sign in the Phase III registration trial), Restasis has been a major revenue generator for Allergan. In 2011, it became the single largest prescription ophthalmic pharmaceutical in the US, and Allergan recorded $697 million in net sales of Restasis that year. Restasis comes off patent in 2014, and generic and competitive cyclosporine drug products are being developed in anticipation of Allergan's loss of patent protection. Dry eye disease has an inflammatory component. Cyclosporine is an immunosuppressant, and there is evidence the anti-inflammatory activity is what drives the acceptance of this product. Topical corticosteroids are also used in the management of dry eye, but no steroid drug product has demonstrated superiority in one sign of dry eye and one symptom of dry eye versus vehicle in randomized controlled trials in dry eye subjects. One of the major reasons for the inability of prescription products to reach statistically significant efficacy in dry eye is that the control formulations are essentially artificial tears products, which as previously mentioned, are effective. In controlled trials, subjects use the vehicle regularly, and it consistently provides a benefit. With that being said, soft steroids, such as loteprednol etabonate ophthalmic suspension (0.2% or 0.5%) by Bausch and Lomb are used off label in the management of dry eye. There are a host of new actives under development by both small and large pharmaceutical companies, including resolvins, lymphocyte function associated antigen-1 antagonists, secretagogues, and other types of anti-inflammatory agents. Some of these programs are in Phase III clinical trials at this time; however, a detailed analysis of these agents is beyond the scope of this article.

Drug formulation is critical to the success of pharmaceutical products, including dry eye therapeutics. It is conceivable that prescription drug products could have fared better in Phase III trials had the active agent been formulated to maximize the activity and duration of action of the API. In the artificial tear category, it is common to see new formulations launched frequently by small and large players.

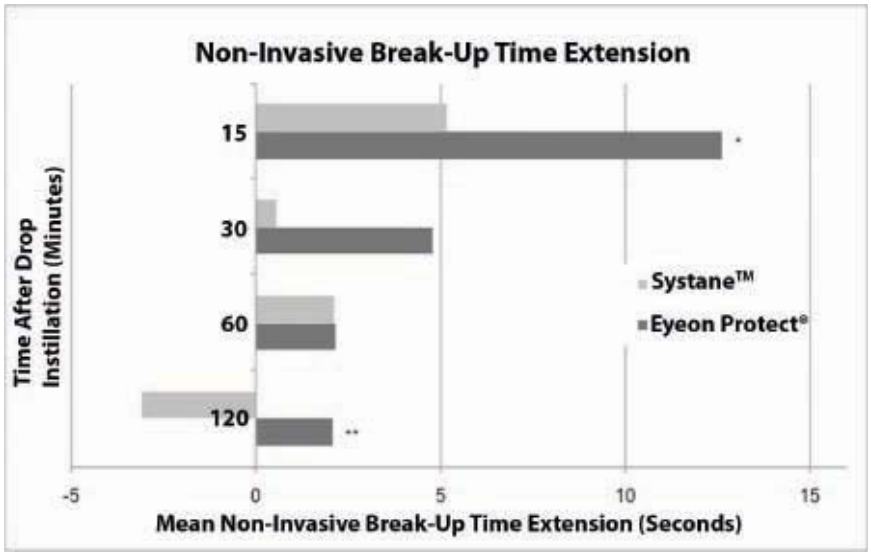

Figure 5. outliers removed; n = 13 * p = 0.08 ** p = 0.03

Viscosity of Eyeon Protect™ & Commercial Samples	
Sample	Viscosity in cP
Eyeon Protect™	2.703
Refresh®	3.422
Systane®	5.211
blink® Tears	9.734
Optive®	12.67

Figure 6.

A Fresh Approach

Particle Sciences Inc. and Eyeon Therapeutics, Inc. formed a joint venture to formulate better ophthalmic drug products. The two companies brought important and diverse expertise to ophthalmic drug development. Eyeon Particle Sciences LLC was born out of the cooperation to advance a novel multifunctional graft copolymer as an excipient in ophthalmology.

The rationale beyond the program, which has focused on dry eye, is that current demulcents are effective; they simply do not last long enough. That is where PEGPLUS™ [poly(L-lysine)-graft-poly(ethylene glycol) (PLL-g-PEG)] comes into play. PEGPLUS is a versatile molecule with many applications in vitro and in vivo.[13-22] For example, PEGPLUS has been shown to reduce both the adhesion of cells and bacteria to coated surfaces. A PEGPLUS-coated surface shows improved wettability when applied to hydrophobic surfaces. The polymer also plays a role in proprietary drug delivery (work in progress at Particle Sciences). The molecule has several components that may be adjusted allowing for the fine tuning of its activity. The chain length of the PLL backbone can be selected, as can the PEG side chain molecular weight. The graft ratio can also be adjusted to increase or decrease adherence to negatively charged surfaces. The lead PLL-g-PEG embodiment used by Eyeon Particle Sciences LLC was selected for its versatility in multiple applications. An illustrative structure is shown in Figure 2.

PEGPLUS was believed to be an ideal excipient for a topical OTC artificial tear because the cationic backbone of PLL will adhere to epithelial surfaces, including the cornea and conjunctiva, as well as some mucins, and project the PEG side chains away from the surface, creating a hydrophilic coating and conditions conducive to corneal moisture retention. The side chains allow for the capture of water and actives.

Clinical Evaluation

PEGPLUS was formulated at a 1% w/w concentration in a novel artificial tear, named Eyeon Protect™, containing 1% glycerin as the active. Preclinical safety and toxicity testing in a rabbit model showed perfect safety. There was no genotoxicity. The excellent preclinical safety profile is not surprising as PEGPLUS is a large polymer created by joining two large and safe polymers, both of which are GRAS. A clinical trial was carried out by James Aquavella, MD, and sub-investigators in the Ocular Surface Research Group at the Flaum Eye Institute to evaluate the performance of this novel artificial tear. Impressive, clinically meaningful, and statistically significant results were generated. This clinical trial has been published online.[22] (22) The paper is titled Novel Formulation of Glycerin 1% Artificial Tears Extends Tear Film Break-Up Time Compared with Systane Lubricant Eye Drops.

This randomized, controlled, double-masked study evaluated 16 subjects in a single visit, single instillation, and fellow-eye controlled study. The entire spectrum of dry eye patients - from mild to severe - was included in this exploratory trial, and enrollment was stratified into three groups: mild, moderate, and severe. The study was designed to compare the extension of tear film break-up time between Systane, the market-leading brand, and Eyeon Protect at several time points following instillation of test article or active control. Tear film break-up time is one of the best known and most commonly used metrics to assess dry eye both in the clinic and for clinical trials. This study utilized non-invasive break-up time, which has shown excellent reliability and

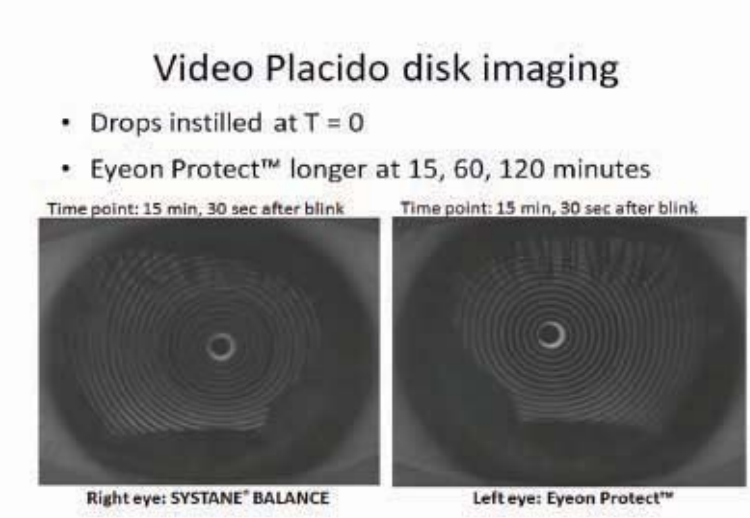

Figure 7.

reproducibility in the Aquavella lab. The advantages of non-invasive measures are that placing dyes and anesthetics in the eye before measure can affect the outcomes. As an additional data point, a fluorescein break-up time was performed at the conclusion of all other measures in the study. A questionnaire addressing comfort and blur was administered concomitantly during the 2-hour trial.

No subject was permitted to use an eye drop within 36 hours of the study start or wear contact lenses the day of the trial. Each subject had their tear film break-up time measured in each eye before instillation of the artificial tear product. Tear film break-up times were repeated at 15, 30, 60, and 120 minutes following instillation. The environment (humidity, room temperature, and airflow) was controlled, and participants' activities were restricted to ensure ideal comparisons between subjects.

Eyeon Protect showed a statistically significant extension of tear film break-up time at the 15-minute time point ($p = 0.05$), doubling Systane's extension. Systane extended tear break-up time by 7.4 seconds, while Eyeon Protect showed a 14.67-second extension at this same time point (Figure 3). The Eyeon Protect fluorescein break-up time was 4.92 seconds longer than Systane's at the 120-minute time point ($p = 0.12$; Figure 4). Area under the curve and predicted return to baseline were higher for Eyeon Protect than Systane.

Prior to unmasking the data, it was determined by the principal investigator and biostatistician that several outliers with very long baseline tear break-up time values skewed the mean values at some time points in the trial. A secondary post-hoc analysis with the three outliers removed is presented in Figure 5.

Eyeon Protect showed superiority at 15 minutes and 2 hours. No subjects reported visual blur after receiving Eyeon Protect, while two subjects reported blurring after eye drop instillation with Systane. The two drops were reported to be similarly soothing. These results support the continued development of PEGPLUS in topical ophthalmic products, particularly in formulating better therapies for dry eye.

Additional data supports this contention. Less-viscous artificial tears are preferred by patients. Eyeon Protect had the lowest viscosity of a host of commercial tears tested rheologically by Particle Sciences (Figure 6).

Eyeon Protect has also fared well in pilot evaluations using wave front analysis and tear film videography. In a subsequent clinical evaluation, Eyeon Protect was compared to the latest-generation product from Alcon in the Systane portfolio, Systane Balance. Figure 7 shows the crisp and more uniform concentric circles seen when a Placido disk is reflected off the Eyeon Protect corneal surface as compared to Systane Balance. This image was obtained from the Ocular Surface Research Group, and the methodology was similar to the aforementioned trial (Figure 7).

Summary

In summary, PEGPLUS helps improve the performance of artificial tears. This multifunctional graft copolymer is safe and can be used in a host of topical ophthalmic applications. The lead product is Eyeon Protect, which is being commercialized at this time. Advanced formulation and proper use of excipients can play an important role in bringing better topical ophthalmic drug products to the growing ophthalmology market.

Authors' Note

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Dr. David M. Kleinman is President, CEO, and Co-founder of Eyeon Therapeutics, Inc., an early stage ophthalmology firm developing novel technologies to treat eye diseases. Eyeon Therapeutics and Particle Sciences, Inc. have formed a joint venture to commercialize PEGPLUSTM as an improved therapy for dry eye syndrome. Dr. Kleinman is a board-certified ophthalmologist with fellowship training in vitreoretinal surgery, and he also serves as a part-time Associate Professor of Ophthalmology at the Flaum Eye Institute at the University of Rochester. In addition to running Eyeon Therapeutics and working at the Flaum Eye Institute, he consults for biotechnology, medical device, pharmaceutical, and investment firms nationally. He has helped multiple start-ups develop intellectual property, generate preclinical data, raise money, submit regulatory filings, and complete proof-of-principle and Phase I clinical trials. He also assists larger companies with due diligence and pharmaceutical development in ophthalmology. He is the former Chief of Ophthalmology at Denver Health Medical Center in Denver. He earned his BA from Brown University, his MD with honors from the University of Colorado School of Medicine, and graduated as a Dean's Scholar from the Simon School of Business.

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Dr. Andrew Loxley is Director of New Technologies at Particles Sciences Inc., where he runs a formulation group applying emerging formulation technologies, including engineered particles and hot melt extrusion to solving drug delivery problems. Prior to joining Particles Sciences in 2005, he led development efforts in next-generation lithium ion batteries at A123 Systems Inc, electrophoretic displays at EINK Corp., and emulsion polymers at Synthomer Ltd. He earned his BSc in Chemistry and Polymer Science from the University of Sussex, UK, and his PhD in Physical Chemistry focusing on Microencapsulation from the University of Bristol, UK. Dr. Loxley is the inventor on more than 40 patents and author of two book chapters and several peer-reviewed and trade-journal articles.

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