Trehalose & Eye Care

A Molecule Poised to Revolutionize Ocular Surface Care

By Marguerite McDonald, MD, FACS

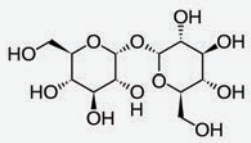
Ocular surface disease and dry eye disease are prevalent and pervasive diseases impacting the eye health of patients. The Dry Eye Workshop II (DEWS II) and current research offer new insights on the characteristics of pathophysiology of Dry Eye Disease (DED), as well as best practices for treatment and management.

Therapeutic strategies that support the ocular surface, counteract hyperosmolarity and restore the tear film can aid in rehabilitating the eye's structures. This knowledge offers an opportunity to introduce new ways to stabilize the tear film and improve patient comfort through rehydration, reduction of surface inflammation, and protection against future dessication.

An expanding pool of clinical data is supporting the benefits and sustained efficacy of therapies that include bioprotectants such as trehalose to protect cells against hyperosmolarity and promote exit of the vicious cycle of DED physiopathology.[1]

As such, lubricant eye drops enhanced with trehalose can provide patients with a new, successful way to rehabilitate the tear film in Ocular Surface Disease (OSD) and DED.

What is Trehalose?



Trehalose—a bisacetal, non-reducing homodisaccharide in which two glucose units are linked together in a α-1,1-glycosidic linkage (α-d-glucopyranosyl-α-d-glucopyranoside; mycose, mushroom sugar)[1]—is found abundantly in nature and in the biological world. The "extraordinary" properties of trehalose are responsible for this molecule's bioprotective role.[1]

1. Jain NK, Roy I. Effect of trehalose on protein structure. Protein Sci. 2009 Jan;18(1):24-36.

OSD & DED Prevalence & Impact

The 2017 Gallup Study of Dry Eye (conducted by Multi-sponsor Surveys, Inc.) revealed that 56% of adults report experiencing dry eyes frequently (14%) or occasionally (42%).[2] Projected to the U.S. population, this translates to a staggering 140 million dry eye sufferers.[2]

From a pathophysiological standpoint, DED amplifies hyperosmolarity in an unforgiving cycle either directly or by inducing a cascade of inflammatory events, contributing to a loss of epithelial and goblet cells that decreases surface wettability and promotes early tear film breakup.[3]

In addition to the physical toll this disease takes on patients, it also has significant quality-of-life impacts. A number of studies have reported measurable negative effects of DED on daily-living tasks such as reading, carrying out professional tasks and driving.

Insights on Addressing the Problem

The Tear Film & Ocular Surface Society (TFOS) published the Dry Eye

Trehalose – Enhancing as an Excipient

Excipient—an inactive substance that serves as the vehicle or medium for a drug or other active substance. It confers a therapeutic enhancement on the active component in the form of, for example, additional absorption, solubility or strength.

Essentially, an excipient serves to enhance the effectiveness of an active ingredient.

Workshop II report, which includes a more comprehensive DED definition that keenly accounts for the pivotal role that tear film hyperosmolarity plays, often resulting in ocular surface inflammation. As well, DEWS II, an evidence-based report involving 150 worldwide experts, further illuminates the pathophysiology of dry eye and its central mechanism of evaporative water loss leading to hyperosmolar tissue damage.[3]

When it comes to DED treatment, longstanding research advocates the use of lubricating eye drops as a palliative technique for symptom relief to rehabilitate some of the eye structures, such as the cornea and conjunctiva, which may have suffered the sequelae of dry eye.

New research shows that recent attempts to counteract tear hyperosmolarity in DED have included bioprotectant features and small organic molecules used in many cell types throughout the natural world to restore cell volume and stabilize protein function.[1] These molecules may directly protect cells against hyperosmolarity and promote exit from the vicious circle of DED physiopathology.[1] There is an expanding pool of clinical data on the efficacy of DED therapies that include trehalose, whose unique properties have shown exceptional osmotic and bioprotectant abilities enabling them to act as a water replacement and prevent against desiccation stress.[1,4,5]

How Trehalose Works

Trehalose maintains cell protein integrity during drying and rehydration, and it has been shown to protect against oxidative strain and stabilize protein function.[6]

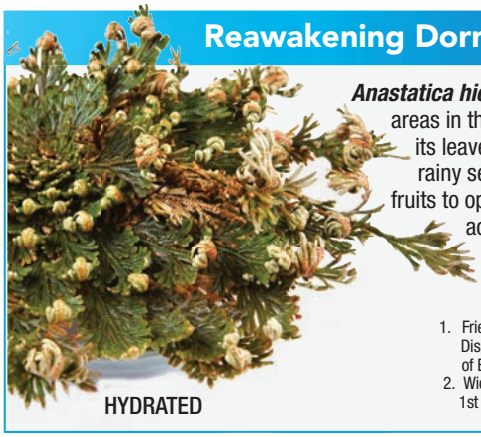
The mechanism by which this member of the polyhydroxyl compound molecules works is by increasing compactness and stability in organisms, thereby aiding in the overcoming of stress conditions such as heat, cold

Clinical Support for Trehalose

Studies have shown that trehalose offers the following ocular surface benefits:

- Protection of human corneal epithelial cells from desiccation-induced death in culture.[7] One trehalose-containing solution was found to be "effective and safe" for treatment of moderate to severe dry eye syndrome.
- Increased tear film thickness after instillation of one trehalose-containing drop up to 240 minutes compared with drops without trehalose.[8]
- Better patient satisfaction and a therapeutic advancement in treatment of moderate to severe DED when comparing an eyedrop containing hyaluronic acid-trehalose with an HA-only eyedrop.[9]
- Increased tear production at day 14 of treatment in a dry eye mouse model.[10]
- Decreased eye surface apoptosis at day 14 of treatment in a dry eye mouse model.[10]
- Improved appearance of ocular surface epithelial disorders through suppression of apoptosis and serum-like response upon topical application, as well as maintained corneal health.[10]
- Suppressed inflammatory and proteolytic MMP-9 and HSP70 expression and keratinization, and restored ocular surface integrity in mice with dry eye damaged by a desiccative model.[11]

Reawakening Dormant Desert Life



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Anastatica hierochuntica or white mustard flower, commonly called Rose of Jericho, is found in arid areas in the Middle East and the Sahara Desert.[1] After the rainy season, the plant dries up, drops its leaves and curls its branches into a tight ball to hibernate. Once re-wetted in a subsequent rainy season, the ball uncurls and awakens from its dormant state, causing the capsular fruits to open and disperse seeds. The plant's extraordinary ability to achieve this reawakening activity is attributed to the presence of trehalose, a disaccharide sugar involved in several mechanisms of cryptobiosis.[2]

1. Friedman J, Stein J. The Influence of Seed-Dispersal Mechanisms on the Dispersion of Anastatica Hierochuntica (Cruciferae) in the Negev Desert, Israel. Journal of Ecology 1980;68(1):43-50.
2. Wickens GE. Ecophysiology of Economic Plants in Arid and Semi-Arid Lands 1st ed. Berlin, Germany: Springer-Verlag Heidelberg; 1998.

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Trehalose Use in Dry Eye Disease

Trehalose has been shown to:

1. Rehydrate Tear Film
- Retain moisture when drying out
- Help increase tear film thickness[8]

2. Protect Against Future Irritation
- Help improve corneal staining[7]
- Help protect corneal epithelial cells from apoptosis after desiccation[3,5]

3. Support Homeostasis of Tear Film
- Restore osmotic balance to ocular surface[10]
- Help maintain homeostasis of corneal cells[10]

"Trehalose helps retain moisture in the tear film when the patient is in a desiccating environment, thereby assisting in increasing tear film thickness. It decreases future irritation by protecting corneal epithelial cells from apoptosis after desiccation. It also supports homeostasis of the tear film by restoring osmotic balance to the ocular surface."— Marguerite McDonald, MD, FACS

and desiccation.[6] As a result, trehalose has the unique ability to stabilize proteins and the lipid bilayer.[6]

Remarkably, trehalose can also act as a water substitute. Classified as a kosmotrope or water-structure maker, this molecule is involved in various bioprotective actions.[6]

Future of Treatment

New trehalose-containing solutions are becoming available to help eye care professionals offer patients an alternative treatment and management strategy. As one example, TheraTears® is launching a new lubricant eye drop, TheraTears® EXTRA Dry Eye Therapy, which contains trehalose as an excipient, serving to enhance the action of the solution's active ingredient, Carboxymethylcellulose (CMC). Doctors are excited about the potential of lubricant eye drops enhanced with trehalose.

With dry eye, trehalose helps retain moisture in the tear film when the patient is in a desiccating environment, thereby assisting in increasing tear film thickness. It decreases future irritation by protecting corneal epithelial cells from apoptosis after desiccation. It also supports homeostasis of the tear film by restoring osmotic balance to the ocular surface.

The increased bioprotectant features and enhancement of tear film thickness contribute to greater patient comfort and less fluctuating vision—the end goal of any ocular surface therapy.

Clinicians should absolutely consider using these drops as a first-line treatment against OSD and DED. Artificial tears are considered first tier treatment for even the mildest of dry eyes, and continue to be a part of the treatment algorithm for moderate and severe dry eyes.

For more advanced cases, eye care professionals should consider using trehalose-containing lubricants in conjunction with a prescription medication.

I think that trehalose will increase the efficacy of artificial tears in the treatment of dry eye. This unique disaccharide offers the bioprotectant benefits that lead to comfort and maintenance of a stable tear film, which yields better and more stable vision.

Dr. McDonald practices at Ophthalmic Consultants of Long Island, a Dry Eye Center of Excellence in Lynbrook, New York.

1. Baudouin C, Aragona P, Messmer EM, et al. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. Ocul Surf. 2013 Oct;11(4):246-58.
2. The 2017 Gallup Study of Dry Eye Sufferers (conducted by Multi-sponsor Surveys, Inc.).
3. Nelson JD, Craig, JP, Esen A, et al. TFOS DEWS II Report. Ocul Surf 2017; 2017 July;15(3):269-650.
4. Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. Ocul Surf. 2017 Jul;15(3):575-628.
5. Matsuo T. Trehalose protects corneal epithelial cells from death by drying. Br J Ophthalmol. 2001;85:610-2.
6. Jain NK, Roy I. Effect of trehalose on protein structure. Protein Sci. 2009 Jan;18(1):24-36.
7. Matsuo T, Tsuchida Y, Morimoto N. Trehalose eye drops in the treatment of dry eye syndrome. Ophthalmology. 2002 Nov;109(11):2024-9.
8. Schmidl D, Schmetterer L, Witkowska KJ, et al. Tear film thickness after treatment with artificial tears in patients with moderate dry eye disease. Cornea. 2015 Apr;34(4):421-6.s
9. Chiambaretta F, Doan S, Labetoulle M, et al. A randomized, controlled study of the efficacy and safety of a new eyedrop formulation for moderate to severe dry eye syndrome. Eur J Ophthalmol. 2017 Jan 19;27(1):1-9.
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Trehalose Current and Future Uses

- Major industries: Food, cosmetics, medicine
- An excipient in each of: Herceptin®, Avastin®, Lucentis® and Advate®
- Future applications: Solid dosage formulations, most notably in quick-dissolving tablets

new!

thera tears EXTRA

HARNESS EXTRA POWER FROM A NATURAL WONDER

NEW TheraTears® Extra Dry Eye Therapy
is **enhanced with trehalose** for superior relief

Trehalose is a natural disaccharide found in plants with moisture retention properties that help organisms survive in absence of water. In ophthalmic products, trehalose enhances active ingredients to help[1]:

- Protect corneal cells from desiccation
- Restore osmotic balance to the ocular surface
- Maintain the homeostasis of corneal cells

-2017 DEWS II Report

Learn about our complete line of
dry eye therapy products at **theratears.com**

Reference: 1. Jones L, Downie L, Korb D, et al. TFOS Dews II Management and Therapy Report. The Ocular Surface Jul 2017; 575-628.