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S P E C I A L R E P O R T

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## Supplement Perspectives: A New Look at Eye Health

**Industry experts dish on new delivery forms, exciting ingredient research and tips on marketing in the e-gadget age**

# Protective Nutraceutical Delivery Systems for Optimal Eye Health

by **Bob Berger, MVSc, Ph.D.**

**T**he ability to deliver nutrients and compounds for overall eye health is important for everyone. They allow the eyes to function in many capacities; mainly, to keep vision optimal.

Parents tell children to eat carrots for eye health because they contain beta-carotene. When ingested and absorbed, the nutrient is converted to the biologically active form of vitamin A, which is essential for proper eye health. Liver is also good for the eyes as it already provides the biologically active form of vitamin A, which doesn't have to be converted.

Besides cooking and other factors that degrade nutrients such as vitamin A, additional factors may not allow foods to deliver the nutrients in either the right amounts or in their active forms (e.g., due to enzyme degradation or poor dispersion of the nutrients when they are released from the food source) that would be considered "therapeutic" for eye health. Thus, we turn to supplements.

Some supplements work better than others due to purity differences, coatings, dispersion and other factors. The age, health, genetics, absorption, etc., of the individual who is taking the supplements also play a role in absorption. The "human factors" are unpredictable and inconsistent.

When it comes to the eyes, supplements designed for their health work either indirectly with other organs that perform specific duties that determine eye function, or work directly in the eye itself. Regardless, in order to be effective, a supplement must get to the right place in the body, and when it gets there, it must be in its active form.

## **Delivery Systems that Circumvent the "Traditional"**

Many systems are used for delivering drugs and supplements. Three successful ones that show promise, specifically for delivery, are microencapsulation, mucoadhesive compounds and phospholipid suspensions. When utilized for supplementation, these delivery systems are an alternative to the mainstream ingestion of pills, gels, liquids and powders.

The benefits of these systems, if properly applied, have the potential to:

- Deliver the supplement where it is needed (to the target), whether it be directly or indirectly associated with the eye itself;
- Sustain therapeutic concentrations of the active for a longer period of time;

- Allow for combination therapy of ingredients beneficial for eye health (such as vitamin A and lutein delivered together in a suspension or in an encapsulated envelope) to increase synergy and therapeutic value; and
- Provide better safety profiles for delivered supplements.

Although only proven, safe supplements should be utilized, tissue targeting through micro-encapsulation, microadhesion and phospholipid suspensions (which may ensure better and more efficient passage of a nutrient or supplement through the cell membrane) will allow for the use of lower dosages of a ingredients. In higher dosages, these ingredients could overwhelm the liver during a given period of time. Take vitamin A (the active form), for example. In many cases, high oral doses of vitamin A may be required for an eye condition, but these high oral doses may cumulatively overwhelm or be toxic to the liver. This type of scenario could be circumvented if a direct delivery system was incorporated into a given protocol.



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## Microencapsulation and Transport Envelopes

Both microencapsulation and transport envelopes, although they are mechanically different, are functionally about the same. Both use a protective shell of biocompatible material to encase the actives.

The importance of a protective transport envelope for any compound is to deliver that functional compound to where it is needed intact. Transport envelopes are designed to protect the actives from enzymatic attack, provide an internal environment for the actives that allows stability and keep the actives functional until they arrive at the target site. Once at the site, the actives are released. Because there are thousands of different substances (e.g., proteins, hormones, enzymes, etc.) circulating in the body that are capable of reacting with the actives, these protective transporters are vital for this system to function properly. The encapsulating envelope acts like a submarine; it protects the contents on the inside until it surfaces and the “crew” disembarks.

University of Massachusetts scientists stated a multitude of studies have shown that carotenoid consumption has many health benefits (i.e., on the cardiovascular system, as an anti-tumor agent, etc.), including for eye health.<sup>1</sup> Degradative oxidation and other pathways induced by heat, oxygen, acids, transition metals or interactions with free radicals reduce carotenoid efficacy, so it is important to consider the utilization of protective delivery systems.

In an in vivo Brazilian study, investigators used Wistar rats to show how microencapsulation techniques can protect beta-carotene against oxidative damage.<sup>2</sup> Beta-carotene's use as an additive in foods is limited due to its instability. In the study, researchers compared the antigenotoxic potential of pure and microencapsulated beta-carotene (MBC) to that of non-encapsulated beta-carotene (BC) in rats. Two doses of MBC (2.5 and 5.0 mg/kg) and the same doses of non-encapsulated beta-carotene were administered to all four groups by oral gavage during a 14-day period. On the last day, all four groups were injected with doxorubicin (DXR), an intercalating drug primarily used against cancer tumors. Doxorubicin works by intercalation (interferes with DNA replication by inclusion of a "fake" molecular strand) between the DNA strands of a cell.

What doxorubicin does to cancer cells is the same as it does to healthy cells, so investigators were looking for cellular damage differences between the four groups. Twenty-four hours post administration of DXR, the animals were euthanized. The micronucleus test (for pinpointing DNA damage) showed only the higher dose of MBC (5.0 mg/kg) was antigenotoxic (prevented genetic damage) and had protective effects in the liver. The BC rats given both doses were not protected genetically nor hepatically.

The study concluded that although MBC does not lose its protective properties, higher doses of beta-carotene must be used in order to observe antigenotoxic effects. This also showed microencapsulation envelopes were protective, and this type of delivery requires protection in order to keep full potency.



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## Phospholipid Suspensions

The ability to deliver supplements for eye health through solubilized formulations in vivo is another essential factor for optimal bioavailability. An excess amount of surfactants and/or emulsifiers are used to solubilize a drug or supplement; this alone can pose a health issue, due solely to the inherent nature of the surfactant itself. This is important when it involves the eye, which is so delicate.

Lutein is a vital and well-established supplement for overall eye health. It is a xanthophyll carotenoid, which acts as a powerful antioxidant to protect the underlying structures of the retina against oxidative damage.

Korean investigators found a self-emulsifying (solubilizing) phospholipid suspension (SEPS) consisting of a high concentration of phospholipids, which is safe and compatible for the eye, combined with a relatively low concentration of

surfactant works well to enhance the bioavailability of lutein.<sup>3</sup> This was shown using animal study data (Sprague Dawley rats and beagle dogs) where accumulation studies demonstrated the ability of SEPS to enhance the bioavailability of lutein. From this study, researchers concluded that SEPS containing lutein could be promising as a lipid-based delivery system for the prevention of ocular diseases. This study is another example how an alternative delivery system improves the potential via a direct application of a stabilized suspension and improves the bioavailability of a well-established ingredient (lutein) for the eye.

## Mucoadhesive Compounds

As people age, they become more susceptible to diseases and age-related conditions, especially of the eyes. Although we try to keep our eyes healthy by taking supplements and eating the right foods, we may not get all the nutrients we need directly to the structures in the eye. And both young and old people with compromised health may be inefficient at getting proper nutrients to the eyes. Conditions such as glaucoma, senile cataracts, dry eye, macular degeneration, diabetic retinopathy and general aging of the eyes are all common. Many of these conditions are instigated by the generation of reactive oxygen species (ROS) and the accumulation of advanced glycation end products (AGEs).

Because the eye and its surrounding structures exist in a combination of an aqueous and a lipid-soluble environment, getting water-soluble and fat-soluble nutrients into the eye is a challenge that traditional methods (e.g., oral supplementation) alone may not efficaciously resolve. In a comprehensive review, scientists at Innovative Vision Products Inc. (IVP) developed a lubricant eye drop designed for the sustained release of a 1-percent N-Acetylcarnosine (NAC) solution, a pro-drug of L-carnosine.<sup>4</sup> NAC has a history of maintaining proper eye health and has been shown to be effective against many aging conditions of the eye. But just as with other supplements/drugs of this nature, dosing of the active, due to the physiology of the eye itself, requires a better delivery system to be most effective. Thus, the technology importance here is more about the delivery than about the pro-drug/supplement itself.

Scientists at IVP used the power of NAC with a mucoadhesive cellulose-based compound combined with corneal absorption promoters and glycerine in order to deliver the pro-drug directly into the eye. The NAC topical eye drops take advantage of the mucoid-adhesive properties of the eye while utilizing cellulose



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as a sustained-release vehicle for keeping more pro-drug in the eye, maintaining it there for a longer period of time, while also targeting the eye directly. The NAC didn't have to travel through the bloodstream to get to the target, and thus, wasn't broken down in the process. NAC topical eye drop technology is an example of targeted release and sustainability, and has demonstrated significant efficacy, safety and good tolerability for the prevention and treatment of visual compromise and impairment, especially in the aged population.

Many other alternative delivery systems have amazing potential for the advancement of eye health that utilize dietary ingredients as either integral parts of their delivery system, as transport vehicles themselves or as the actual protected therapeutic ingredients.

A major health issue for many people of all ages is dry eyes. Many people supplement with the omega-3 fats—docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and gamma-Linolenic acid (GLA)—to alleviate this condition. Epidemiological studies suggest dietary omega-3 polyunsaturated fatty acids (PUFAs) may protect against dry eye.<sup>5</sup> It has also been noted that dietary DHA, EPA and GLA may reduce the increases in specific prostaglandins associated with dry eye. Supporting research on this was performed on rats, where dry eye was induced by the use of the anti-emetic scopolamine.<sup>6</sup> In this study, PGE1 and PGE2 levels were inhibited in the exorbital lachrymal glands of the scopolamine-induced dry eye rodents supplemented with PUFAs.

Although the omega-3 fish oils and PUFAs are usually added to the diet or taken orally in pill, capsule, powder or gel form, investigators have shown that the topical administration of PUFAs has also been deemed effective for dry eye through preliminary human studies as well as on animal data results. DHA and its derivatives appear to be safe and effective when the topical route has been utilized for dry eye patients. Investigators hypothesize that these positive results in humans may be the result of inflammatory subsidence as well as from regeneration of damaged corneal nerves.<sup>7</sup> A topical route appears to be safe and circumvents the likely breakdown and oxidation of these supplements that may readily occur during the processes of digestion, absorption and transport in the body. □



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## References:

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1. Boon, C.S. et al. (2010) "Factors influencing the chemical stability of Carotenoids in Foods." *Crit. Rev. Food Sci. Nutr.* 2010;50:515.
2. Aissa, A.F. et al. "Comparative study of  $\beta$ -carotene and microencapsulated  $\beta$ -carotene: evaluation of their genotoxic and antigenotoxic effects." *Food Chem. Toxicol.* 2012;50:1,418
3. Shanmugam, S. et al. "Enhanced bioavailability and retinal accumulation of Lutein from self-emulsifying phospholipid suspension (SEPS)." *Int. J. Pharm.* 2011;412:99.
4. Babizhayev, M.A. et. al. "N-acetylcarnosine lubricant eye drops possess all-in-one universal antioxidant protective effects of L-carnosine in aqueous and lipid membrane environments, aldehyde scavenging, and transglycation activities inherent to cataracts: a clinical study of the new vision-saving drug N-acetylcarnosine eyedrop therapy in a database population of over 50,500 patients." *Am. J. Ther.* 2009; 16:517.
5. Viau, S. et al. "No consequences of dietary n-3 polyunsaturated fatty acid deficiency on the severity of scopolamine-induced dry eye." *Graefes Arch. Clin. Exp. Ophthalmol.* 2011;249:547.
6. Viau, S. et. al. "Efficacy of a 2-month dietary supplementation with polyunsaturated fatty acids in dry eye induced by scopolamine in a rat model." *Graefes Arch. Clin. Exp. Ophthalmol.* 2009;247:1,039.
7. Cortina, M.S. and Bazan, H.E. "Docosahexaenoic acid, Protectins, and Dry Eye." *Curr. Opin. Clin. Nutr. Metab. Care.* 2011;14:132.

# The Eyes Are the Window to Our Health

by **Blake Ebersole**

**A**n old proverb said that our eyes are the window to our souls. But in today's supplement industry, eye care is often overlooked as a "niche" category unrelated to overall health.

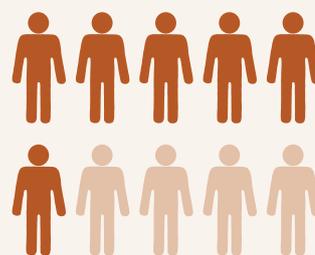
Yet, traditional practices in medicine, along with new research, may give pause to the isolation of the eyes within our approach to support healthy aging. For instance, a good physician will inspect the eyes during a physical examination, as many observations of the eye are indicative of health conditions affecting other organs; for example, liver jaundice is initially diagnosed by a yellow tint of the sclera (white part) of the eye.

Research continues to stress the importance of eyes as a window to health, with key mitigating factors being both our genetics and the environment—both exerting strong influence over how well the eyes (not to mention our bodies) age over time.

Diabetic retinopathy, which is a major cause of blindness, remains one of the most prevalent complications of diabetes, affecting 29 percent of the diabetic population in the United States. Yet, 78 percent of people with retinopathy in the AGES-R Study in Iceland were non-diabetic.<sup>1</sup> In this study, non-diabetic retinopathy was significantly correlated with microalbuminuria, suggesting a key link between kidney function and eye health.

In a European study with more than 4,000 subjects, age-related macular degeneration (AMD) was present in nearly 40 percent of the population, with a very strong correlation between AMD and expression of the genetic variant ARMS2.<sup>2</sup> This relationship was further confounded by cigarette smoking. Findings from another study mirrored these results, with the authors noting the data "suggests a more important role for genetic factors than environmental factors" in the development of this well-defined subtype of AMD.<sup>3</sup>

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In several large studies, a strong inverse relationship has been shown between macular content of carotenoids such as lutein and zeaxanthin and AMD, most recently in the Irish Longitudinal Study on Ageing.<sup>4</sup>

Looking at the overall data, a simple paradigm emerges that is repeated in intervention and longitudinal studies outside of the eye care field as well. Environmental and genetic factors cause the body to inadequately deal with chronic inflammation and oxidative stress, which as we age, manifest in health issues that can adversely affect the eyes, among other organs. In this paradigm, it is easy to see why compounds generally regarded as antioxidant and anti-inflammatory agents might be effective ways to stave off issues.

Like many other real-world outcomes, it is not all so simply wrapped up with a simple paradigm or theory. Another meta-analysis on the preventive effects of vitamin E and beta-carotene supplementation suggested no positive effect.<sup>5</sup> And a study recently published in *JAMA* suggested another environmental factor, the long-term use of nonsteroidal anti-inflammatory drug (NSAID) aspirin, may also increase the severe “wet” form of AMD (although this finding may be an anomaly or outlier, as other sub-sets of the population in the trial taking aspirin were not affected).<sup>6</sup> Also, like most other studies, these trials are flawed in several ways, one being that they do not provide a clear view of mitigating environmental and genetic factors for the population or sub-populations within the trial.

As genetic testing and electronic information management become more prevalent in large trials, we expect to have a clearer picture of the effects of medical history, genetics and environment to determine what works for whom, and to what extent, paving the way for supplement regimens personalized to achieve maximum efficacy. The eye care category will continue to benefit from improved resolution in large-scale clinical research efforts investigating the effect of dietary interventions, and we see with increasing clarity the path for future research and market opportunities. □



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The eye care category will continue to benefit from improved resolution in large-scale clinical research efforts investigating the effect of dietary interventions.

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## References:

1. Gunnlaugsdottir E et al. "Retinopathy in old persons with and without diabetes mellitus: the Age, Gene/Environment Susceptibility—Reykjavik Study (AGES-R)." *Diabetologia*. 2012 Mar;55(3):671-80. DOI: 10.1007/s00125-011-2395-y.
2. Chakravarthy U et al. "ARMS2 increases the risk of early and late age-related macular degeneration in the European Eye Study." *Ophthalmology*. 2013 Feb;120(2):342-8. DOI: 10.1016/j.ophtha.2012.08.004.
3. van de Ven JP et al. "Association analysis of genetic and environmental risk factors in the cuticular drusen subtype of age-related macular degeneration." *Mol Vis*. 2012;18:2271-8.
4. Murray IJ et al. "Lutein supplementation over a one-year period in early AMD might have a mild beneficial effect on visual acuity: the CLEAR study." *Invest Ophthalmol Vis Sci*. 2013 Mar 11;54(3):1781-8. DOI: 10.1167/iovs.12-10715.
5. Evans J. "Antioxidant supplements to prevent or slow down the progression of AMD: a systematic review and meta-analysis." *Eye (Lond)*. 2008 Jun;22(6):751-60. DOI: 10.1038/eye.2008.100.
6. Liew G et al. "The association of aspirin use with age-related macular degeneration." *JAMA Intern Med*. 2013 Feb 25;173(4):258-64. DOI: 10.1001/jamainternmed.2013.1583.

# Eye Health is Based on Basics Society Has Neglected

by C. Leigh Broadhurst

**W**hat if seniors understood that keeping their eyes young isn't a separate task, but accomplished by the same strategies that keep hearts, muscles, backs and brains strong and youthful? Or if they knew the strategies for preventing cancer also protect eyesight? It's true: eyes slide downhill with the rest of our body if we don't exercise and eat a whole-foods diet.

The retina is the most metabolically active tissue in the human body. Sustaining this high metabolic rate requires a lot of oxygen. A high oxygen demand requires a high oxygen supply, but the dark side is that the retina is exceedingly prone to oxidative stress. We're all aware that aging reduces our overall metabolic rate. As we age, we gain body fat with relative ease, but lose our ability for the strenuous exercise we could do to compensate.

Inactivity reduces blood flow to the brain and the eyes, which in turn reduces oxygenation to these critical signal-processing areas, slowing their ability to function and repair themselves.

Remarkably, eye health is dependent on fruit and vegetables.

**Vitamin A** from animal products or converted beta-carotene is required to construct retinal, the molecule in the eye that picks up incoming photons. However, a variety of carotenoids are found throughout the eye's tissues. **Lutein** and **zeaxanthin** make up the yellow pigment in the macula, part of the retina that contains color detection cells that absorb blue light. Lutein and zeaxanthin deficiency causes macular degeneration, often resulting in central blindness. Other **carotenoids** in ocular tissues act as antioxidants, balancing the required high oxygen demands. Also, certain **anthocyanins** and **flavonoids** reduce oxidative stress in eye tissue, supporting the use of **bilberry**, **blueberry** and **black currant**. Interestingly, anthocyanins may play a direct role in the transfer of visual signals.

All primates, including humans, are unusual among mammals because they have binocular color vision and grasping hands, but have lost the ability to synthesize **vitamin C**. Presumably these are adaptations to eating ripe fruit—we see the bright fruit and pluck it cleanly, getting so much vitamin C we no longer



It's true: eyes slide downhill with the rest of our body if we don't exercise and eat a whole-foods diet.

need to make it. Seniors to infants, we should understand that like vitamin C, numerous carotenoids and other phytochemicals became essential nutrients, especially for vision. We evolved continually gaining carotenoids in our diet. Our vision improved, and we became even more adept at finding bright colored fruits and vegetables. In the future, at least lutein and zeaxanthin will be considered vitamins. □



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# Eye Health for Today's Digital Consumers

by Kathleen Dunn

**F**rom toddlers to teens and adults of all ages, Americans are now clocking more up-close screen time than ever before, thanks to ready access to a growing number of hand-held e-gadgets. Staring into all this digital haze can lead to dry, irritated eyes. For ingredient suppliers and supplement manufacturers, this is an emerging trend that makes exploring nutrients for eye comfort and healthy tear production worth a closer look (pardon the pun).

## An E-Gadget for Every Age

Smartphones, tablet computers, e-readers and other handheld electronic devices that demand close-tolerance viewing are trending among adults and teens, according to the PEW Internet and American Life Project. This is a key project of the PEW Research Center that explores the impact of the Internet on Americans, including usage trends for handheld e-gadgets. Separately, e-books for children are more popular than ever, with tens of thousands of titles now available for e-readers. The result? A growing number of tech-loving consumers who could benefit from supplements that help maintain eye comfort, including healthy tear production.

## Look this Way for Nutrient Support

One nutrient group that could help suppliers and manufacturers up their game in the eye health category is the omega-3 essential fatty acids (EFAs) alpha linolenic acid (ALA) and its longer biochemical cousins eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Why? According to the 2007 Report of the International Dry Eye WorkShop (DEWS), consuming a diet low in omega-3s (or with a low ratio of omega-3 to omega-6 fatty acids) is a known risk factor for dry eyes (*Arch Soc Esp Ophthalmol.* 2007 Dec;82(12):733-4). Unfortunately, this fatty acid profile is one of the not-so-healthy hallmarks of the typical American diet.



Good research is the first step in developing science-based products, including those that target the special eye health needs of today's digital consumers.

## Popular at Every Age

Omega-3 fatty acids continue to enjoy plenty of consumer awareness and interest thanks to the growing body of research supporting a wide range of health benefits—heart health, joint comfort and positive mood—that are top of mind for many adults. In addition, many dietitians and other health care professionals champion the benefits of omega-3s for kids, particularly for brain and eye health. In short, omega-3s are a popular option ideally suited for products targeting all ages.

## In Search of Eye Comfort

Just how do omega-3s help reduce dry eyes and promote healthy tear production? Researchers point to several potential mechanisms of action, including the ability to reduce inflammation, stimulate tear production or alter the lipid composition of tear film, among others. It's an exciting area of research for suppliers and manufacturers to not only follow, but also be active participants. After all, good research is the first step in developing science-based products, including those that target the special eye health needs of today's digital consumers. □



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