General Optical Council Approved CET For Optometrists
General Optical Council Approved CET For Dispensing Opticians
General Optical Council Approved CET For Specialist Optician Contact Lenses

Dry eye

Part 3 – Treatments

In the third of our series looking at dry eye, Jim Farrell covers tear replacement treatments. CET Module C14109, one general CET point, suitable for optometrists and dispensing opticians, one specialist point for contact lens opticians

A successful cure for the group of diseases categorised under the term 'dry eye' has still to be found. At present treatment goals are directed towards either 'tear replacement' or 'tear retention', and are aimed primarily at relieving the subjective symptoms associated with this malady. However, the underlying treatment goals will always be aimed at appropriate healing, epithelialisation, and the re-establishment of a normal ocular surface.[1] Before selecting the most appropriate treatment option the cause and severity of the dry eye should initially be established, and the management plan chosen to effectively target the nature of the condition.

This article aims to discuss the main treatment options available to the practising clinician for managing tear deficient dry eye, and is not intended to be an in-depth review of all the treatments available.

Tear replacement

There is currently a range of products available on the market for the 'dry eye' patient to choose from. Ideally these products should meet the following requirements:[2]

- They must not irritate the eye
- They must have a good lubricating effect
- They must have a long retention time
- They must not disturb the optics of the eye.

Unfortunately, it is not possible to meet all of these requirements in a single formulation, and at best a single product is only a compromise. For this reason various products have been made available from the pharmacy industry and new ones are continually being developed and introduced. In order to reduce irritation on the eye, following instillation (Figure 1), the formulary is adjusted for hydrogen ion concentration (pH). The pH of tears is very similar to that of blood plasma at around 7.4-7.5, and a pH value of 7.4 is normally selected for artificial tears. Out with this value, the tears will be required to neutralise (buffer) the pH of the solution on contact with the eye, which may lead to discomfort and irritation. In order to maintain its normal thickness, and thereby reduce the possibility of visual disturbance, the cornea should be bathed in an isotonic solution. In the presence of a hypotonic solution, osmosis effects a physiological flow of water into the corneal stroma, as there is very little salt (sodium chloride) in the water, resulting in a degree of corneal swelling. The reverse process will occur in the presence of a hypertonic solution bathing the eye. Both situations may well give rise to a disturbance in vision. Most artificial tears have a sodium chloride concentration of 0.9 per cent, which is similar to that of natural tears. In the presence of severe tear deficient dry eye, the instillation of a hypotonic solution (ie reduced osmolarity polyvinyl alcohol), to increase corneal absorption, may offer the cornea a vehicle for improving the transportation of essential nutrients into the corneal stroma. To meet the requirements for lubrication and retention, the viscosity of the solution is extremely important. If the solution has a low viscosity (more liquid in nature)

this will inherently reduce the surface tension and increase spreading across the corneal epithelial tissues. However, the low viscosity will also increase the aqueous evaporation rate and thereby reduce the effective retention time. In contrast, a high viscosity (gel structure) lubricant will significantly reduce evaporation and increase the retention time. The increased viscosity may, however, increase the surface tension to the point where spreading is compromised and the vision disturbed from greasing.

Numerous formulations and active ingredients have been introduced over the years, with varying success, and these may broadly be classified as aqueous artificial tears, ocular lubricants and viscoelastics. Table 1 lists some of the more common polymers in use at the present time.

TABLE 1

Tear replacement classification and active ingredients

Tear replacement – classification	Active ingredient (polymer)
1) Aqueous artificial tears (low viscosity) Flowing liquid that replaces/replenishes the tear aqueous element.	Cellulose derivatives: - methylcellulose (MC) - hydroxyethylcellulose (HEC) - carboxymethylcellulose (CMC) - hydroxypropylmethylcellulose (HPMC) Polyvinyl alcohol (PVA) Polvinylpyrrolidone (PVP)
2) Ocular lubricants (high viscosity) Ointments – resistant to flowing and reduce friction between palpebral and ocular surface.	White soft paraffin Liquid paraffin Lanolin alcohol
3) Viscoelastics (thixotropic) Exhibit both liquid and gel properties.	Polyacrylic acid (Carbomer 940) Sodium hyaluronate

1) Aqueous artificial tears

For many years the backbone of therapy has been the use of topical 'artificial tears' of varying formulary to supplement the depleted natural aqueous tear film in tear-deficient dry eye.[3,4] The formulary includes cellulose derivatives, mucomimetics, polyvinyl alcohol and povidone.

Cellulose derivatives are water-soluble polymers that can be formulated in a range of viscosities. The range of cellulose ethers (organic compounds) used includes methylcellulose (MC), hydroxyethylcellulose (HEC), carboxymethylcellulose (CMC or carmellose sodium) and hydroxy-propylmethylcellulose (HPMC or hypromellose). They have all been used at various times to enhance the viscous action of artificial tears (viscosity building agents). The synthetic polymers have several properties that make them especially suitable for use as artificial tears. They are chemically inert, non-toxic, have a stable pH and a similar refractive index to that of natural tears (1.336). However, cellulose derivatives are generally fluid/watery in substance, particularly methylcellulose, have a short retention period and frequent instillation is required.[5] According to Marquardt,[2] one of the main requirements for artificial tears is that 'they must have a long retention time'. Cellulose derivatives are not ideal for meeting this requirement as their low molecular weight allows for them to be absorbed, relatively easily, by the corneal epithelium thus reducing their retention (effective bathing) time. The relief that is offered to patients following instillation is therefore only temporary. However, when used as temporary comfort drops in mild cases of aqueous deficiency or adverse environments (warm offices, smoke filled rooms etc) they are ideal, as they do not blur the vision through greasing. They are also used in combination with tear gels in moderate cases of aqueous deficiency, as their low surface tension effects an increase in spreading, to help maintain the corneal epithelium in

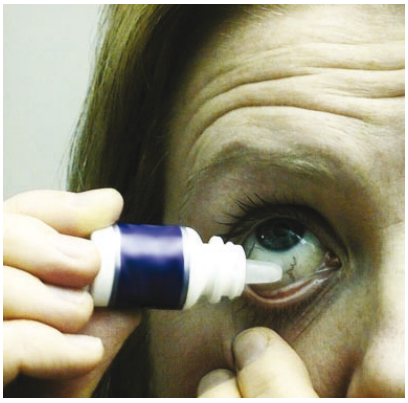

Figure 1 pH influences comfort on instillation

a moist state and limit further tissue damage.

Mucomimetics contain the cellulose derivative hydroxypropylmethylcellulose (HPMC) or carboxymethylcellulose (CMC or carmellose sodium), in a slightly more viscous preparation, with a higher molecular structure. In this formulary they act as mucoadhesives, mimicking the action of tear mucus glycoprotein to enhance tear stability. In 0.5 per cent CMC can also be used as a comfort drop with all types of contact lenses. Due to the increased molecular weight, which reduces corneal absorption, the viscous substance improves the retention time and prolongs the effect of the solution, and other topical eyedrops, on the eye surface. The viscous nature of the formulation also increases surface tension and reduces evaporation. Lenton and Albietz[6] reported a significantly increased recovery time for the ocular surface following Lasik surgery, when using CMC compared with a less viscous balanced salt solution. Nevertheless, it may also increase surface tension to the point where the surface activity of the formula is limited in severe dry eye cases,[7] ie it may reduce surface spreading, which is essential for aqueous lubrication of damaged epithelial tissues on the corneal surface. In addition, the increased viscosity may result in matting or stickiness of eyelashes, viscous drag and transient blurring of vision, which should be considered carefully for patients who may be driving or operating machinery.

Polyvinyl alcohol (PVA), on the other hand, is a hydrophilic polymer that reduces surface tension. It is used moderately as a viscosity enhancer and mainly as a wetting agent, due to its excellent lubricating function, in both artificial tear and contact lens solutions. It is less viscous than mucomimetics and offers improved aqueous lubrication to the epithelial tissues, in cases of moderate and severe aqueous deficiency, especially in patients where the natural mucin is reduced. PVA has been shown to prolong tear break-up time as a measure of tear stability.[8] In cases of aqueous deficiency the tear film is often in a state of hyperosmolarity[9,10] and the hydrophilic properties of PVA, combined with reduced osmolarity, may therefore help to restore tonicity. In addition, it has the property to reduce surface tension without compromising the vision, which is in keeping with point 4 of Marquardt's requirements for artificial tears.[2] PVA has a significantly longer retention time than a viscosity-increasing agent acting on its own and continues to maintain its wetting properties even in low concentrations.[11] It is also compatible with most preservatives and there are no reported inhibitory effects on corneal healing. However, PVA is very unstable in alkaline solutions and has an optimum effective pH value of between 5 and 6. Buffering pH levels must be minimised therefore to maintain PVA stability, and the tear film is required to neutralise the slightly acidic pH following instillation. This may cause the dry eye patient, or contact lens wearing patient, minor discomfort for several minutes.

Polyvinylpyrrolidone (PVP or povidone) is a hydrophilic polymer with a similar structure and lubricating properties to PVA. The molecular weight of the polymer can be varied during production for several uses, including a dispersing agent, suspending agent and a vehicle for pharmaceuticals. PVP exhibits a reliable rate of dissolution, which makes it ideal as a lubricating agent for use in artificial tears. It enhances the solubility of formulations to increase their retention rate and hence availability to spread across the epithelial tissue. However, in severe cases of aqueous deficiency instillation has to be carried out as frequently as once every two hours throughout the day, which limits its use in severe cases of KCS. In many patients, KCS is a relatively benign disease that responds to the use of artificial tears.[12] However, the retention of artificial tear drops on the eye is generally poor and they must be used frequently, although increased frequency of use does not improve their effectiveness, and may actually intensify patient symptoms.[13] The frequent use of eyedrops will dilute the natural tears and may wash away essential antibodies and anti-bacterial agents. In addition, the preservatives (namely 0.01 per cent benzalkonium chloride) used in most commercially available artificial tears may be toxic to ocular tissues and intensify the adverse effects of frequent instillation.[14,15] Benzalkonium chloride is known to reduce the corneal epithelial barrier, destabilise the tear film and reduce the measured tear break-up time. For those patients unfortunate enough to develop solution toxicity, unpreserved saline or hydroxyethylcellulose are available in single dose Minims form. As an alternative the pharmaceutical industry has gradually introduced many of their formulations in single-

dose preservative-free options. Several of these products are now the 'artificial tears' of first choice preferred by patients and recommended by many clinicians.

2) Ocular lubricants
As an alternative to traditional teardrops, and in order to increase the retention period in cases of severe lacrimal deficiency, ocular lubricants containing various concentrations of white soft paraffin, liquid paraffin (mineral oil) and/or lanolin alcohol (wool fat) as a base, have been developed. The formulation is very similar to that of E45 cream, which is used as a moisturiser for dermatitis. These are high viscosity ointments that are resistant to flowing (compared with aqueous tears) and help to reduce the friction generated between the palpebral conjunctiva and ocular surface during the blink process. They have a high molecular structure, which is designed to increase the retention time of the lubricant upon the ocular surface, as the viscous ointment is unable to penetrate the tear-cornea barrier and has a reduced evaporation rate compared with traditional aqueous solutions. As an ointment it is very practical for improving lubrication overnight in cases of severe aqueous disorders and filamentary keratitis (Figure 2). Furthermore, it is a useful aid for protecting the cornea in conditions such as exposure keratitis, decreased corneal sensitivity, recurrent corneal erosions and as a prophylactic in ophthalmic surgery. However, the presence of these ointments on the pre-ocular surface, remaining for several hours after instillation, creates problems with blurring of vision[16] and therefore limits their daytime use, especially for driving etc. In addition, ointments may disrupt the tear film to such an advanced state that increased evaporation of the depleted underlying aqueous may follow.[14] Hypersensitive responses to lanolin are also possible. Ocular lubricants should not be used with contact lens wear.

3) Viscoelastics
These are primarily gel polymers that demonstrate thixotropic properties ie have the ability to become fluid when agitated and set again when left at rest. When stationary they exhibit a high viscosity, while in motion during blinking their viscosity reduces significantly to a level similar to that of water. This unique property is referred to as 'non-Newtonian' (pseudoplastic) and is believed to simulate the function of the tear glycoprotein. This

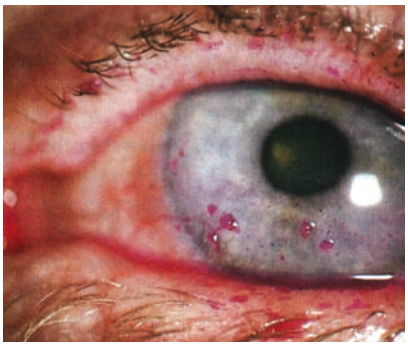

Figure 2 Filamentary keratitis

characteristic allows the combined gel-fluid and natural tear film to spread more effectively during blinking, and conversely helps with the formation of a more stable tear film between blinks. Retention time is also improved significantly when compared with aqueous tear alternatives. In the UK at present, there are primarily two different, and separate, actives that pharmaceutical companies use in the formulation of their viscoelastic products, namely carbomer and sodium hyaluronate.

Carbomers are high molecular weight polymers of polyacrylic acid, which remain in the conjunctival sac for several hours and dissolve slowly. The increased retention time,[16] minutes compared with two minutes for PVA,[17] will offer a prolonged symptomatic relief and reduced frequency of application to patients with moderate and severe aqueous deficiency. Furthermore, Gambaro et al[18] noted that carbomer gel increased the stability of the tear film, and also improved the quality of the corneal and conjunctival epithelium in patients with KCS. However, ocular irritation and blurring of vision have been reported when this polymer is administered in large doses or too frequently.[19] Due to the high viscosity of carbomers and the significantly increased ocular retention time, an increase in the occurrence of sticky eyelids has also been reported.[17] For these reasons, the use of carbomers overnight may be preferred and supplemented with the use of less viscous drops during the day.

Sodium hyaluronate is a naturally occurring (biological) polymer responsible for the jelly-like consistency of the vitreous humour and the synovial fluid of joints. It is pharmacologically inert, making it non-toxic, and protects the eye by virtue of its physicochemical and rheological properties. The polymer has good water binding properties that reduce evaporation and aid retention. Spreading is enhanced during blinking, as the polymer increases its elasticity, which improves the aqueous lubrication of the epithelial tissues on the anterior eye. This may account for the reduced rose bengal staining reported by Sand et al[20] following a controlled study using sodium hyaluronate in patients with KCS. Between blinks, the polymer increases its viscosity, which helps stabilise the tear film and increases the measured tear break-up time.[21,22] Sodium hyaluronate has also been shown to act as a muco-adhesive,[23] and may therefore mimic the action of tear mucus glycoprotein to further enhance stability in medium or severe aqueous deficiency cases.

From a patient perspective, the symptoms of 'burning' and 'grittiness', commonly reported in KCS, are significantly relieved when hyaluronate is used in place of hydroxypropylmethylcellulose (hypromellose).[24] Apart from minor initial blurring following instillation, there appear to be no reports in the available literature of any significant drawbacks to the use of hyaluronate polymers in KCS patients. As a viscoelastic substance, the long-term prospects for this polymer therefore look promising, with regard to meeting the ideal requirements for 'artificial tears' as proposed by Marquardt.[2] This is further supported anecdotally by reports from the British Sjögren's Syndrome Association (BSSA) that this polymer is popular as a treatment with dry eye sufferers. ●

● In the final part of this series we will look at treatments aimed at improving retention of the tear film as opposed to replacing it.

References
1 Göbbels M & Spitznas M. Corneal Epithelial Permeability of Dry Eyes Before and After Treatment with Artificial Tears. Ophthalmology, 1992; 99: p873-878.
2 Marquardt R. The Treatment of Dry Eye with a New Liquid Gel. Klinische Monatsbl Augenheilk, 1986; 189: 51-54.
3 Holly FJ. What is New in Artificial Tears. Contact Lens Forum, 1991; 16(4): 19-20.
4 Bernal DL & Ubels JL. Artificial Tear Composition and Promotion of Recovery of the Damaged Corneal Epithelium. Cornea, 1993; 12: 115-120.
5 Gilbard JP & Farris RL. Tear Osmolarity and Ocular Surface Disease in Keratoconjunctivitis Sicca. Arch Ophthalmol, 1979; 97: 1642-1646.
6 Lenton LM & Albietz JM. Effect of Carmellose-based Artificial Tears on the Ocular Surface in Eyes after Laser in situ Keratomileusis. J Ref Surg, 1999; 15:

7 Lemp MA & Holly FJ. Ophthalmic Polymers as Ocular Wetting Agents. Ann Ophthalmol, 1972; 4: 15-20.
8 Nelson JD & Farris RL. Sodium Hyaluronate and Polyvinyl Alcohol Artificial Tear Preparations: A Comparison in Patients with Keratoconjunctivitis Sicca. Arch Ophthalmol, 1988; 106: 484-487.
9 Edwards C & Stillman P. Minor Illness or Major Disease? (5) Eye Disorders, Pharm J, 1993; 250: 839-843.
10 Smith G. Pathology of the Tear Film. In: The Tear Film, Structure Function and Clinical Examination, 2002 (Eds Korb et al), Butterworth-Heineman, Oxford, pp114.
11 Hardberger R, Hanna C & Boya CM. Effects of Drug Vehicles on Ocular Contact Time. Arch Ophthalmol, 1975; 93: 42-45.
12 Hamilton W & Wood TO. Filamentary Keratitis. Am J Ophthalmol, 1982; 93: 466-469.
13 Farris RL. Staged Therapy For the Dry Eye. CLAO J, 1991; 17: 207-215.
14 Holly FJ. Surface Chemical Evaluation of Artificial Tears and Their Ingredients. II. Interaction with a Superficial Lipid Layer. Contact Lens Forum, 1978; 4(3): 52-65.
15 Bernal DL & Ubels JL. Quantitative Evaluation of the Corneal Epithelial Barrier: Effect of Artificial Tears and Preservatives. Curr Eye Res, 1991; 10: 645-656.
16 Rieger G. Lipid Containing Eye Drops: A Step Closer to Natural Tears? Ophthalmologica, 1990; 201: 206-212.
17 Brodwall J, Alme G, Gedde-Dahl S, Smith J, Lilliedahl NP, Kunz PA & Sunderraj P. A Comparative Study of Polyacrylic Acid (Viscotears) Liquid Gel versus Polyvinyl Alcohol in the Treatment of Dry Eyes. ACTA Ophthalmol Scand, 1997; 75: 457-461.
18 Gambaro S, Bellussi M, Formenti F, Lore V & Spinelli D. The Use of a Carbopol-Mannitol Gel Combination in the Treatment of Dry Eye. In: The Lacrimal System, (Ed. van Bijsterveld OP, Lemp MA & Spinelli D), Kruger & Ghedini Publications, Amsterdam, 1991: pp103-105.
19 Lebowitz HM, Chang RM & Mandell AL. Gel Tears: A New Medication for the Treatment of Dry Eyes. Ophthalmology, 1984; 91: 1199-1204.
20 Sand BB, Marner K & Norn MS. Sodium Hyaluronate in the Treatment of Keratoconjunctivitis Sicca. Acta Ophthalmol, 1989; 67: 181-183.
21 Mengher LS, Pandher KS, Bron AJ & Davey CC. Effect of Sodium Hyaluronate (0.1%) on Break-up Time (NIBUT) in Patients with Dry Eyes, Br J Ophthalmol, 1986; 70: 442-447.
22 Limberg MB, McCaa C, Kissling GE & Kaufman HE. Topical Application of Hyaluronic Acid and Chondroitin Sulfate in the Treatment of Dry Eyes. Am J Ophthalmol, 1987; 103: 194-197.
23 Saettone MF, Chetoni P, Torracca MT, Burgalassi S & Giannaccini B. Evaluation of Muco-adhesive Properties and in vivo Activity of Ophthalmic Vehicles Based on Hyaluronic Acid. Intern J Pharmaceutics, 1989; 51: 202-212.
24 Bron AJ & Tiffany JM. Pseudoplastic materials as Tear Substitutes. In: The Lacrimal System, (Ed. van Bijsterveld OP, Lemp MA & Spinelli D), Kruger & Ghedini Publications, Amsterdam, 1991: pp27-33.

MULTIPLE-CHOICE QUESTIONS – take part at opticianonline.net

1 Which one of the following statements is true regarding the ideal requirements for dry eye tear replacement products?
A They must all be hypertonic
B They must all be hypotonic
C They must have a good lubricating effect
D They must all have a short retention time

2 To reduce ocular irritation the formulary for artificial tears is normally adjusted for a pH value of:
A 7.3
B 7.4
C 7.5
D 7.6

3 What is the refractive index of natural tears?
A 1.0
B 1.336
C 1.636
D 1.836

4 Which one of the following statements is true regarding polyvinyl alcohol?
A It is a hydrophobic polymer
B It is only used in contact lens preparations
C It is very stable in alkaline solutions
D It reduces surface tension to enhance corneal epithelial wetting

5 Hypromellose is a cellulose derivative that is also known as the abbreviated active ingredient:
A CMC
B PVP
C HE
D HPMC

6 Which one of the following statements is true with regard to dry eye tear replacement products?
A High molecular weight polymers increase the retention time
B High molecular weight polymers reduce the retention time
C Viscoelastics have a Newtonian property
D Carbomers have a reduced retention time compared with PVA

Successful participation in this module counts as one credit towards the GOC CET scheme administered by Vantage and one towards the Association of Optometrists Ireland's scheme. The deadline for responses is July 15 2010

● Jim Farrell is professional programme manager with Boots Opticians, examiner and assessor for the College of Optometrists and formerly researcher in tear film at Glasgow Caledonian University