Nemera

Novelia®

Using intelligent design to deliver safe preservative free multi-dose eye drops

A significant patient population requires the long term use of eye drops multiple times a day. Maintaining the sterility of eye drops is important for patient health. Single use doses are expensive and preservatives can cause allergies and irritation, but the intelligent design of multi-dose bottles provides a viable means of delivering safe, preservative free eye drops.

Patients need sterile eye drops

A large number of patients has conditions that require the long term daily use of eye drops. For example, dry eye syndrome is associated with aging, contact lens use and environmental factors such as windy or sunny weather. It affects an estimated 5% of over 50s in the USA [1] and is usually managed using an artificial tear solution which needs to be applied up to four to six times a day, often for the rest of the patient's life. Conditions such as hay fever and glaucoma also require the long-term use of self-administered eye drops.

It is important that all eye drops are kept free from bacteria. The microbial contamination of eye drops is a significant risk factor in the development of bacterial keratitis [2]. Post-operative patients are at particular risk of infection, as are patients who have used topical steroids, since they lower the ocular defenses [3].

Preservative free formulations are better for patient health

One way of keeping multi-dose eye droppers safe for patients is to add preservatives to the formulation. However, the use of preservatives can cause allergies or ocular irritation, and some can even cause a toxic response, damaging patients' eyes [4]. Any such reactions are particular issues for patients who rely on the long term use of eye drops for chronic conditions. In 2009 the European Medical Agency stated that the, 'inclusion of antimicrobial preservatives or antioxidants in a finished product needs special justification.'

Even when preservatives are tolerated in an adult population there are still questions over tolerance for the paediatric population. The EMA have stopped short of a general recommendation not to use preservatives in eye drops, but they recommend that, 'preservative free formulations whenever possible should be considered' and that 'ophthalmic preparations without preservatives are strongly recommended for use in pediatric patients, especially neonates'.

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Preservative-free unidoses are effective but expensive

Unidose eye droppers are a commonly used delivery method for preservative free eye drops. By virtue of being single use, there is no opportunity for bacterial contamination at the point of use.

Unidoses are ideal for clinical settings, especially during surgery. However they are too costly and inconveniently bulky to make them suitable for home use for chronic conditions. Single unit preservative free drops have been calculated to be 1169% more expensive to produce than the equivalent preserved eye drops in a multi-dose bottle [6].

Intelligent design for preservative-free multidoses

The alternative way to keep eye droppers clean is by the intelligent use of technology. Rather than relying on the anti-microbial properties of preservatives to kill any bacteria that enter the bottle, the ideal approach is to prevent any entry of bacteria into the bottle in the first place.

Multi-dose bottles dispense drops using either a non-return valve or a filtering system. Most commercially available bottles designed for multi-dose preservative free eye drops rely on a filtering system to stop the entry of bacteria. When a drop is dispensed the volume of the dose is compensated by air. Eye drops can become contaminated in two main ways: by contaminated air entering the device or by contaminated liquid re-entering through the filter.

Filtering out the bacteria?

Anti-microbial filters are typically made of a nylon fiber membrane that consists of tightly packed layers of strands of nylon fibers (Figure 1). Filters work on the mechanical principle that bacteria are large molecules that do not fit through the very small holes, while air and non-viscous solutions are able to pass through without hindrance.

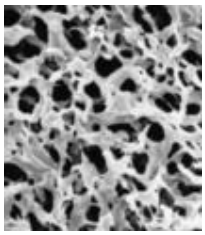

Figure 1: A scanning electron micrograph of a nylon membrane filter (pore size 0.22 µm).

0.22 µm sterile filters are industry standards, but their effectiveness as bacterial filters has been challenged in the literature. Unfortunately it has been found that bacteria are capable of routinely penetrating 0.22 µm filters, even when the molecules seem to be too big to fit through the holes.

In the 2002 paper 'Big bacteria pass through very small holes' [7], Wainwright et al found that, 'common, potentially pathogenic, bacteria (which are nominally larger than 0.2 µm) can cross a 0.2 µm nylon membrane. All of the bacteria crossed from the upper membrane surface to the solid medium below the membrane; this ability was highly repeatable and did not depend on the make of membrane used. Bacteria growing below the membrane exhibited normal size and morphology.'

Even where filters are shown to be effective, the filtered bacteria clearly remain on the filter. A 2006 study on the efficacy of single use bacterial filters showed, 'a significantly greater bacterial growth on the proximal side of the filter compared with the distal side' [9]. Eye drop filters act in two directions: pressure on the sides of the plastic bottle dispenses a dose through the filter to the patient's eye; when the pressure is released, air and a small amount of liquid passes back through the filter and into the bottle. Therefore bacterial growth on the filter represents a contamination risk for the delivered dose.

What makes filters unreliable?

The evidence that bacteria can pass through 0.2 µm filters is clear, but the reasons are not obvious.

One possibility for the observed passage of bacteria through filters could be due to the nature of the material of the filters. The sponge-like structure includes holes of varying sizes (Figure 2), some of which are statistically likely to be larger than 0.2 µm. In fact, one study found that 0.2 µm filters have a distribution of pore sizes that includes some as big as 0.5 µm [10].

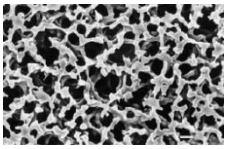

Figure 2: A scanning electron micrograph of a Millipore membrane filter (pore size 0.22 µm) showing a distribution of pore sizes [12]. The bar in the bottom right hand corner of the image is 1 µm long.

Individual testing would eliminate doubt over the viability of each filter, but the process used to test filters is destructive [11]. The testing method introduces bacteria and liquid onto the surface of the filter. This starts bacterial growth on the filter and therefore decreases the subsequent shelf life of the dispenser. Therefore, in-line testing of multi-dose dispensers that rely on filter technology is not possible. Instead, testing is carried out statistically on only a proportion of the dispensers.

However, it is likely that larger holes in the filters is not the sole mechanism of bacterial penetration. Hasegawa et al [12] found that the bacteria, 'P. aeruginosa passed through a 0.22 µm pore size filter. The membranes which allowed passing-through of bacteria showed normal bubble point values in the integrity test.' This demonstrates that bacteria are still capable of passing through a reliable 0.22 µm pore size filter.

Bacterial motility is a cause of filter penetration

Bacteria come in a variety of shapes and sizes, but many of them share the ability to self-propel by twitching, rotating or gliding. Twitching is the most common form of motility and is achieved through movement of the flagella in a way that makes the bacteria appear to swim. Studies have shown that this motility enables bacteria to move through very small channels relative to their size.

Hasegawa et al [12] demonstrated that P. aeruginosa were able to pass through a reliable 0.22 µm pore size filter. They then experimented with a strain of the bacteria P. aeruginosa that was defective in twitching motility and found that it was unable to pass through the 0.22 µm filter. They concluded that it is the flagellum-dependent motility of P. aeruginosa that enabled it to penetrate fine filters.

Bacteria also penetrate by growth and division

Männik et al [13] went on to find that E.coli bacteria lose their ability to swim in channels narrower than their diameter. Surprisingly, they found that despite this they are still able to penetrate narrow channels. They observed that over time, through the mechanism of growth and division, E. coli bacteria were able to penetrate filter channels 'with a width that is smaller than their diameter by a factor of approximately 2. Within these channels, bacteria are considerably squeezed but they still grow and divide.'

This has clear implications for the effectiveness of filters for multi-dose preservative free eye droppers. Filtering liquid several times a day means that the filter remains wet throughout the usable lifetime of the device, presenting ideal conditions for bacterial growth.

An alternative to filters based on silicone: Novelia®

A viable alternative to the use of sterile filters for multi-dose preservative free eye droppers is a non-return valve system used in conjunction with a silicone membrane to filter the returning air (Figure 3). The one-way valve ensures that no contaminated liquid can be re-introduced to the container after the drop has been dispensed, completely removing the need to filter the liquid. The intake of air into the dispenser takes place via a separate venting system with a silicone membrane called the PureFlow™ Technology.

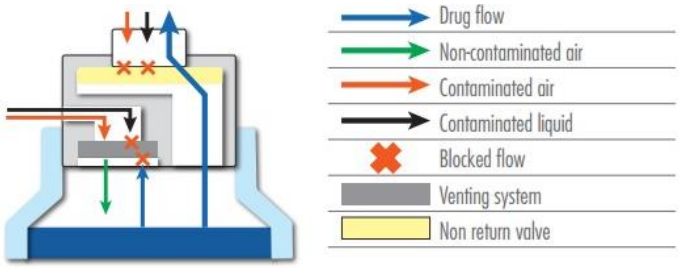

Figure 3: The Novelia® system uses a non-return valve that removes the need to filter the liquid. This makes it possible to use a silicone membrane to filter the air.

The venting system filters the intake of air using a very fine membrane manufactured from silicone polymer.

The silicone membrane is a solid, non-porous material. It is homogenous and does not contain any holes therefore its characteristics can be precisely engineered. The membrane's intermolecular distance is of the order of nanometers, allowing the passage of air through the membrane, but completely preventing the passage of any liquid or solid, including bacteria.

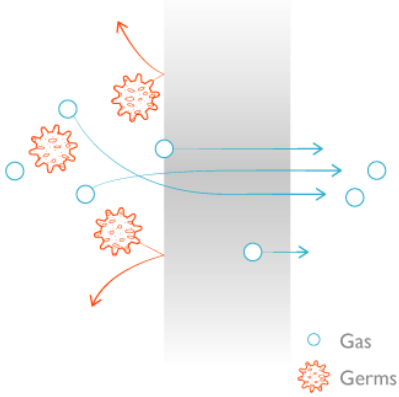

Figure 4: The PureFlow™ Technology consists in using the air permeation property of the silicone to allow the air flow and avoid any bacteria penetration

The function of the silicone membrane can be compared to an inflated balloon. The balloon is a continuous, waterproof material, yet gas slowly passes through the wall of the balloon until the pressures inside and outside reach equilibrium.

The separation of the dose delivery from the venting system means that the membrane is kept dry. This minimizes the risk of bacterial growth on the surface of the membrane, and also means that the testing process is non-destructive. In fact, devices that use this technology can be tested individually in-line as a consistent part of the manufacturing process to ensure robust quality standards. This provides an even greater assurance of safety for the patients.

Novelia® key advantages

FOR THE PHARMACEUTICAL COMPANY…

- **100% controlled and safe** thanks to its **patented PureFlow™ technology**
- Functional with **suspensions** and **solutions** up to high viscosities
- Large **range of bottles**
- Compatible with most **existing filling lines** (screw cap)
- Simplified manufacturing process thanks to **preassembled cap and nozzle**

… AND OF COURSE FOR THE PATIENT

- **Preservative-free** to protect the ocular surface
- **User-friendly** and **intuitive**, as easy to use as any standard eyedropper
- **Blue tip** for a better precision when targeting the eye
- **One drop at a time** in the patient's eye, **calibrated drops**
- **Low squeeze force**
- **More sustainable and affordable** compared to unit-dose, easier to carry

With Novelia®, preserve patient's eyes, not drugs!

A non-return valve combined with a silicone membrane venting system demonstrates how intelligent design can be used to prevent the entry of bacteria into a bottle, making it possible to deliver safe, multi-dose preservative free eye drops.

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References

1. In the US an estimated 3.2 million women age 50 and over and 1.68 million men age 50 and over are affected by dry eye syndrome:
   a. Schaumberg D A, Sullivan D A, Buring J E, Dana M R, Prevalence of dry eye syndrome among US women. Am J Ophthalmol. 2003; 136:318-26.
   b. Schaumberg D A, Dana R, Buring J E, Sullivan D A, Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. Arch Ophthalmol. 2009; 127:763-8.
2.
   a. Templeton W C, 3rd, Eiferman R A, Snyder J W. et al Erratia keratitis transmitted by contaminated eyedroppers. Am J Ophthalmol 1982 93723–726.726 [PubMed]
   b. McCulloch J C, Origin and pathogenicity of Ppyocyanea in conjunctival sac. Arch Ophthalmol 1943; 29:924-36.
   c. Hogan M J, The preparation and sterilization of ophthalmic solutions. Calif Med 1949; 71:414-6.
   d. Theodore F H, Contamination of eye solutions. Am J Ophthalmol 1951; 34: 1764.
   e. Theodore F H, Practical suggestions for the preparation and maintenance of sterile ophthalmic solutions. Am J Ophthalmol 1952;35:656-9.
   f. Vaugh D G, Jr, The contamination of fluorescein solutions with special reference to Pseudomonas aeruginosa (Bacillus pyocyaneus). Am J Ophthalmol 1955;39:55-61.
3. Rahman M Q, Tejwani D, Wilson J A, Butcher I, and Ramaesh K, Microbial contamination of preservative free eye drops in multiple application containers, Br J Ophthalmol. 2006 Feb; 90(2): 139–141.
4. Report of the International Dry Eye Workshop. Ocul Surf 2007; 5[2]; 65-204.
5. EMEA Public Statement on Antimicrobial Preservatives in Ophthalmic Preparations for Human Use (Doc. Ref.: EMEA/622721/2009). http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2010/09/WC500096784.pdf
6. Hertel F, Pfeiffer N, Einzeldosisapplikationen in der Glaukomtherapie. Vergleich der Kosten mit Mehrdosis. Ophthalmologe 1994; 91:602-5.
7. Wainwright M, Al Talhi A, Gilmour D J, Anderson R W, Killham K, Big bacteria pass through very small holes, June 2002 Volume 58, Issue 6, Pages 558–560.
8. Onyango L A, Dunstan R H, Roberts T K, Filterability of staphylococcal species through membrane filters following application of stressors, BMC Research Notes 2010, 3:152.
9. Unstead M, Stearn M D, Cramer D Chadwick M V, Wilson R, An audit into the efficiency of single use bacterial/viral filters for the prevention of equipment contamination during lung function assessment. *Respir Med* 2006; 100: 946–950.
10. Osumi M, Yamada N, Toya M, Bacterial retention mechanisms of membrane filters. PDA J Pharm Sci Technol 1996, 50:30-34.
11. Benezech T, A method for assessing the bacterial retention ability of hydrophobic membrane filters, Trends in Food Science & Technology 12 (2001) 36–38.
12. Hasegawa H, Naganuma K, Nakagawa Y, Matsuyama T, Membrane filter (pore size, 0.22-0.45 µm; thickness, 150 µm) passing-through activity of Pseudomonas aeruginosa and other bacterial species with indigenous infiltration ability, FEMS Microbiology Letters 223 (2003) 41-46.
13. Männik J, Driessen R, Galajda P, Keymer J E, Dekker C, Bacterial growth and motility in sub-micron constrictions, PNAS, 2009, 106: 35 14861–14866.