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# Preservatives and the Eye

This article aims to explain what preservatives used in eye drops are and why we have them. Advice is given on when they should be avoided in preference for preservative free drops. The importance of preservatives and their effect on the eye which can easily be overlooked, possible immediate and delayed adverse consequences for the patient, are discussed.

## Preservatives: what, why, how and when

A preservative is a chemical that creates an environment that either kills microbes (bacteriocidal) or prevents their proliferation (bacteriostasis). Some preservatives work by destroying cell membranes by surfactant or free radical action. Those with surfactant properties also aid drug penetration. Other preservatives work by chelating and depriving microbes of essential nutrients for growth and reproduction.

Preservatives are useful for increasing the shelf life of a drug by delaying the decay of the active drug. They prevent contamination from exposure to microbes (viruses, bacteria, and fungi).<sup>1</sup> This is especially important when you consider the typical environment eye drops are kept in: pockets, purses, toiletry kits. Many people do not know how to use drops in a hygienic manner (avoiding touching the tip of the bottle with their fingers or eye) further increasing the likelihood of contamination. For this reason most manufacturers recommend disposal of multidose bottles after four weeks from opening.

Preservatives facilitate use of multidose bottles which are cheaper to produce than multiple single dose vials. This means cheaper drugs for patients and a better competitive price and resultant profit for drug companies. Preserved drops can be as much as five times cheaper than the preservative free equivalent. Larger

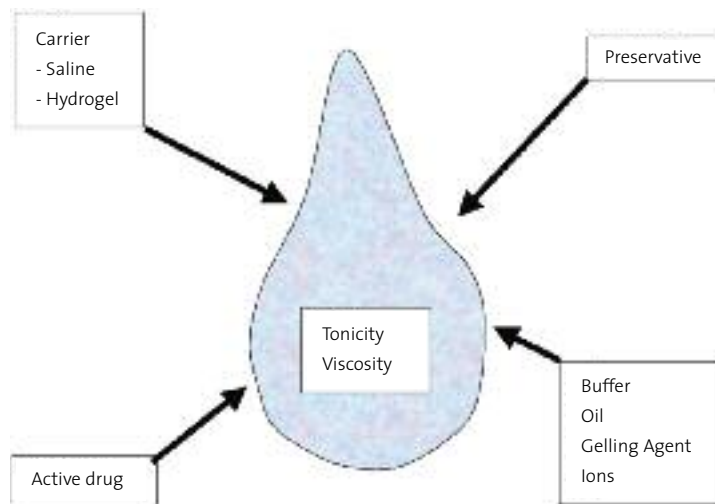


Figure 1: Ingredients used in eye drops.

bottles are easier for the elderly and arthritic to handle, grip and squeeze, improving compliance.

It can be confusing to work out whether a drop contains a preservative or not because of the various ingredients which are used (Figure 1). This is made even more challenging by the variety of possible preservatives (Table 1).

The most commonly used preservatives are Benzalkonium Chloride (BAC) and Chlorobutanol. Both can cause irritation, allergy, inflammation, toxicity and disruption of the tear film. Newer preservatives such as GenAqua (Sodium Perborate) and Polyquad (Polyquaternium-1) are less damaging to the eye surface.<sup>2,3</sup>

### Benzalkonium chloride

This is the most commonly used and well known preservative found in eye drops. It is a quaternary ammonium salt with surfactant qualities. Alkyl triethanol ammonium chloride, benzethonium chloride, cetrimide (cetyltrimethylammonium bromide), dymed and polyquad are also examples of quaternary ammonium compounds that are used in ophthalmic preparations.

Benzalkonium chloride (BAC) can be bacteriostatic or bacteriocidal depending on the concentrations used. It gained popularity when it was first introduced because it also enhances corneal penetration of some

**Table 1: Names of preservatives used in eye drops**

Names of preservatives
<ul style="list-style-type: none"> <li>• perborate</li> <li>• polyquaternium-1 (Polyquad<sup>®*</sup>)</li> <li>• Purite<sup>®**</sup></li> <li>• benzalkonium chloride</li> <li>• methylparaben</li> <li>• propylparaben</li> <li>• stabilised oxyborate complex (Dissipate<sup>TM***</sup>)</li> <li>• phenoxyethanol</li> <li>• sorbic acid EDTA</li> <li>• sodium perborate</li> <li>• sodium silver chloride complex</li> <li>• chlorobutanol</li> </ul>

\*Polyquad is a registered trademark of Alcon Laboratories, Inc.  
\*\*Purite is a registered trademark of Allergan, Inc.  
\*\*\*Dissipate is a trademark of Ocusoft, Inc.

## Long-term topical combination therapy using preserved eye drops is a significant risk factor for the failure of subsequent glaucoma surgery

drugs by causing epithelial separation. This has recently been shown not to be true with travoprost.<sup>4</sup> It is effective against most bacteria with a few exceptions, such as *Pseudomonas aeruginosa*, or picornaviruses, such as the common cold. It inactivates HIV and herpes simplex virus in vitro. Eye drops which contain BAC have from only 0.01% (most eye drops) to 0.4%; stronger concentrations than this risk a chemical burn or at least some irritation. BAC comes under many aliases (Table 2).

Several authors have demonstrated cytotoxic effects of BAC on the cornea, even with percentages as low as 0.005%.<sup>5,6</sup> One study, though, found little corneal epithelial damage despite exaggerated use, matching unpreserved against 0.02% BAC solutions in methylcellulose.<sup>7</sup>

Interestingly, the Sussex Eye Hospital found out, inadvertently, what happens when BAC enters the eye. Nineteen patients were exposed to intraocular BAC preserved viscoelastic during cataract surgery and all developed severe striate keratopathy immediately postoperatively. This demonstrates that BAC is toxic to corneal endothelium when used intraocularly. Most patients recovered with varying degrees of residual stromal thickening. Two patients required penetrating keratoplasty and were reported to have successful outcomes following this procedure.<sup>8</sup>

### Disappearing preservatives

Noecker et al. showed that stabilised oxychloro complex (SOC) caused less damage to corneal epithelial cells than BAC. They recommended that physicians should consider treatment with new generation

preparations containing low-risk preservatives such as SOC, especially in patients receiving multiple ophthalmic medications.<sup>9</sup> These newer so-called 'disappearing' preservatives are now found in many brands of artificial tears. They are often borate or hydrogen peroxide and dissolve from H<sub>2</sub>O<sub>2</sub> to H<sub>2</sub>O on coming into contact with tears. This requires that patients have sufficient tears to dissolve the preservative, which many do not. In these cases the H<sub>2</sub>O<sub>2</sub> can be toxic to an already compromised cornea. They should only be used in patients without significant keratoconjunctivitis sicca and with moderate tear production sufficient to dissolve the preservative (Table 3, 4).

Any patient who requires more than 8-10 artificial tear drops a day should switch to true preservative free tears or consider punctal occlusion. Punctal occlusion is an excellent option for elderly, arthritic patients who lack the dexterity to instil artificial tears regularly.<sup>10</sup>

Symptoms and signs are less prevalent than when preservative free drops are used. Most of the adverse reactions induced by preserved glaucoma medication are reversible after removing preservatives.<sup>11</sup> This is important to consider when ensuring compliance. Although the adverse effects of glaucoma medications on the ocular surface are likely to be multifactorial, a one-month of treatment with glaucoma medications containing higher levels of BAC resulted in greater corneal damage and conjunctival cell infiltration than medications preserved with Purite or with lower levels of BAC. By implication, using glaucoma medications with alternative preservatives or low levels of BAC may help preserve ocular health.<sup>12</sup> Indeed, long-term topical combination therapy using preserved eye drops is a significant risk factor for the failure of subsequent glaucoma surgery. This is thought to be caused predominantly from past inflammation due to preservative use.<sup>13,14,15</sup>

### Glaucoma drops and preservatives

The use of preservatives in glaucoma eye drops deserves a special mention.

### Preservative free drops

Now that the problems of using preservatives in the eye are becoming more widely

**Table 2: Aliases of benzalkonium chloride**

Aliases of benzalkonium chloride
<ul style="list-style-type: none"> <li>alkyl dimethylbenzyl ammonium chloride</li> <li>alkyldimethyl(phenylmethyl) quaternary ammonium chloride</li> <li>ammonyx</li> <li>arquad DMMCB-75</li> <li>barquat MB-50</li> <li>bayclean</li> <li>benirol</li> <li>benzalkonium A</li> <li>empigen</li> <li>roccal</li> <li>zephiran chloride</li> </ul>

**Table 3: Indications and contraindications of preservative free eye drops**

Preservative eye drops	
Indications	Contraindications
<ul style="list-style-type: none"> <li>&lt; 4 drops/day</li> <li>only occasional dry eye symptoms</li> <li>hot climate without access to refrigeration (&gt;30 degrees)</li> </ul>	<ul style="list-style-type: none"> <li>&gt; 6 drops/day</li> <li>known hypersensitivity to the preservative</li> <li>soft contact lenses (some preservatives, particularly BAC, accumulate in soft contact lenses and cause irritation).</li> <li>abnormal ocular surface conditions</li> <li>conditions requiring healing of cornea</li> </ul>

**Table 4: Conditions where preserved eye drops contraindicated**

Conditions where preserved eye drops contraindicated		
Frequent use of drops required	Abnormal ocular surface	Healing of cornea required
<ul style="list-style-type: none"> <li>corneal ulcer</li> <li>severe dry eye</li> <li>glaucoma</li> <li>postoperative</li> <li>inflammatory eye disease</li> </ul>	<ul style="list-style-type: none"> <li>delayed tear clearance</li> <li>aqueous deficiency</li> <li>limbal stem cell failure</li> <li>chemical burns</li> <li>Stevens-Johnson syndrome</li> <li>multiple surgeries</li> </ul>	<ul style="list-style-type: none"> <li>persistent corneal epithelial defect</li> <li>penetrating keratoplasty</li> <li>corneal epithelial erosions</li> </ul>

appreciated by both medical staff and patients there is an expanding market for preservative free drops. This is especially true with respect to the advent of artificial tear use following refractive laser eye surgery. There are now many preservative free artificial tear drops and an increasing number of preservative free glaucoma drops (Table 5).

The down side of preservative free drops is that they require more frequent replacement and the small disposable vials are not good for those with arthritis, poor dexterity or vision. Patients may

keep disposable vials for more than one application to save money with the attendant risk of infection. Preservative free eye drops in multiple application containers are at risk of contamination by potentially pathogenic microorganisms.<sup>1</sup>

**Conclusion**

When prescribing drops for a patient it is important to be mindful of whether it is preserved or not, what with, and what non-preserved alternatives exist. Particular care should be exercised when prescribing for patients with dry eye or ocular surface disease requiring frequent and prolonged administration of drops. Issues of maintaining health of the eye, availability, compliance and cost need to be balanced against each other. **EN**

**Table 5: Examples of preservative free glaucoma drops**

<p><b>Examples of preservative free glaucoma drops (not all available in UK, list may not be complete).</b></p> <ul style="list-style-type: none"> <li>• betagan unit dose</li> <li>• betoptic suspension single dose</li> <li>• Cosopt (MSD)</li> <li>• minims metipranolol 0.1% or 0.3%</li> <li>• minims pilocarpine 1%, 2% or 4%</li> <li>• timoptol unit dose 0.25% or 0.5%</li> <li>• Travatan Z (Alcon)</li> <li>• Trusopt (MSD)</li> </ul>
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**Take Home Message:**

Consider using preservative free drops when:

- Frequent and prolonged drop use required.
- Dry eye or other surface pathology.
- Irritative symptoms and signs on current drops.