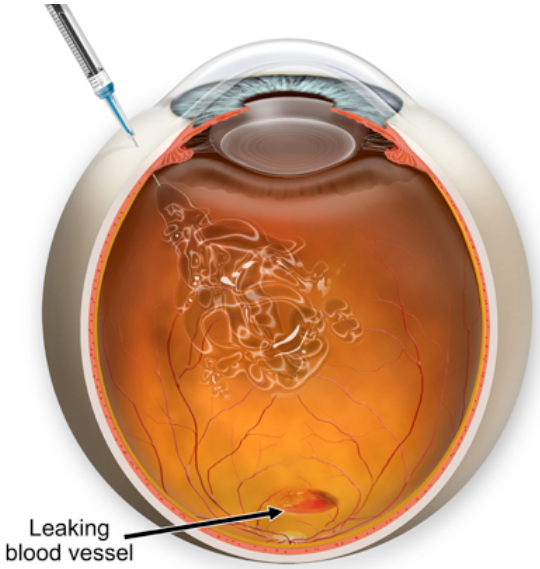
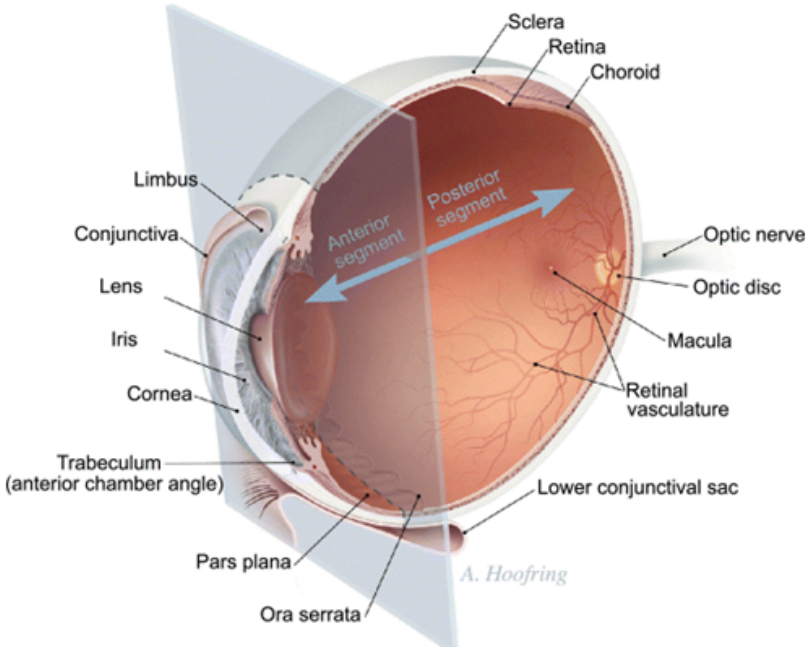
Ophthalmic Preparations 1

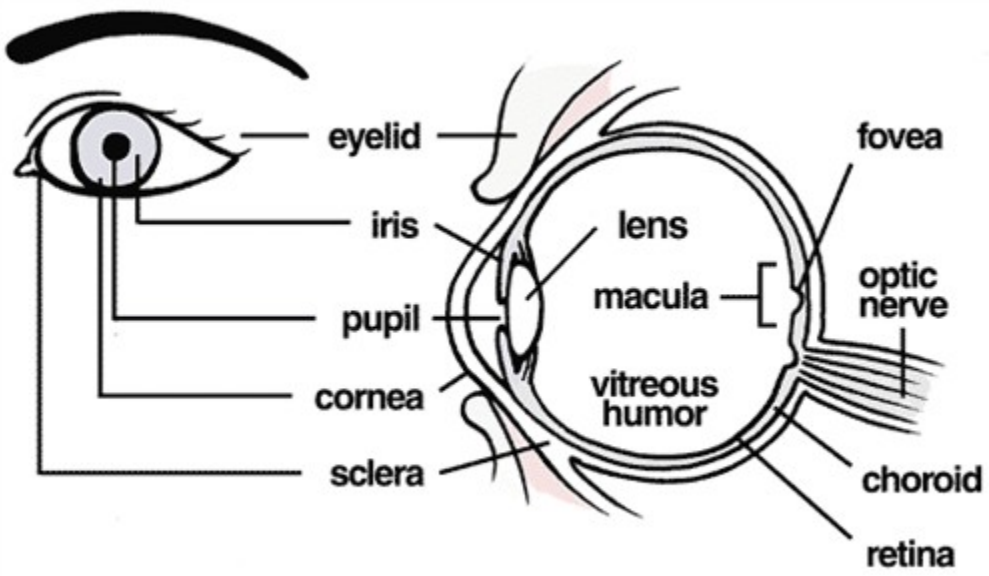
Definition

- Specialized dosage forms designed to be instilled onto the external surface of the eye (topical), administered inside (intraocular) or adjacent (periocular) to the eye or used in conjunction with an ophthalmic device.



Eye Anatomy and Physiology





Eye Anatomy and Physiology

- The **sclera:** The protective outer layer of the eye, referred to as the “white of the eye” and it maintains the shape of the eye.

- The **cornea:** The front portion of the sclera, is transparent and allows light to enter the eye. The cornea is a powerful refracting surface, providing much of the eye's focusing power.

- The **choroid** is the second layer of the eye and lies between the sclera and the retina. It contains the blood vessels that provide nourishment to the outer layers of the retina.

- The **iris** is the part of the eye that gives it color. It consists of muscular tissue that responds to surrounding light, making the **pupil,** or circular opening in the center of the iris, larger or smaller depending on the brightness of the light.

Eye Anatomy and Physiology

- The **lens** is a transparent, biconvex structure, encased in a thin transparent covering. The function of the lens is to refract and focus incoming light onto the retina.

- The **retina** is the innermost layer in the eye. It converts images into electrical impulses that are sent along the optic nerve to the brain where the images are interpreted.

- The **macula** is located in the back of the eye, in the center of the retina. This area produces the sharpest vision.

Eye Anatomy and Physiology

- The inside of the eyeball is divided by the lens into two fluid-filled sections.
- The larger section at the back of the eye is filled with a colorless gelatinous mass called the **vitreous humor (gel)**.
- The smaller section in the front contains a clear, water-like material called **aqueous humor.**
- The **conjunctiva** is a mucous membrane that begins at the edge of the cornea and lines the inside surface of the eyelids and sclera, which serves to lubricate the eye.

Ocular Routes of Administration

A. Eye drops

B. Scleral plug

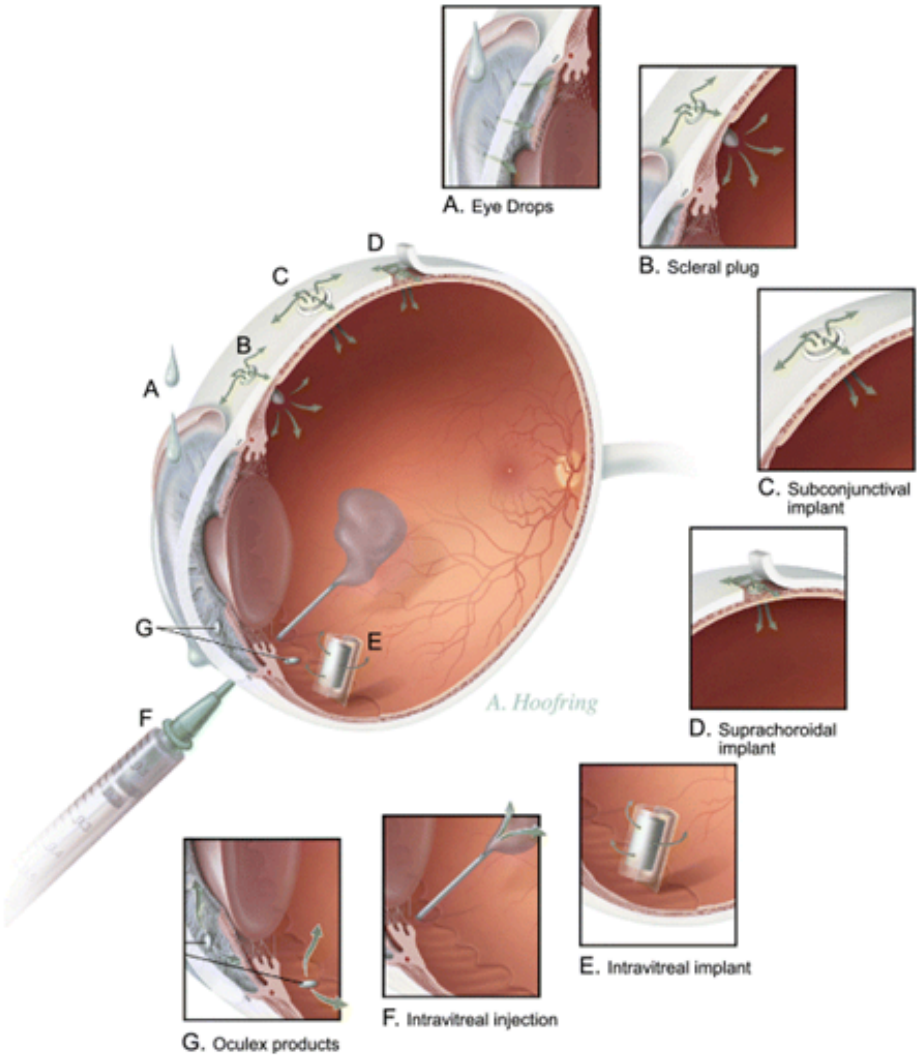
C. Subconjunctival implant

D. Suprachoroidal implant

E. Intravitreal implant

F. Intravitreal injection

G. Oculex products



Components of Ophth. Prep.

Active ingredient(s) to produce desired therapeutic effect.

Vehicle, usually aqueous.

Antimicrobial preservative to eliminate any microbial contamination during use and thus maintain sterility.

Adjuvant to adjust tonicity, viscosity or pH in order to increase the comfort in use and to increase the stability of the active ingredient(s).

Suitable container for administration of eye drops which maintains the preparation in a stable form and protects from contamination during preparation, storage and use.

Consideration in Ophth. Prep.

- Sterility
- Ocular toxicity
- Preservation

Sterility

- The single most important requirement of eye drops is **sterility**.

- During the 1940s and 1950s there were several incidents reported where microbial contaminated eye drops were used and consequently introduced infected into the eyes being treated.

- The results were particularly damaging when the contaminating organism was *Pseudomonas aeruginosa* which is difficult to treat successfully and can cause loss of the eye.

Sterility

- Ideally, all ophthalmic products would be terminally sterilized in the final packaging.

- Only a few ophthalmic drugs formulated in simple aqueous vehicles are stable to normal autoclaving temperatures and times (121°C for 20-30 min).

- Such heat-resistant drugs may be packaged in glass or other heat-deformation-resistant packaging and thus can be sterilized in this manner.

Sterility

- Most ophthalmic products are aseptically manufactured and filled into previously sterilized containers in aseptic environments using aseptic filling-and-capping techniques.

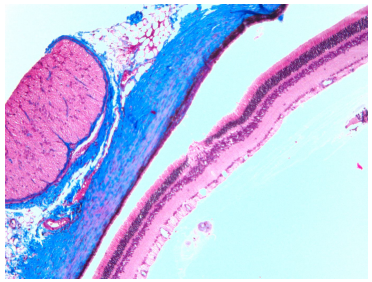
Ocular Toxicity

- Albino rabbits are used to test the ocular toxicity and irritation of ophthalmic formulations (Ocular Tolerability Test)

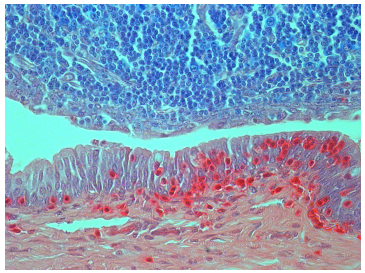
- The procedure based on the examination of the conjunctiva, the cornea or the iris.

Acute Local Toxicity

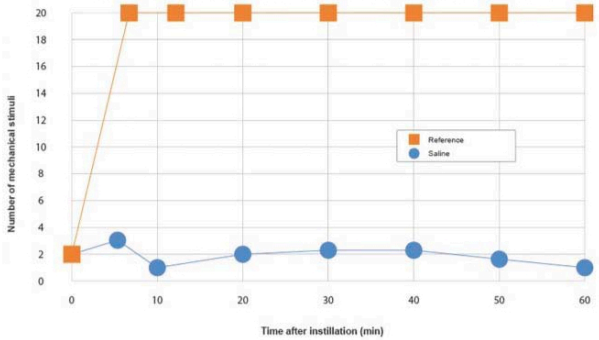
Chronic Local Toxicity



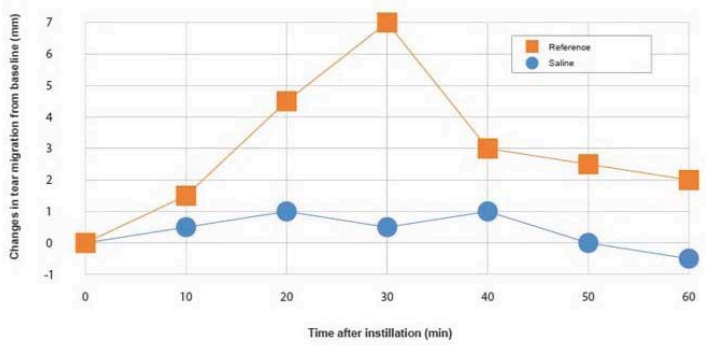
Histopathology



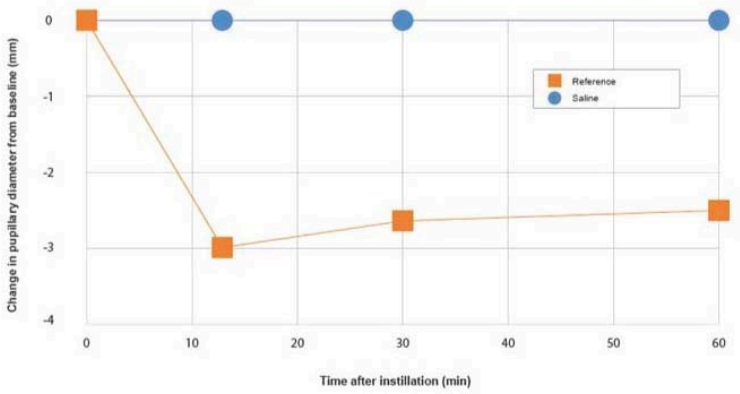
Corneal Anesthesia Testing



Lacrimation Tests

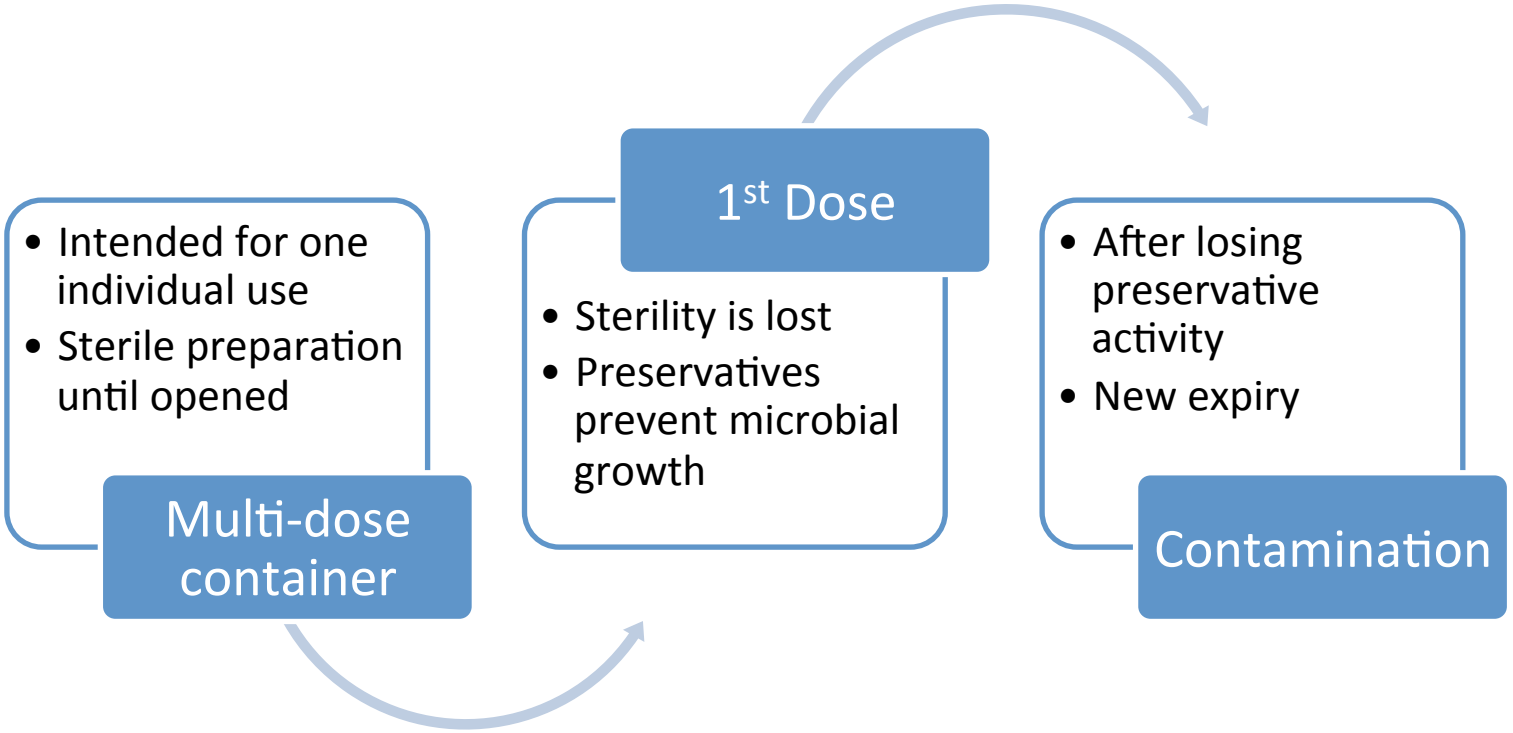


Pupillary Diameter



Preservation

- Preservatives are included in multiple-dose eye solutions for maintaining the product sterility during use.
- Preservatives may not be included in unit-dose package.



Preservation

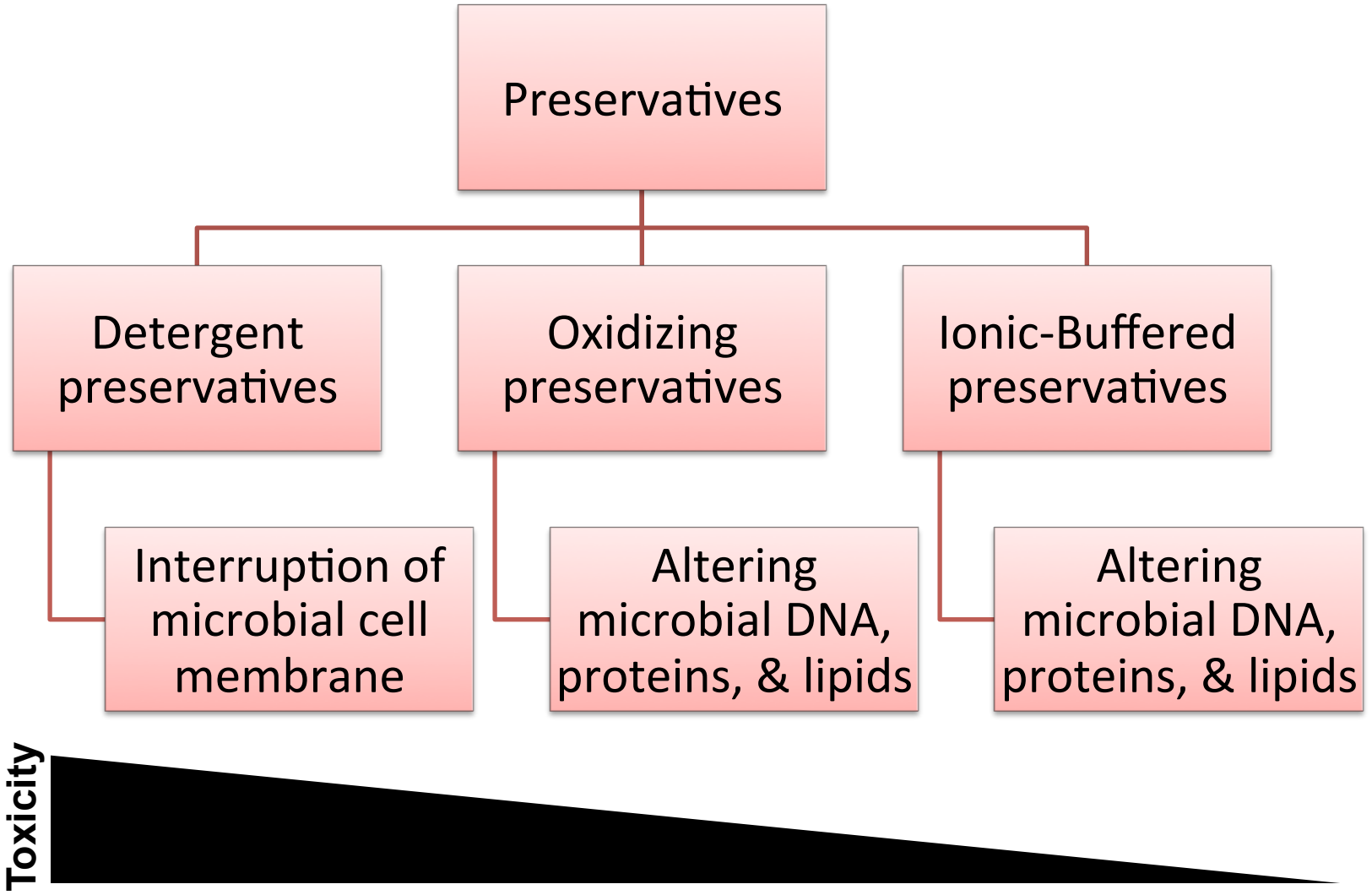
- The use of preservatives is prohibited in ophthalmic products that are used at the of eye surgery because, if sufficient concentration of the preservative is contacted with the corneal endothelium, the cells can become damaged causing clouding of the cornea and possible loss of vision.

Preservation

- Preservatives should be used that do not cause patient sensitivity or that are incompatible with the other ingredients in the formulation.

- Preservatives that are commonly used in ophthalmic formulations are listed in the table below. The FDA Advisory Review Panel on OTC Ophthalmic Drug Products (Dec. 1979) established that the concentrations are for formulations that will have direct contact with the eye and not for ocular devices such as contact lens products.

Preservation



Preservation

Maximum Concentration of Preservatives Approved for Use in Ophthalmic Solutions

Agent	Maximum Concentration
Benzalkonium chloride	0.013%
Benzethonium chloride	0.01%
Chlorobutanol	0.5%
Phenylmercuric acetate	0.004%
Phenylmercuric nitrate	0.004%
Thimerosal	0.01%
Methylparaben	0.1- 0.2%
Propyl-parabens	0.04%

FDA Advisory Review Panel on OTC Ophthalmic Drug Products, Final report, Dec. 1979.

Preservation

- Preservatives do not immediately produce sterility and should not be the sole means of sterilizing a product. Patients should be counseled that the product may be easily contaminated by touching it to the eyes.

- Self-contained dropper bottles are less likely to be contaminated than those which must be opened and the dropper removed. However, the plastics used to make these are reactive with a number of solutions and may not be as acceptable as glass bottles.

Examples of Common Preservation

1- Cationic wetting agents:

- Benzalkonium chloride (0.01%)
  - It is generally used in combination with 0.01-0.1% disodium edetate (EDTA). The chelating, EDTA has the ability to render the resistant strains of *Pseudomonas aeruginosa* more sensitive to benzalkonium chloride.
  - Side effects include: disruption of tear film and damage of ocular surface epithelial cells

2- Organic mercurials:

- Phenylmercuric nitrate 0.002-0.004%

  phenylmercuric acetate 0.005-0.02%.

Preservation

3-Esters of p-hydroxybenzoic acid:

- Mixture of 0.1% of both methyl and propyl hydroxybenzoate

  (2 :1)

4- Alcohol Substitutes:

- Chlorobutanol(0.5%). Effective only at pH 5-6.
- Phenylethanol (0.5%)

Preservative	Class	Advantages	Disadvantages	Medication examples
SofZia®	Oxidative	Modified into harmless elements upon instillation; smaller amounts of conjunctivo–corneal inflammation compared with BAK	Newer agent requiring more studies to understand ocular safety profile of the preservative independent of active ingredients	Travatan Z®
Sodium perborate (GenAqua®)	Oxidative	Catalyzed into hydrogen peroxide, water and oxygen upon instillation; activity against *Aspergillus*; less toxicity than BAK	Few studies documenting ocular tolerability and side-effect profile	Genteal®
Stabilized oxychloro complex (SOC/Purite®)	Oxidative	Dissociates into water, oxygen, sodium and chlorine free radicals	As with sofZia, more studies are needed to assess ocular side effects independent of active ingredients	Alphagan-P®, Refresh Tears®
Polyquaternium-1 (Polyquad®)	Detergent	Less toxicity to corneo–conjunctival surface than BAK	Superficial corneal epithelial damage reduces density of conjunctival goblet cells	Tears Naturale II®, Opti-Free® Express Disinfecting Solution
Chlorobutanol	Detergent	Toxic effects take longer to manifest than BAK; doesn't affect stability of lipid component of tear film; extensive antimicrobial activity	Causes keratitis and irritation to ocular surface; decreased amount of mitoses to corneal epithelial cells; unstable when stored at room temperature	TobraDex® Ointment
Cetrimonium chloride	Detergent	Excellent antiseptic qualities	Causes keratinization and inflammatory infiltrates at the limbus and within the conjunctival stroma and epithelium	Civigel®
Benzalkonium chloride	Detergent	Excellent antimicrobial efficacy; disruption of corneal cell–cell junctions allow medicinal entry to anterior chamber; well-established familiarity in industry	Breakdown of corneal epithelium; apoptosis of ocular surface cells; accumulation in surface tissues; tear-film instability	Timoptic®, Azopt, Lumigan®, Xalatan
Edetate disodium	Chelating agent	Inactivates trace amounts of heavy metals	Few studies documenting chronic side effects	Acular®, Betagan®

BAK: Benzalkonium chloride.

Medscape

Evolution of Preservatives Since Benzalkonium Chloride: Summary of Ophthalmic Preservatives