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Remington: The Science and Practice of Pharmacy

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Remington: The Science and Practice of Pharmacy . . . *A treatise on the theory and practice of the pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also, a guide to the professional responsibilities of the pharmacist as the drug information specialist of the health team . . . A textbook and reference work for pharmacists, physicians, and other practitioners of the pharmaceutical and medical sciences.*

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PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE

methylcellulose, polyvinyl alcohol, and hydroxypropylmethyl cellulose are added frequently to increase viscosity.

Various investigators have studied the effect of increased viscosity on contact time in the eye. In general terms, viscosity increased up to the 15 to 50 cps range significantly improves contact time in the eye. Results tend to plateau beyond the 50-centipose range; higher viscosity values offer no significant advantage and have a tendency to leave a noticeable residue on the lid margins.

ADDITIVES—The use of various additives in ophthalmic solutions is permissible; however the choices are few. An antioxidant, specifically sodium bisulfite or metabisulfite, is permitted in concentrations up to 0.3%, particularly in solutions containing epinephrine salts. Other antioxidants such as ascorbic acid or acetylcysteine also may be used. The antioxidant acts in this case as a stabilizer to minimize oxidation of epinephrine.

The use of surfactants in ophthalmic preparations is restricted similarly. Nonionic surfactants, the class of such compounds that are least toxic to the ophthalmic tissues, are used in low concentrations particularly in steroid suspensions and as aids in achieving solution clarity. Surfactants may be used rarely as cosolvents to increase solubility.

The use of surfactants, particularly in any significant concentration, should be tempered by recognition of the sorption characteristics of these compounds. Nonionic surfactants, in particular, may react by binding with antimicrobial preservative compounds and inactivate much of the preservative system.

Cationic surfactants are used frequently in ophthalmic solutions but almost invariably as antimicrobial preservatives. Benzalkonium chloride is typical of this class of substances. Concentrations are in the range of 0.005 to 0.02%, with toxicity the limiting factor on the concentration used. Because of its large molecular weight the benzalkonium cation is inactivated easily by macromolecules of opposite charge or by sorption. Despite such limitations, benzalkonium chloride is the preservative used in the large majority of commercial ophthalmic solutions and suspensions.

PACKAGING

The traditional ophthalmic glass container with accompanying glass dropper has been supplanted almost completely by the low-density polyethylene dropper unit called the *Drop-Tainer* (Alcon). In only a very few instances are glass containers still in use, usually because of stability limitations. Large-volume intraocular solutions of 250 and 500 mL have been packaged in glass, but even these parenteral-type products are beginning to be packaged in specially fabricated polyethylene/polypropylene containers.

One should be ever mindful that plastic packaging, usually low-density polyethylene, is by no means interchangeable with glass. Plastic packaging is permeable to a variety of substances including light and air. The plastic package may contain a variety of extraneous substances such as mold-release agents, antioxidants, reaction quenchers, and the like, which readily may leach out of the plastic and into the contained solution. Label glues, inks, and dyes also may penetrate polyethylene readily. In the opposite sense, volatile materials may permeate from solution into or through plastic containers.

Glass containers remain a convenient package material for extemporaneous preparation of ophthalmic solutions. Type 1 glass should be used. The container should be well rinsed with sterile distilled water and may be sterilized by autoclaving. Droppers normally are available presterilized and packaged in a convenient blister pack.

Ophthalmic ointments invariably are packaged in metal tubes with an ophthalmic tip. Such tubes are sterilized conveniently by autoclaving or by ethylene oxide. In rare cases of metal reactivity or incompatibility, tubes lined with epoxy or vinyl plastic may be obtained.

Regardless of the form of packaging, some type of tamper-evident feature must be used for consumer protection. The common tamper-evident feature used on most ophthalmic preparations is the moisture- or heat-sensitive shrink band. The band should be identified in such a way that its disruption or absence constitute a warning that tampering, either accidental or purposeful, has occurred.

The eyecup, an ancillary packaging device, fortunately seems to have gone the way of the community drinking cup. An eyecup should not be used. Its use inevitably will spread or aggravate eye infections. Pharmacists should not fail to discourage such use just as they should take the time to instruct patients in the proper use and care of eye medications. While ophthalmic administration may seem simple enough, it may be a foreign and difficult task for many people. The suggestions and precautions given on page 824 may be useful in instructing patients.

ANTIMICROBIAL PRESERVATIVES

The USP states that ophthalmic solutions may be packaged in multiple-dose containers. Each solution must contain a substance or mixture of substances to prevent the growth of, or to destroy, microorganisms introduced accidentally when the container is opened during use. The preservative is not intended to be used as a means of preparing a sterile solution. Appropriate techniques, discussed elsewhere, are to be employed to prepare a sterile solution.

Preservatives are not to be used in solutions intended for intraocular use because of the risk of irritation. Ophthalmic solutions prepared and packaged for a single application, ie, a unit dose, need not contain a preservative because they are not intended for reuse.

The need for proper control of ophthalmic solutions to prevent serious contamination was recognized in the 1930s. The first preservative recommended for use in ophthalmics was chlorobutanol, as an alternative to daily boiling!

The selection of an ophthalmic preservative can be a rather difficult task, in part because of the relatively small number of suitable candidates. There is, of course, no such thing as an ideal preservative; however, the following criteria may be useful in preservative selection.

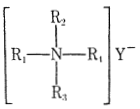
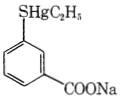
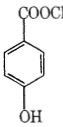
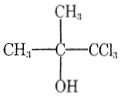
1. The agent should have a broad spectrum and be active against gram-positive and gram-negative organisms as well as fungi. The agent should exert a rapid bactericidal activity, particularly against known virulent organisms such as *P aeruginosa* strains.
2. The agent should be stable over a wide range of conditions including autoclaving temperatures and pH range.
3. Compatibility should be established with other preparation components and with package systems.
4. Lack of toxicity and irritation should be established with a reasonable margin of safety.

Preservative substances must be evaluated as a part of the total ophthalmic preparation in the proposed package. Only in this way can the adequacy of the preservative be established. The USP includes a test for preservative effectiveness; additionally, certain manufacturers have developed a panel of test organisms for further challenge and verification of preservative activity.

In addition to preservative effectiveness as an immediate measure, its adequacy or stability as a function of time also must be ascertained. This often is done by measuring both chemical stability and preservative effectiveness over a given period of time and under varying conditions.

Many of these test procedures are, of course, not completely pertinent to the preparation of an extemporaneous ophthalmic solution. In such a situation the pharmacist must make selections based upon known conditions and

Table 43-1. Ophthalmic Preservatives[12]

TYPE	TYPICAL STRUCTURE	CONCENTRATION RANGE	INCOMPATIBILITIES
Quaternary ammonium compounds		0.004–0.02%, 0.01% most common	Soaps Anionic materials Salicylates Nitrates
Organic mercurials		0.001–0.01%	Certain halides with phenylmercuric acetate
Parahydroxy benzoates		Maximum 0.1%	Adsorption by macromolecules; marginal activity
Chlorobutanol		0.5%	Stability is pH-dependent; activity concentration is near solubility maximum
Aromatic alcohols		0.5–0.9%	Low solubility in water; marginal activity

physical and chemical characteristics. In such circumstances it would be prudent to prepare minimum volumes for short-term patient use.

The choice of preservatives suitable for ophthalmic use is surprisingly narrow. The classes of compounds available for such use are described in Table 43-1.[12] In each case or category there are specific limitations and shortcomings.

QUATERNARY AMMONIUM COMPOUNDS—Benzalkonium chloride is a typical quaternary ammonium compound and is, by far, the most common preservative used in ophthalmic preparations. Over 65% of commercial ophthalmic products are preserved with benzalkonium chloride. Despite this broad use the compound has definite limitations. As a cationic surface-active material of high molecular weight it is not compatible with anionic compounds. It is incompatible with salicylates and nitrates and may be inactivated by high-molecular-weight nonionic compounds. Conversely, benzalkonium chloride has excellent chemical stability and very good antimicrobial characteristics. Given the alternative it would be preferable to modify a formulation to remove the incompatibility, rather than include a compatible but less effective preservative.

The literature on benzalkonium chloride is somewhat mixed; however, this is not unexpected given the wide variation in test methods and, indeed, the chemical variability of benzalkonium chloride itself. The official substance is defined as a mixture of alkyl benzyldimethylammonium chlorides including all or some of the group ranging from n-C_8H_{17} through n-$C_{16}H_{33}$.The n-$C_{12}H_{25}$ homolog content is not less than 40% on an anhydrous basis.

Reviews[13] of benzalkonium chloride indicate that it is well suited for use as an ophthalmic preservative. Certain early negative reports have been shown to be quite erroneous; in some cases adverse tissue reactions were attributed to benzalkonium chloride when, in fact, a totally different compound was used as the test material. Although benzalkonium chloride is by far the most common quaternary preservative, others occasionally referred to include benzethonium chloride and cetyl pyridinium chloride. All are official compounds. More recently, quaternary ammonium compounds have been attached to soluble, reasonably high molecular weight polymers. These agents possess good antimicrobial effectiveness with fewer compatibility problems than the official quaternary

ORGANIC MERCURIALS—It generally is stated that phenylmercuric nitrate or phenylmercuric acetate, in 0.002% concentration, should be used instead of benzalkonium chloride as a preservative for salicylates and nitrates and in solutions of salts of physostigmine and epinephrine that contain 0.1% sodium sulfite. The usual range of concentrations employed is 0.002 to 0.004%. Phenylmercuric borate sometimes is used in place of the nitrate or acetate.

Phenylmercuric nitrate has the advantage over some other organic mercurials of not being precipitated at a slightly acid pH. As with other mercurials, it is slow in its bactericidal action, and it also produces sensitization reactions. Phenylmercuric ion is incompatible with halides, as it forms precipitates.

The effectiveness of phenylmercuric nitrate against *P aeruginosa* is questionable; it has been found that pseudomonads survive after exposure to a concentration of 0.004% for longer than a week.

Development of iatrogenic mercury deposits in the crystalline lens resulting from use of miotic eye drops containing 0.004% phenylmercuric nitrate, 3 times daily, for periods of 3 to 6 years, has been reported. No impairment of vision was found, but the yellowish brown discoloration of the lens capsule is reported to be permanent.

Thimerosal (*Merthiolate,* Lilly) is an organomercurial with bacteriostatic and antifungal activity and is used as an antimicrobial preservative in concentrations of 0.005 to 0.02%. Its action, as with other mercurials, has been reported to be slow.

PARAHYDROXYBENZOIC ACID ESTERS—Mixtures of methylparaben and propylparaben sometimes are used as ophthalmic antimicrobial preservatives; the concentration of methylparaben is in the range of 0.1 to 0.2%, while that of propylparaben approaches its solubility in water (~0.04%). They are not considered efficient bacteriostatic agents and are slow in their antimicrobial action. Ocular irritation and stinging have been attributed to their use in ophthalmic preparations. In a review of OTC drugs for use in ophthalmology, the FDA expert panel found the parabens unacceptable as ophthalmic solution preservatives.

SUBSTITUTED ALCOHOLS AND PHENOLS—Chlorobutanol is stated to be effective against both gram-positive and gram-negative organisms, including *P aeruginosa* and some fungi. It broadly is compatible with other ingredients and normally is used in a concentration of 0.5%. One of the products of

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