



RESEARCH

Constituents of Ophthalmic Preparations

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Ophthalmic solutions and ointments

Eyedrops are sterile aqueous liquids, usually solutions or suspensions of electrolytes and polymers with additional ingredients. The ophthalmic preparations discussed here are designed for instillation into the conjunctival cul-de-sac and must be initially sterile. Preparations used to clean or disinfect contact lenses are not intended for direct application to the eye. Ophthalmic preparations usually contain pharmaceutical adjuvants such as antioxidants, buffers, complexing agents, excipients, preservatives, stabilizing agents, suspending agents, tonicity agents and viscosity enhancers that are designed to assist in the formulation or stability of the product rather than for their therapeutic effect. The properties of some adjuvants enable them to perform several functions even though the specific substance is incorporated mainly for one of its roles.

The following types of ingredients may be included in ophthalmic preparations or in products designed for use with contact lenses:

- (1) Adjuvants enhance the action or help delay the deterioration of the principal ingredients and include agents such as polyethylene glycol and povidone (polyvinyl pyrrolidone).
- (2) Chelating, complexing or sequestering agents such as disodium edetate help to remove divalent metal ions and aid the action of preservatives and antibacterials.
- (3) Suspending agents¹ include: aluminum monostearate, aluminum tristearate, carboxymethylcellulose, gelatin, glyceryl monostearate, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, liquid petro-

tum, methylcellulose, polyvinyl alcohol, povidone, polyoxyl-40 stearate and propylene glycol. (See also drug vehicles).

- (4) Antioxidants and stabilizers may be thought of as preservatives because they help to keep the preparations in its preferred state. The antioxidants inhibit the interaction between oxygen and the active ingredient.¹ Antioxidants include: ascorbic acid, isoascorbic acid (erythorbic acid), N-acetyl cysteine, sodium bisulfite, sodium metabisulfite, sodium thiosulfate and thiourea. Epinephrine, phenylephrine, ephedrine and physostigmine require the presence of antioxidants. Disodium edetate is a chelating agent which stabilizes the activity of antioxidants.²
- (5) The purpose of a vehicle is to carry the drug. To do so effectively in ophthalmic preparations, the vehicle should be: non-toxic, compatible with the active ingredients, optically transparent and have a suitable refractive index, pH, tonicity, viscosity, wetting ability and emolliency. The solvent vehicle for ophthalmic solutions is usually aqueous or saline in nature but often contains some polyethylene glycol, cellulose derivatives, ethyl alcohol, glycerol, isopropyl alcohol, polyvinyl alcohol, and mixtures of these and other substances. (See also suspending agents).
- (6) Excipients are inert substances which are added to modify the form or consistency of the preparation and to provide bulk. E.g. carboxymethylcellulose, hydroxypropyl methylcellulose, mannitol.
- (7) Buffering agents stabilize solutions against pH changes which would otherwise be produced by the addition of acids or bases either from other drugs or from body secretions. Buffers by donating or accepting hydrogen ions enable a solution to resist change in pH when small quantities of acids or alkalis are added. As salts the alkaloids and other organic electrolytes have improved stability, better solubility and cause less irritation when in a slightly acid

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solution.³ Most alkaloid drugs (as the salt) are 100 times more stable at pH5 than at pH7. Making a solution more alkaline increases the amount of lipid-soluble, undissociated, alkaloidal free base. The more alkaline a drug is the less stable it is but the better it penetrates the cornea.⁴ To adjust the pH of a solution, hydrochloric acid or sodium hydroxide may be added. The pK indicates the ionization constant of an acid. A buffer system has its greatest buffering power when its pK equals the pH.

$$\text{pH} = \text{pK} + \log \frac{\text{concentration of salt}}{\text{concentration of acid}}$$

Buffers decrease pain, promote drug stability and preserve the therapeutic action of the drug⁵ but for ophthalmic solutions only low buffering capacity should be sought.³ This allows the tears to make small adjustments in pH as required.⁶ Tears are good buffers because they contain about 1% protein. Table 1 shows buffer pairs^{1,7,8} which may be employed in the make-up of a buffering agent:

Table 1
Buffers

Acid or Base	Salt	Remarks
acetic acid CH_3COOH	sodium acetate $\text{CH}_3\text{COONa} \cdot 3\text{H}_2\text{O}$	Acetate buffers are most effective at a pH of 4 or 5. The pK of acetic acid is 4.8. The concentration of acetic acid used in buffers ranges from 0.2% to 1%. Acetate buffers are incompatible with some other components.
barbital $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_3$	barbital sodium $\text{NaC}_8\text{H}_{11}\text{N}_2\text{O}_3$	Barbiturate buffers are used in a few ophthalmic products.
boric acid H_3BO_3	sodium borate $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O} = \text{borax}$	The concentration of boric acid ranges from 0.5% to 2.62% and that of borax from 0.05% to 0.41% The pH ranges from 7.4 to 9.0.
boric acid H_3BO_3	potassium tetraborate $\text{K}_2\text{B}_4\text{O}_7 \cdot 4\text{HO}$	Borate buffers are used for solutions of alkaloidal salts and may be used for salts of benoxinate, cocaine, phenylephrine, proparacaine, tetracaine and zinc. ⁹ Borate buffers are not advised for use with pilocarpine intended for home application ⁴ ; use instead a phosphate buffer with a pH of 6.8.
sodium hydroxide NaOH	borax $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$	This combination gives a buffer with a pH range from 9.3 to 10.1. Borate buffers should not be used for sodium fluorescein, sulfonamides, ⁹ or other alkaline drugs; use distilled water instead. Borate buffers are incompatible with benzalkonium chloride and should not be used with alkaline products containing polyvinyl alcohol as gummy deposits will form on hard contact lenses. Borate buffers are preferred for the solutions used with soft contact lenses. ⁸

citric acid $C_6H_8O_7$	sodium citrate $Na_3O_6H_5O_7 \cdot 2H_2O$
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citric acid $C_6H_8O_7$	potassium citrate $K_3O_6H_5O_7 \cdot H_2O$
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monobasic potassium phosphate KH_2PO_4	dibasic potassium phosphate K_2HPO_4
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sodium phosphate NaH_2PO_4	dibasic sodium phosphate $Na_2HPO_4 \cdot 12H_2O$ (or anhydrous)
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The citric acid concentration may range from 1% to 2% and the sodium citrate from 0.17% to 0.3%. Citrate buffers are volatile and can be incompatible with other components. The pH range is 3.0 to 6.6. Citrate buffers are incompatible with divalent cations.

Phosphate buffers (pH range 5.8 to 8.0) are suitable for use with most alkaline ophthalmic drugs e.g. pilocarpine solutions.^{5,9}

Phosphate buffers decrease the immediate pain response to pilocarpine.⁴ Solutions of pilocarpine hydrochloride or epinephrine bitartrate at a pH of about 6.8 should be buffered to improve comfort.⁹ Phosphate buffers have also been advised for use with atropine, ephedrine, homatropine and scopolamine.

Buffers may also be made up with dextrose (glucose) or disodium edetate.

- (8) Demulcents and viscosity enhancing agents serve several purposes.¹ Demulcents are hydrophilic colloids, they act as "substitutes" for mucin, they protect and lubricate the ocular surface which has a mucin layer and they help to alleviate dryness and irritation.¹⁰ Because their molecules assume a particular orientation and attract water to a surface demulcents cause surfaces to become more hydrophilic. Viscosity enhancers help to put and to keep a coating on the surface of hydrophobic lenses. Demulcents, being water soluble polymers, also act as cushioning agents for contact lens wear and facilitate handling of contact lenses. Demulcents increase viscosity and are commonly present in preparations described as comfort, lubricating or rewetting solutions for use with contact lenses. Although viscosity enhancers are water soluble they decrease the fluidity of the tear film and can lengthen the contact time of a drug on the eye. However, the retention time of drugs on the eye is mostly determined by the rate of tear production. The viscosity enhancers include several cellulose derivatives, dextran 70, gelatin and the liquid polyols including: glycerol, polyethylene glycol 300 or 400, polysorbate 80 (= Tween 80), polyoxyl-40 stearate, propylene glycol, polyvinyl alcohol, polyvinyl glycol and povidone.¹⁰
- (9) Wetting agents, like the demulcents, have some ability to change a hydrophobic surface (e.g., a contact lens or the cornea) into a hydrophilic one. A deficiency of either the aqueous

or mucin layer of the tear film causes a dry eye. Wetting agents mimic the action of mucin, they interact with the surface, they orient their lipophilic end toward the corneal surface or toward a rigid contact lens and direct their hydrophilic end toward the aqueous portion of the tear film. Wetting solutions may be used with or without viscosity enhancers. A viscosity enhancer increases the thickness of the tear film and acting as a demulcent, helps to make a hydrophobic lens more tolerable on the eye. Hard lenses require a wetting agent when first placed on the eye each day. Tears contain sialomucin which functions as a natural wetting agent. Common wetting agents are: polyvinyl alcohol, povidone, polyethylene glycols, and polysorbate 80.

- (10) Surface-active agents concentrate at surfaces, these surfactants lower interfacial tension, have a detergent-type cleaning action and facilitate corneal wetting but their effect is short lived (minutes). Surfactants lower the surface tension of a solution and some improve the comfort of ophthalmic solutions, they include:
 - (a) Anionic agents, e.g., soaps, are effective cleaners of hard and soft lenses and have some antibacterial action against gram-positive and acid-fast bacteria but little against gram-negative bacteria. The anionic agents are incompatible with many ingredients, e.g., benzalkonium chloride and they irritate the eyes,⁹ but have been used with hard lenses because of the belief that particles attached to the lens surface are positively charged so a negatively charged

cleaner should be effective. The skin cleanser pHisoHex contains sodium octylphenoxyethoxyethyl ether sulfonate plus hexachlorophene. It must not contact the eye.

- (b) Cationic surfactants e.g. benzalkonium chloride have their hydrophobic moiety in the cation. They can be effective antibacterials, but they do not inhibit viruses. Generally they should not be used with soft lenses.
- (c) Nonionic surfactants are not incorporated for their antibacterial ability but are useful as cleaners. They facilitate the cleaning of contact lenses and do not interact with the lens material but some have an adverse effect on the antibacterial activity of preservatives. The poloxamers are nonionic surfactants.
- (d) Amphoteric or ampholytic surfactants may be useful but their activity depends on the pH which can shift them toward becoming anionic or cationic.

Surfactants reduce the size of the drops which are produced when one squeezes a drop bottle.⁹ Small drops of medication are more effective than large drops. Surfactants by lowering surface tension increase the penetration of drugs into the eye¹¹ and help to solubilize (in micelles) ingredients of poor water solubility.¹² They are useful because of their antibacterial activity and their detergent action. They include: alkyltriethanolammonium chloride, benzalkonium chloride, benzethonium chloride, chlorhexidine, myristyl-gamma-picolinium chloride,¹ oxyethylene octyphenol, oxyphenol, propanediol, poloxamer 188, poloxamer 407, polysorbate 80, polyoxyl-40 stearate and polyethylene glycols.

- (11) Components whose purpose is to raise the osmotic pressure of lacrimal fluids need to be used at a fairly high concentration if they are to function as ocular hypertonicity agents.¹ By increasing the movement of water out of the cornea they decrease corneal edema.¹⁰ For ophthalmic solutions the eye can tolerate a tonicity equivalent to that of sodium chloride solutions ranging from 0.5% to 1.5%. Suitable tonicity agents are: calcium chloride, dextrose, glycerol, mannitol, magnesium chloride, potassium chloride and sodium chloride.
- (12) Astringents act locally to precipitate protein and thus help to clear mucus from the eye. Zinc sulfate and antipyrine are employed. Some preparations contain an infusion of rose petals but the usefulness of this infusion is questionable.
- (13) Vasoconstrictors produce transient constriction of the conjunctival blood vessels. The commonly used vasoconstrictors are: ephedrine, epinephrine, hydrastine, naphazoline,

oxymetazoline, phenylephrine, tetrahydrozoline, xylometazoline and possibly zinc sulfate. More than 350,000 liters of ophthalmic vasoconstrictors are dispensed each year in U.S.A.¹³ Rebound hyperemia follows one to four hours after the application of a vasoconstrictor.

- (14) Antihistamines are relatively ineffective histamine antagonists when applied topically. Most have a little local anesthetic activity. The following antihistamines are present in some ophthalmic preparations: antazoline hydrochloride (or the sulfate or the phosphate), chlorpheniramine maleate, pheniramine maleate and pyrilamine maleate.
- (15) Ocular anesthetics are rarely present in over-the-counter preparations but are routinely applied by eyecare practitioners. Examples are: amyllocaine, antipyrine, benoxinate, cocaine (rarely), menthol, phenacaine, piperocaine, proparacaine and tetracaine. Benzyl alcohol and chlorobutanol are principally used as preservatives but have some local anesthetic action and so do some beta blockers and some antihistamines, e.g., pyrilamine.
- (16) Antimicrobial agents inhibit the multiplication of microorganisms. Whether an antibacterial agent is bactericidal or bacteriostatic depends not only on the local concentration of the agent but on the strain of bacteria, the temperature, and the presence of other materials as well as other less important factors. Some antibacterials are only questionably effective for example: boric acid, methylene blue, mild silver protein, sorbic acid, yellow mercuric oxide and zinc sulfate. Modern topical anti-infectives (mostly antibiotics) are more potent and these include bacitracin, chloramphenicol, erythromycin, gentamycin, neomycin and polymyxin B as well as sulfacetamide and vidarabine.
- (17) Another role for antibacterial agents in these ophthalmic preparations is the preservation of solutions.¹⁴ Here the concept of a preservative is understood to mean performing an antibacterial role. The purpose of the antibacterial agent in these ophthalmic preparations is to inhibit the multiplication of any microorganisms that gain entry into the opened container. F.D.A. guidelines in U.S.A. require that the antimicrobial preservative be capable of reducing an inoculum of 10^5 to 10^6 organisms/ml (*S.aureus*, *P. aeruginosa*, *A. niger*, *E. coli* and *Candida albicans*) to no more than 0.1% of the initial concentration of viable bacteria by the 14th day. The concentration of viable yeasts and molds must remain at or below the initial concentration during the first 14 days. The concentration of each test organism must remain at or below these levels during the

remainder of the 28 day test period.¹⁵ Ophthalmic solutions must be sterile when packaged but become contaminated (2.5% to 44%) when the bottle is opened.¹⁵ Antimicrobial preservatives in the preparation are responsible for restoring the sterility of the solution in spite of the entry of a small number of microorganisms. The viruses, spores and most of the fungi are not inhibited by these preservatives at the usual concentration. To sterilize ophthalmic solutions autoclaving is effective against all these organisms but some solutions cannot be autoclaved. In many cases the effectiveness of the antibacterial is enhanced by the addition of disodium edetate. Most single preservatives are slow acting and many have a narrow spectrum. The presence of a preservative in no way diminishes the need for correct technique to avoid contaminating ophthalmic solutions. Preservatives should have little tendency to induce sensitization, be compatible with the other components and be chemically stable.³ Although increasing the preservative concentration in an ophthalmic solution increases its ability to inhibit microorganisms the concentration can not be increased to the point where the preservative harms the eye. Preservatives which bind to contact lenses may concentrate there and then be released on the eye and be harmful. Some preservatives can interact with plastic containers and with plastic lenses. Preservatives used to maintain sterility of ophthalmic solutions include: ^{1, 16-20}

- (a) Quaternary ammonium compounds (present in about 40%) include: alkyltriethanol ammonium chloride, benzalkonium chloride, benzethonium chloride, cetrimide and cetylpyridinium chloride.
- (b) Mercurials^{19, 21, 22} (present in about 20%): nitromersol, phenylmercuric acetate, phenylmercuric nitrate and thimerosal.
- (c) Alcohols¹⁹ (present in about 25%): benzyl alcohol, chlorobutanol, isopropyl alcohol, phenoxyethanol and phenylethyl alcohol.
- (d) Esters of parahydroxybenzoic acid¹⁹. These parabens include methyl, ethyl, propyl and butyl derivatives. They are rarely used alone and are not very effective against bacteria but better against fungi.
- (e) Other antibacterial preservatives are: boric acid, camphor, chlorhexidine, chlorocresol, disodium edetate, methylene blue, parachlorometaxyleneol, picolinium chloride, polymyxin B sulfate, salicylic acid, silver protein, sodium benzoate, sodium borate, sodium perborate, sorbic acid and zinc sulfanilate.

Some ophthalmic products are packaged in unit-dosage format. They are sterilized in the container

and contain no preservatives. The absence of preservatives is an advantage if the patient is known (or thought to be) hypersensitive to preservatives. Of course such preparations must be used once only and on only one patient. Barkman et al. recommend not using preservatives and discarding opened bottles after two weeks.¹⁴

- (18) Claims have been made that some agents promote wound healing. Examples are: allantoin, cod liver oil, eucalyptus oil and Vitamins A, C, D, and E.
- (19) A few ophthalmic preparations include ingredients intended to enhance the appearance or odor of the product but these agents may have adverse effects on the eye and are very seldom appropriate for use on the eye.
- (20) A collyrium is an eyewash, a sterile aqueous solution used to irrigate, flush or bathe the eye. Normally it contains no active ingredients but it can be effective for removing foreign material from the surface of the eye.¹⁰ Collyria generally contain water, sodium chloride and/or other tonicity agents, buffers and an antibacterial preservative.
- (21) Tear replacements, sometimes called artificial tears, are designed to provide relief of dry eye symptoms. They may also be employed to lubricate an artificial eye. Tear replacements supplement the available tears or substitute for insufficient tears or improve the quality of the tear fluid. Mucomimetic agents should be more helpful in a mucous-deficient eye and water retaining substances (cellulose derivatives) in aqueous deficiencies. Duration of action of commercial tear substitutes is from 45 to 90 minutes. Several commercial products are marketed, most contain sodium chloride, demulcents, emollients, cellulose derivatives, polyvinyl alcohol, povidone and other polymers.
- (22) Some drugs are said to help increase tear production: riboflavin and thiamine and all those compounds²³ which aid the synthesis of prostaglandin E₁ namely, ascorbic acid, gamma linolenic acid, niacin, oil of the evening primrose, pyridoxine and zinc.
- (23) Some drugs help to retain tears on the eye:
 - (a) Cellulose derivatives (carboxymethyl, hydroxyethyl, hydroxymethyl, hydroxypropyl, hydroxypropylmethyl and methyl derivatives).
 - (b) dextran
 - (c) glycerol, glyceryl monostearate
 - (d) polyvinyl alcohol
- (24) Suspensions by definition consist of solid undissolved microparticles in a liquid or in a semi-solid such as an ointment. They have the advantage of prolonged action and the disadvantage of irritation produced by the

larger particles.⁹ Particles should be less than 10 µm in size to minimize irritation. Suspensions in liquids must be shaken before use.

- (25) Cleaning solutions for hard and soft contact lenses.²⁴ All solutions to which contact lenses are exposed have some ability to alter lens parameters such as thickness, curvature, wettability, power and diameter. Cleaners tend to be more effective in alkaline solutions and in hypertonic solutions. Cleaning solutions should not be viscous. Cleaners are likely to cause discomfort if they contact the eye directly. Cleaning agents may contain any of the following:

- (a) Surfactant molecules have a polar hydrophilic end which is attracted to hydrophilic material and a nonpolar, lipophilic portion which becomes attached to lipid material. Surfactants clean soft lenses more easily in a hypertonic solution. (See earlier section on surface active agents). Daily cleaners usually contain surfactants.
- (b) Enzymatic cleaners (periodic cleaners) will remove protein and lipid deposits which surfactants will not and include:
 - pancreatic enzymes —
 - protein specific enzymes — papain. (See also lactose)
 - lipid specific enzymes — lipases. Lipids may also be removed by isopropyl alcohol. Residues of enzymatic cleaners have caused sensitivity reactions when allowed to contact the eye.
- (c) Oxidizing agents are usually effective cleaners and disinfectants for hydrogel lenses but can damage some contact lenses and will irritate the eye if allowed to contact it. The available types are:
 - peroxides — hydrogen peroxide or sodium peroxide
 - peroxy salts — sodium perborate
 - chlorine releasing — sodium hypochlorite
- (d) Chelating agents help to remove ionic materials.

- (26) Soaking and storage solutions. These solutions keep the lens in a hydrated state thereby allowing the lens to retain its specified curvature and thickness and they prevent tear film contents from drying on the lens surfaces. Storage solutions must contain an appropriate antibacterial agent or agents. Soaking solutions are used with hydrogel lenses and with hard lenses.

- (27) Rinsing solutions are always used with hydrogel lenses. Some advise using a fresh application of the same solution that was used for soaking the lenses but others recommend use of a solution with less preservative,

otherwise too much preservative may be transferred to the eye.

- (28) Ophthalmic ointments are sterile preparations in a semi-solid dosage form. The ointment serves as a vehicle, lubricant and cushioning agent in which active medicinal substances may be suspended. The non-polar components of ointments facilitate the adsorption of the ointment to the cornea. Ointments are likely to contain complexing agents which aid in product formulation. Typical ointment adjuncts are lanolin and the polyethylene glycols. Lanolin absorbs water and thus helps to retain water-soluble drugs in the ointment. The ointment bases consist mostly of white petrolatum (about 60%) and mineral oil (about 40%) and these act as lubricants and emollients. Emollients in ointments soften tissues and protect them by preventing drying and cracking. They either supply moisture to a tissue or act as a moisture barrier to inhibit evaporation. The emollients consist of fats, waxes or oils and include: oleaginous preparations, beeswax, oils, white ointment, white soft paraffin (i.e. bleached petrolatum), petrolatum, white wax and lanolin. Ointments blur vision transiently when applied to the eye. Contrary to earlier reports ophthalmic ointments in small doses do not inhibit corneal healing,²⁵ although they do reduce tear break-up time (BUT).²⁶ Ointments increase ocular contact time due to their viscous nature.²⁷⁻²⁹ Ointments typically remain on the eye at least 3 times as long as saline solutions. One way to avoid some problems is to use aqueous solutions for daytime application and an ointment for nighttime application.

In the United States, the Food and Drug Administration (FDA) has compiled a list of hundreds of Inactive Ingredients for Approved Prescription Drug Products.³⁰ The length of this list emphasizes that it may not always be the "active" ingredient in a preparation that is responsible for an unwanted reaction.

Acknowledgement

This study was supported by a grant from the Canadian Optometric Education Trust Fund.

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