Remington: The Science and Practice of Pharmacy

Volume II

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19TH
EDITION

Remington: Practice of

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The Science and Pharmacy

1995

MACK PUBLISHING COMPANY
Easton, Pennsylvania 18042

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Library of Congress Catalog Card No. 60-53334

ISBN 0-912734-04-3

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Printed in the United States of America by the Mack Printing Company, Easton, Pennsylvania

CHAPTER 89

Ophthalmic Preparations

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Ophthalmic preparations are sterile products essentially free from foreign particles, suitably compounded and packaged for instillation into the eye. Ophthalmic preparations include solutions, suspensions, ointments and solid dosage forms. The solutions and suspensions are, for the most part, aqueous. Ophthalmic ointments usually contain a white petrolatum-mineral oil base.

Ophthalmic preparations can be grouped broadly into two divisions of major significance to the pharmacist. These include single or multidose prescription products and the category described as OTC or over-the-counter ophthalmic products. The latter group has been subjected to a searching review and analysis by a body of experts as a part of the FDA's OTC Drug Review process.

The single dominant factor characteristic of all ophthalmic products is the specification of sterility. Any product intended for use in the eye regardless of form, substance or intent must be sterile. This requirement increases the similarity between ophthalmic and parenteral products, however the physiology of the human eye in many respects imposes more rigid formulation requirements. This will be considered in the following discussion.

Preparations intended for the treatment of eye disorders can be traced to antiquity. Egyptian papyri writings describe eye medications. The Greeks and Romans expanded such uses and gave us the term *collyria*. Collyria refer collectively to materials which were dissolved in water, milk or egg white for use as eyedrops. In the Middle Ages collyria included mydriatic substances to dilate the pupils of milady's eyes for cosmetic purposes, thus the term belladonna or "beautiful lady."

From the time of belladonna collyria, ophthalmic technology progressed at a pharmaceutical snail's pace well into modern times. It was not until after the second World War that the concept of sterility became mandatory for ophthalmic solutions. Prior to World War II and continuing into the 1940s very few ophthalmic preparations were available commercially or were described officially. The USP XIV, official in 1950, included only three ophthalmic preparations and all three were ointments.

Preparations to be used in the eye, either solutions or ointments, invariably were compounded in the community or hospital pharmacy and were intended for immediate (prescription) use. Such preparation and prompt use is reflected in the pharmaceutical literature of the times. The stability of ophthalmic preparations is discussed in terms of days or a few months.

One of the most important attributes of ophthalmic products is the requirement of sterility. Even that, however, is a surprisingly recent event. The USP XV in 1955 was the first official compendium to include a sterility requirement for ophthalmic solutions. The FDA in 1953 adopted the position that a nonsterile ophthalmic solution was adulterated. Sterile ophthalmic products were, of course, available prior to the mid 1950s, however the legal requirement of sterility dates only from 1955.

The sterility requirements for ophthalmic ointments appeared first in the USP XVIII, *Third Supplement* (1972). Prior to that date there was no legal requirement for a sterile ophthalmic ointment. This probably was due to the difficulty (at that time) of testing for sterility in such nonaqueous systems and also for the anticipated difficulties in sterilizing and maintaining sterile conditions during the manufacture and filling of ointments on a large scale.

Anatomy and Physiology of the Eye

The human eye is a challenging subject for topical administration of drugs. The basis of this can be found in the anatomical arrangement of the surface tissues and in the permeability of the cornea. The protective operation of the eyelids and lacrimal system is such that there is rapid removal of material instilled into the eye, unless the material is suitably small in volume and chemically and physiologically compatible with surface tissues. Figures 1[1] and 2[1] include pertinent anatomy of the human eye.

Eyelids—The eyelids serve two purposes: mechanical protection of the globe and creation of an optimum milieu for the cornea. The eyelids are lubricated and kept fluid-filled by secretions of the lacrimal glands and specialized cells residing in the bulbar conjunctiva. The antechamber has the shape of a narrow cleft directly over the front of the eyeball, with pocket-like extensions upward and downward. The pockets are called the superior and inferior fornices (vaults), and the entire space, the cul-de-sac. The elliptical opening between the eyelids is called the palpebral fissure.

Eyeball—The wall of the human eyeball (bulbus, globe) is composed of three concentric layers.

1. The outer fibrous layer.
2. A middle vascular layer—the uvea or uveal tract, consisting of the choroid, the ciliary body and the iris.
3. A nervous layer—the retina.

The outer layer is tough, pliable but only slightly stretchable. In its front portion—the portion facing the outside world—the fine structure of the outer layer is so regular and the water content so carefully adjusted that it acts as a clear transparent window (the cornea). It is devoid of blood vessels. Over the remaining two-thirds the fibrous coat is opaque (the "white" of the eye) and is called the sclera. It contains the microcirculation which nourishes the tissues of this anterior segment and is usually white except when irritated and vessel dilatation occurs.

The eyeball houses an optical apparatus that causes inverted reduced images of the outside world to form on the retina, which is a thin translucent membrane. The optical apparatus consists, in sequence, of the precorneal film, the cornea, the aqueous humor, the pupil, the crystalline lens, the vitreous humor and the retina. The aqueous and vitreous humors are layers of clear fluid or gel-like material interposed between the solid structures. The pupil, a round centric hole in a contractile membranous partition (called the iris), acts as the variable aperture of the system. The crystalline lens is a refractive element with variable power controlled and supported by a muscle incorporated in the ciliary body. The choroid is the metabolic support for the retina.

The optical function of the eye calls for stability of its dimensions, which is provided partly by the fibrous outer coat;

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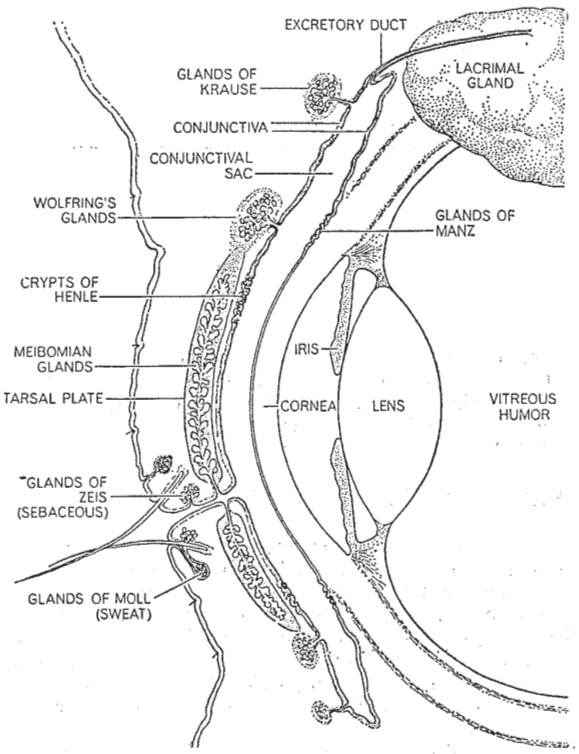

Fig 1. The eye: vertical section.[1]

more effective as a stabilizing factor is the intraocular pressure, which is in excess of the pressure prevailing in the surrounding tissues. This intraocular pressure is the result of a steady production of specific fluid, the aqueous humor, which originates from the ciliary processes and leaves the eye by an intricate system of outflow channels. The resistance

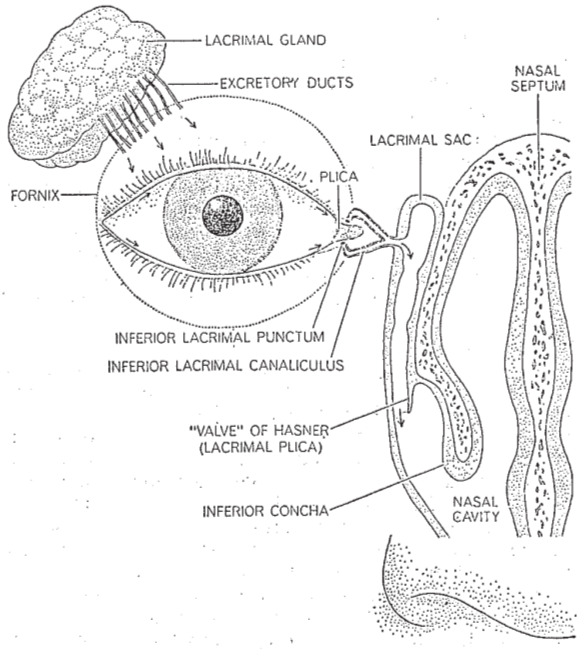

Fig 2. Nasolacrimal duct.[1]

encountered during this passage and the rate of aqueous production are the principal factors determining the level of the intraocular pressure. In addition to this hydromechanical function, the aqueous humor acts as a carrier of nutrients, substrates and metabolites for the avascular tissues of the eye.

The bones of the skull join to form an approximately pyramid-shaped housing for the eyeball, called the orbit.

Conjunctiva—The conjunctival membrane covers the outer surface of the white portion of the eye and the inner aspect of the eyelids. In most places it is attached loosely and thereby permits free movement of the eyeball. This makes possible subconjunctival injections. Except for the cornea the conjunctiva is the most exposed portion of the eye.

Lacrimal System—The conjunctival and corneal surfaces are covered and lubricated by a film of fluid secreted by the conjunctival and lacrimal glands. The secretion of the lacrimal gland, the tears, is delivered through a number of fine ducts into the conjunctival fornix. The secretion is a clear, watery fluid containing numerous salts, glucose, other organic compounds, approximately 0.7% protein and the enzyme, lysozyme. Small accessory lacrimal glands are situated in the conjunctival fornices. Their secretion suffices for lubrication and cleansing under ordinary conditions and for maintaining a thin fluid film covering the cornea and conjunctiva (the precorneal film). The mucin-protein layer of the film is especially important in maintaining the stability of the film. The main lacrimal gland is called into play only on special occasions. The sebaceous glands of the eyelids secrete an oily fluid which helps to prevent overflowing of tears at the lid margin and reduces evaporation from the exposed surfaces of the eye by spreading over the tear film.

Spontaneous blinking replenishes the fluid film by pushing a thin layer of fluid ahead of the lid margins as they come together. The excess fluid is directed into the lacrimal lake—a small triangular area lying in the angle bound by the innermost portions of the lids. The skin of the eyelids is the thinnest in the body and folds easily, thus permitting rapid opening and closing of the palpebral fissures. The movement of the eyelids includes a narrowing of the palpebral fissures in a zipper-like action from the lateral canthus toward the medial canthus (canthi: the corners where the eyelids meet). This aids the transport or movement of fluid toward the lacrimal lake.

Tears are drained from the lacrimal lake by two small tubes—the lacrimal canaliculi—which lead into the upper part of the nasolacrimal duct, the roomy beginning of which is called the lacrimal sac. The drainage of tears into the nose does not depend merely on gravity. Fluid enters and passes along the lacrimal canaliculi by capillary attraction aided by aspiration caused by contraction of muscle embedded in the eyelids. When the lids close, as in blinking, contraction of the muscle causes dilatation of the upper part of the lacrimal sac and compression of its lower portion. Tears are thus aspirated into the sac, and any which have collected in its lower part are forced down the nasolacrimal duct toward its opening into the nose. As the lids open, the muscle relaxes. The upper part of the sac then collapses and forces fluid into the lower part, which at the same time is released from compression. Thus, the act of blinking exerts a suction-force-pump action in removing tears from the lacrimal lake and emptying them into the nasal cavity. Lacrimation is induced reflexly by stimulation of nerve endings of the cornea or conjunctiva. The reflex is abolished by anesthetization of the surface of the eye and by disorders affecting its nerve components.

The normal cul-de-sac usually is free of pathogenic organisms and often found sterile. The sterility may be due partly to the action of lysozyme in the tears, which normally destroys saprophytic organisms but has little action against pathogens. More effective in producing sterility may be the fact that the secretions, which are normally sterile as they leave the glands, constantly wash the bacteria, dust, etc, down in the nose. In certain diseases the lacrimal gland, like other glandular structures in the body, undergoes involution, with the result that

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the lacrimal fluid becomes scanty. Furthermore, changes in the conjunctival glands may lead to alteration in the character of the secretion so that quality as well as quantity of tears may be abnormal. This may lead to symptoms of dryness, burning and general discomfort, and may interfere with visual acuity.

Precorneal Film—The cornea must be wet to be an optically adequate surface; when dry, it loses both its regular gloss and its transparency. The precorneal film, part of the tear fluid, provides this important moist surface. Its character depends on the condition of the corneal epithelium. The film, compatible with both aqueous and lipid ophthalmic preparations, is composed of a thin outer lipid layer, a thicker middle aqueous layer and a thin inner mucoid layer. It is renewed during each blink and when blinking is suppressed, either by drugs or by mechanical means, it dries in patches. It seems to be unaffected by the addition of concentrations of up to 2% sodium chloride to conjunctival fluid. A pH below 4 or above 9 causes derangement of the film. The film affects the movement of contact lenses and forms more easily on glass than on plastic prostheses.

Cornea—The cornea, from 0.5 to 1 mm thick, consists mainly of the following structures (from the front backwards):

1. Corneal epithelium.
2. Substantia propria (stroma).
3. Corneal endothelium.

The cornea is transparent to ordinary diffuse light, largely because of a special laminar arrangement of the cells and fibers and because of the absence of blood vessels. Cloudiness of the cornea may be due to any one of several factors including excess pressure in the eyeball as in glaucoma; scar tissue due to injury, infection or deficiency of oxygen or excess hydration such as may occur during the wearing of improperly fitted contact lenses. A wound of the cornea usually heals as an opaque patch which can be a permanent impairment of vision unless it is located in the periphery of the cornea.

The chief refraction of light for the eye occurs at the outer surface of the cornea where the index of refraction changes from that of air (1.00) to that of precorneal substance (1.38). Any alteration in its shape or transparency interferes with the formation of a clear image; therefore, any pathological process, however slight, may interfere seriously with the resolving power or visual acuity of the eye.

The normal cornea possesses no blood vessels except at the corneoscleral junction. The cornea, therefore, must derive its nutrition by diffusion and must have certain permeability characteristics; it also receives nourishment from the fluid circulating through the chambers of the eye and from the air. The fact that the normal cornea is devoid of blood vessels is an important feature in surgical grafting. The corneal nerves do not supply all forms of sensation to the cornea. Pain and cold are well supplied. The pain fibers have a very low threshold, which makes the cornea one of the most sensitive areas on the surface of the body. It now is agreed generally that the cornea possesses a true sense of touch; nerve endings supplying the sensation of heat are lacking.

The corneal epithelium provides an efficient barrier against bacterial invasion. Unless its continuity has been broken by an abrasion (a traumatic opening or defect in the epithelium) pathogenic bacteria, as a rule, cannot gain a foothold. Trauma, therefore, plays an important part in most of the infectious diseases of the cornea which occur exogenously. Any foreign body that either scratches the cornea or lodges and becomes imbedded in the cornea is of serious moment because of the role it may play in permitting pathogenic bacteria to gain a foothold.

A means of detecting abrasions on the corneal surface is afforded by staining the cornea with sodium fluorescein. If there is an abrasion on the epithelium, the underlying layer stains a brilliant green, so that even pinpoint abrasions show up quite clearly. Abrasion may occur during tonometry, that is, during the measurement of ocular tension (pressure) with a tonometer. Care must be used in applying the device to the cornea to avoid abrasion of the cornea. Corneal abrasions sometimes result from wearing contact lenses. Every corneal abrasion is subject to infection.

Bioavailability

Physical Consideration—Under normal conditions the human tear volume averages about 7 μL.[2] The estimated maximum volume of the cul-de-sac is about 30 μL with drainage capacity far exceeding lacrimation rate. The outflow capacity accommodates the sudden large volume resulting from the instillation of an eyedrop. Most commercial eyedrops range from 50 to 75 μL in volume, however, much in excess of 50 μL probably is unable to enter the cul-de-sac.

Within the rabbit cul-de-sac, the drainage rate has been shown to be proportional to the instilled drop volume. Multiple drops administered at intervals produced higher drug concentrations. Ideally, a high concentration of drug in a minimum drop volume is desirable. Patton[3] has shown that approximately equal tear-film concentrations result from the instillation of 5 μL of 1.61×10^{-2} *M* pilocarpine nitrate or from 25 μL of 1.0×10^{-2} *M* solution. The 5 μL contains only 38% as much pilocarpine, yet its bioavailability is greater due to decreased drainage loss.

There is a practical limit or limits to the concept of minimum dosage volume. There is a difficulty in designing and producing a dropper configuration which will deliver small volumes reproducibly. Also, the patient often cannot detect the administration of such a small volume. This sensation or lack of sensation is particularly apparent at the 5.0–7.5-μL dose-volume range.

The concept of dosage-volume drainage and cul-de-sac capacity directly effects the prescribing and administering of separate ophthalmic preparations. The first drug administered may be diluted significantly by the administration of the second. On this basis combination drug products for use in ophthalmology have considerable merit.

Corneal Absorption——Drugs administered by instillation must penetrate the eye and do so primarily through the cornea. Corneal absorption is much more effective than scleral or conjunctival absorption where removal by blood vessels into the general circulation occurs.

Many ophthalmic drugs are weak bases and are applied to the eye as aqueous solutions of their salts. The free base and the salt will be in an equilibrium which will depend on the pH and on the individual characteristics of the drug molecule. To aid in maintaining storage stability and solubility, the medication may be acidic at the moment of instillation but, usually, the neutralizing action of the lacrimal fluid will convert it rapidly to the physiological pH range (approximately pH 7.4), at which there will be enough free base present to begin penetration of the corneal epithelium. Once inside the epithelium the undissociated free base dissociates immediately to a degree. The dissociated moiety then will tend to penetrate the stroma because it is water-soluble. At the junction of the stroma and endothelium the same process that took place at the outer surface of the epithelium must occur again. Finally, the dissociated drug leaves the endothelium for the aqueous humor. Here it can readily diffuse to the iris and the ciliary body, the site of its pharmacological action.

The cornea can be penetrated by ions to a small, but measurable, degree. Under comparable conditions, the permeabilities are similar for all ions of small molecular weight, which suggests that the passage is through extracellular spaces. The diameter of the largest particles which can pass across the cellular layers seems to be in the range 10–25 Å. An instilled drug is subject to protein binding in the tear fluid and metabolic degradation by enzymes such as lysozyme, in addition to the losses by simple overflow and lacrimal drainage.

Since the cornea is a membrane including both hydrophilic and lipophilic layers, most effective penetration is obtained with drugs having both lipid and hydrophilic properties. Highly water soluble drugs penetrate less readily. As an

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example highly water soluble steroid phosphate esters penetrate the cornea poorly. Better penetration is achieved with the poorly soluble but more lipophilic steroid alcohol; still greater absorption is seen with the steroid acetate form.

In 1976 Lee and Robinson[4] and in 1990, Lee[5] presented a summary of the factors controlling precorneal pilocarpine disposition and pilocarpine bioavailability in the rabbit eye. Combining experimental work and computer simulation the investigators discussed the mechanisms competing with corneal absorption of pilocarpine. Included were solution drainage, drug-induced vasodilation, nonconjunctival loss including uptake by the nictitating membrane, conjunctival absorption, induced lacrimation and normal tear turnover. Subject to experimental conditions the relative effectiveness of the factors involved in precorneal drug removal are drainage ≃ vasodilation > nonconjunctival loss > induced lacrimation ≃ conjunctival absorption > normal tear turnover.

The authors discuss the implications of the mechanisms of precorneal drug loss in the design of ocular drug-delivery systems including the effect of instilled drug volume on aqueous humor concentration and the amount of drug available for systemic absorption. On an absolute basis a smaller volume allows more drug to be absorbed. For a given instilled concentration the opposite is true; however, a smaller volume instilled remains more efficient, ie, the fraction of dose absorbed is greater. Lang[6] discusses the transcorneal route of absorption of a drug into the eye as that route most effective in bringing a given drug to the anterior portion of the eye. This route of absorption is enhanced by the water-lipid gradient found in the cornea. As previously mentioned, the cornea is composed of three general layers: the lipid-rich epithelium, the lipid-poor stroma and the lipid-rich endothelium. Differential studies on the relative lipid contents of these three layers have shown that the corneal epithelium and the corneal endothelium both contain approximately 100 times as much lipid as the corneal stroma. This, coupled with the physiological pH of 7.2 ± 0.2 and its effect on ionizable drug molecules plays the most significant role in corneal penetration.

Ophthalmic ointments generally produce greater bioavailability than the equivalent aqueous solution. Because of the greater contact time drug levels are prolonged and total drug absorption is increased.

Types of Ophthalmic Products

Administration—The instillation of eyedrops remains one of the less precise, yet one of the more accepted means of topical drug delivery. The method of administration is cumbersome at best, particularly for the elderly, patients with poor vision who have difficulty seeing without eyeglasses and patients with other physical handicaps. Perhaps, surprisingly, the majority of patients become quite adept at routine instillation.

The pharmacist should advise each patient to keep the following points in mind to aid in the instillation of eyedrops or ointments:

How to Use Eyedrops

1. Wash hands.
2. With one hand, gently pull lower eyelid down.
3. If dropper is separate, squeeze rubber bulb once while dropper is in bottle to bring liquid into dropper.
4. Holding dropper above eye, drop medicine inside lower lid while looking up; do not touch dropper to eye or fingers.
5. Release lower lid. Try to keep eye open and not blink for at least 30 seconds.
6. If dropper is separate, replace on bottle and tighten cap.

- If dropper is separate, always hold it with tip down.
- Never touch dropper to any surface.
- Never rinse dropper.
- When dropper is at top of bottle, avoid contaminating cap when removed.
- When dropper is a permanent fixture on the bottle, ie, when supplied by a pharmaceutical manufacturer to the pharmacist, the same rules apply to avoid contamination.
- Never use eye drops that have changed color.
- If you have more than one bottle of the same kind of drops, open only one bottle at a time.
- If you are using more than one kind of drop at the same time, wait several minutes before use of other drops.
- It may be helpful in use of the medicine to practice use by positioning yourself in front of a mirror.
- After instillation of drops, do not close eyes tightly and try not to blink more often than usual, as this removes the medicine from the place on the eye where it will be effective.

How to Use Ophthalmic Ointments

1. Wash hands.
2. Remove cap from tube.
3. With one hand, gently pull lower eyelid down.
4. While looking up, squeeze a small amount of ointment (about ¼ to ½ in) inside lower lid. Be careful not to touch tip of tube to eye, eyelid, fingers, etc.
5. Close eye gently and roll eyeball in all directions while eye is closed. Temporary blurring may occur.
6. The closed eyelid may be rubbed very gently by a finger to distribute the drug throughout the fornix.
7. Replace cap on tube.

- Take care to avoid contaminating cap when removed.
- When opening ointment tube for the first time, squeeze out the first ¼" of ointment and discard as it may be too dry.
- Never touch tip of tube to any surface.
- If you have more than one tube of the same ointment, open only one at a time.
- If you are using more than one kind of ointment at the same time, wait about 10 minutes before use of another ointment.
- To improve flow of ointment, hold tube in hand several minutes to warm before use.
- It may be helpful in use of the ointment to practice use by positioning yourself in front of a mirror.

Ophthalmic Solutions—This is by far the most common means of administering a drug to the eye. The USP describes 59 ophthalmic solutions. By definition, all ingredients are completely in solution, uniformity is not a problem and there is little physical interference with vision. The principal disadvantage of solutions is the relatively brief contact time between the medication and absorbing surfaces. Contact time may be increased to some extent by the inclusion of a viscosity increasing agent such as methylcellulose. Inclusions of this sort are permitted by the USP. A viscosity in the range of 15 to 25 cps is considered optimum for drug retention and visual comfort.

Ophthalmic Suspensions—Suspensions are dispersions of finely divided, relatively insoluble drug substances in an aqueous vehicle containing suitable suspending and dispersing agents. There are 29 listed in the USP. The vehicle is, among other things, a saturated solution of the drug substance. Because of a tendency of particles to be retained in the cul-de-sac, the contact time and duration of action of a suspension probably exceeds that of a solution. The drug is absorbed from solution and the solution concentration is replenished from retained particles. Each of these actions is a function of particle size, with solubility rate being favored by smaller size and retention favored by a larger size; thus, optimum activity should result from an optimum particle size.

For aqueous suspensions the parameters of intrinsic solubility and dissolution rate must be considered. The intrinsic solubility determines the amount of drug actually in solution and available for immediate absorption upon instillation of the dose. As the intrinsic solubility of the drug increases, the concentration of the drug in the saturated solution surrounding the suspended drug particle also increases. For this reason, any comparison of different drugs in suspension systems should include their relative intrinsic solubilities. The observed differences in their biological activities may be ascribed wholly or in part to the differences in this physical parameter. As the drug penetrates the cornea and the initial saturated solution becomes depleted, the particles must dissolve to provide a further supply of the drug. The requirement here is that the particles must undergo significant disso-

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lution within the residence time of the dose in the eye if any benefit is to be gained from their presence in the dosing system.

For a drug whose dissolution rate is rapid, the dissolution requirement may present few problems, but for a slowly soluble substance the dissolution rate becomes critical. If the dissolution rate is not sufficiently rapid to supply significant additional dissolved drug, there is the possibility that the slowly soluble substance in suspension provides no more drug to the aqueous humor than does a more dilute suspension or a saturated solution of the substance in a similar vehicle. Obviously, the particle size of the suspended drug affects the surface area available for dissolution. Particle size also plays an important part in the irritation potential of the dosing system. This consideration is important, as irritation produces excessive tearing and rapid drainage of the instilled dose. It has been recommended that particles be less than 10 μm in size to minimize irritation to the eye. It should be kept in mind, however, that in any suspension system the effects of prolonged storage and changes in storage temperature may cause the smallest particles to dissolve and the largest particles to become larger. In summary, aqueous suspensions should, in general, give a more extended effect than aqueous solutions.

The pharmacist should be aware of two potential difficulties inherent in suspension dosage forms. In the first instance dosage uniformity nearly always requires brisk shaking to distribute the suspended drug. Adequate shaking is a function of the suitability of the suspension formulation but also, and most importantly, patient compliance. Studies have demonstrated that a significant number of patients may not shake the container at all, others may contribute a few trivial shakes. The pharmacist should stress the need of vigorous shaking whenever an ophthalmic suspension is dispensed.

A second and infrequent characteristic of suspensions is the phenomenon of polymorphism or the ability of a substance to exist in several different crystalline forms. A change in crystal structure may occur during storage resulting in an increase (or decrease) in crystal size and alteration in the suspension characteristics causing solubility changes reflected in increased or decreased bioavailability.

The pharmacist should be aware of the procedures used by pharmaceutical manufacturers in the preparation of commercial sterile ophthalmic suspensions and ointments, when called upon to compound such preprations extemporaneously.[7]

Ophthalmic Ointments—Despite disadvantages, ophthalmic ointments remain a popular and frequently prescribed dosage form. There are 58 ophthalmic ointments listed in the USP. Dosage variability probably is greater than with solutions (although probably not with suspensions). Ointments will interfere with vision unless use is limited to bedtime instillation.

Ointments do offer the advantage of longer contact time and greater total drug bioavailability, albeit with slower onset and time to peak absorption. The relationship describing the availability of finely divided solids dispersed in an ointment base was given by Higuchi[8] where the amount of solid (drug) released in unit time is a function of concentration, solubility in the ointment base and diffusivity of the drug in the base.

Special precautions must be taken in the preparation of ophthalmic ointments. They are manufactured from sterilized ingredients under rigidly aseptic conditions and meet the requirements of the official sterility tests. Terminal sterilization of the finished ointment in tubes is accomplished occasionally using a validated dose of gamma radiation. If the specific ingredients used in the formulation do not lend themselves to routine sterilization techniques, other ingredients that meet the sterility requirements described under the official sterility tests, along with aseptic manufacture, may be employed. Ophthalmic ointments must contain a suitable substance or mixture of substances to prevent growth of, or to destroy, microorganisms introduced accidentally when the container is opened during use. The antimicrobial agents currently used are chlorobutanol, the parabens or one of the organic mercurials. The medicinal agent is added to the ointment base either as a solution or as a micronized powder. The finished ointment must be free from large particles. Most ophthalmic ointments are prepared with a base of white petrolatum and mineral oil, often with anhydrous lanolin. Some contain a polyethylene-mineral oil gel. Whichever base is selected, it must be nonirritating to the eye, permit diffusion of the drug throughout the secretions bathing the eye and retain the activity of the medicament for a reasonable period of time under proper storage conditions.

It is obligatory that ophthalmic ointments not contain particulate matter that may be harmful to eye tissues. Hence, in preparing such ointments special precautions must be taken to exclude or to minimize contamination with foreign particulate matter, eg, metal particles fragmented from equipment used in preparing ointments and also to reduce the particle size of the active ingredient(s) to impalpability. The official compendium provides tests designed to limit to a level considered to be unobjectionable the number and size of discrete particles that may occur in ophthalmic ointments. In these tests the extruded contents of 10 tubes of ointment, previously melted in flat-bottom Petri dishes and then allowed to solidify, are scanned under a low-power microscope fitted with a micrometer eyepiece for metal particles 50 μm or larger in any dimension. The requirements are met if the total number of metal particles in all 10 tubes does not exceed 50 and if not more than one tube is found to contain eight such particles.

Testing for sterility of products such as ophthalmic ointments has been facilitated greatly by the use of sterile, bacteria-retaining membranes (those having a nominal porosity of 0.45 or 0.22 μm are used commonly). For ointments soluble in isopropyl myristate (the solvent used in the official test for sterility) a sample of the ointment is dissolved in the sterile test solvent. For ointments insoluble in isopropyl myristate the sample is suspended in a suitable aqueous vehicle that may contain a dispersing agent and tested by the conventional *General Procedure* (see the USP for details).

For a long time the technology available for manufacture of ophthalmic ointments was considered inadequate to produce sterile products; indeed, it was believed by some to be impossible to operate a tube-filling machine so as to maintain sterility even in a sterile room. In recent years technological advances have made it possible to manufacture sterile ophthalmic ointment units. Major improvements have been achieved in the area of filtration technology. Membrane filters have improved the reliability of both sterile filtration procedures and sterility-testing methods. Use of laminar flow of HEPA-filtered air in appropriately designed rooms and hoods has been a major factor in the successful aseptic operation of the roller mill and of devices for filling tubes with ointment. While the ideal method of sterilization is one in which the finished ointment is sterilized in its final container, at present it does not appear feasible to do so by any method with the possible exception of the use of ionizing radiation.

As previously noted, the official compendium directs that ophthalmic ointments be prepared from previously sterilized ingredients, under rigidly aseptic conditions. This is the procedure followed in commercial manufacture as well as in extemporaneous preparation of ophthalmic ointments. In extemporaneous compounding the following information may be helpful: petrolatum vehicles and many medicaments may be sterilized by being heated in a hot air oven and utensils required for compounding may be sterilized by autoclaving. A sterile disposable syringe without a needle may be used to transfer the finished ointment, if it is semifluid, to the presterilized ointment tube, or sterile aluminum foil or powder paper may be used for the same purpose. Probability of microbial contamination may be reduced greatly by carrying out selected steps of the procedure in a laminar-flow hood.

Ocular Inserts—The use of solid dosage forms in the eye actually dates from the *lamellae* of the British Pharmacopeia of the 1940s. These drug-impregnated wafers were designed to dissolve on insertion beneath the eyelid. Other

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slowly soluble or erodible matrices were investigated from time to time. Each is characterized by a form of enhanced-pulse drug activity. That is, the bioavailability curve of the drug instilled in aqueous solutions was greatly enhanced both in peak absorption and in duration. Drug side effects were enhanced concomitantly as well.

More recently, ocular inserts have been developed in which the drug is delivered based on diffusional mechanisms. Such a device delivers an ophthalmic drug at a constant known rate, minimizing side effects by avoiding excessive absorption peaks. The delivery of pilocarpine by such a device is a well-known commercial product (*Ocusert*, Alza).

Ocular inserts are plagued with some of the same manipulative disadvantages as conventional eyedrops. The insert must be placed in the eye in a manner similar to the insertion of a contact lens. Additionally, the insert, exhausted of its drug content, must be removed from the eye. Such manipulations can be difficult for the elderly patient. Nonetheless, such therapeutic inserts represent a notable scientific contribution to ophthalmic therapy.

Intraocular Solutions—Ophthalmic solutions intended for intraocular use are relatively recent additions to the armamentarium of the ophthalmologist-surgeon. Surgical procedures such as cataract removal require two types of intraocular solutions. During surgery the operating site is rinsed frequently with an irrigating solution. Late in the surgical procedure the surgeon may choose to constrict the iris by the use of a miotic solution such as carbachol or acetylcholine chloride. Drugs such as the latter usually are used in a unit-dose, minimum-volume form. Irrigating solutions, in contrast, may be used over a period of hours during surgery and are available in volumes ranging from 15 to 500 mL.

The formulation of intraocular ophthalmic products presents requirements that differ depending on the type of product. Medicated solutions such as carbachol or acetylcholine are formulated best in relatively simple isotonic vehicles. Preservatives should not be used and buffers should be avoided if possible. The product pH should be adjusted as close to the physiological range as possible. Needless to say, the product should be sterile and particle-free.

Intraocular irrigating solutions present a considerable formulation challenge distinct from the active ingredient solutions described above. Intraocular irrigating solutions are in contact with the delicate internal structures of the eye throughout the course of various surgeries, ie, for time periods measured in hours. The requirements of tonicity, pH, sterility and clarity are obvious; additionally, however, such irrigating solutions require a balanced ionic structure to prevent or minimize deleterious effects on structures such as the corneal endothelium. Edelhauser[9] has shown that isotonic sodium chloride can be toxic to corneal epithelial, endothial, iris and conjunctival cells. The same cells in contrast are unchanged after exposure to Ringer's Solution containing glutathione, bicarbonate and adenosine.

The question of particulate matter in intraocular irrigating solutions is particularly important. In view of the volumes used for irrigations in the surgically opened eye, any particulates could physically block the trabecular meshwork and canals of Schlemm. The latter are vital in the outflow of aqueous humor and help maintain proper intraocular pressure in the intact eye.

Other Modes of Administration

Packs—These sometimes are used to give prolonged contact of the solution with the eye. A cotton pledget is saturated with an ophthalmic solution and this pledget is inserted into the superior or inferior fornix. Packs may be used to produce maximal mydriasis. In this case the cotton pledgets can be, for example, saturated with phenylephrine solution.

Intracameral Injections—Injections may be made directly into the anterior chamber (eg, acetylcholine chloride, alpha-chymotrypsin, carbamylcholine chloride, certain antibiotics and steroids) or directly into the vitreous chamber (eg, amphotericin B, gentamicin sulfate and certain steroids). Injections are not made into the posterior chamber.

Iontophoresis—This procedure keeps the solution in contact with the cornea by means of an eyecup bearing an electrode. Diffusion of the drug (eg, fluorescein sodium, an antibiotic, etc) is effected by difference of electrical potential.

Subconjunctival Injections—Subconjunctival injections (Fig 3[10]) are used frequently to introduce medications which, if applied topically, either do not penetrate into the anterior segment or penetrate too slowly to attain the concentration required. The drug is injected underneath the conjunctiva and probably passes through the sclera and into the eye by simple diffusion. The most common use of subconjunctival injection is for the administration of antibiotics in infections of the anterior segment of the eye. Subconjunctival injections of mydriatrics and cycloplegics also are used to achieve maximal pupillary dilation or relaxation of the ciliary muscle. If the drug is injected underneath the conjunctiva and the underlying Tenon's capsule in the more posterior portion of the eye, effects on the ciliary body, choroid and retina can be obtained.

Retrobulbar Injections—Drugs administered by retrobulbar injection (Fig 1) may enter the globe in essentially the same manner as the medications given subconjunctivally. The orbit is not well-vascularized and the possibility of significant via-blood stream effects from these injections is very remote. In general, such injections are given for the purpose of getting medications (eg, antibiotics, local anesthetics, enzymes with local anesthetics, steroids, vasodilators, etc) into the posterior segment of the globe and to affect the nerves and other structures in that space.

Preparation

The preparation of ophthalmic solutions, suspensions or ointments by the community pharmacist, or even the hospital pharmacist, is becoming less common. The pharmacist may be called upon to prepare a special concentration, particularly of an antibiotic, in the hospital setting. However, the extemporaneous compounding of ophthalmic prescriptions is becoming rare. In those cases where the pharmacist is called upon to compound an ophthalmic preparation extemporaneously, careful documentation, along with physician consultation, is required. Meticulous attention to detail and the use of a detailed, preapproved preparation plan must be in place prior to compounding.[11] In the view of many, the advantages of commercial preparations such as stability, uniformity and sterility outweigh possible disadvantages such as standardization of dosage. A general discussion concerning the preparation of ophthalmic solutions is found in the USP.

Vehicles—Sterile isotonic solutions, properly preserved, are suitable for preparing ophthalmic solutions (see Chapter 36). In most cases, where the concentration of active ingre-

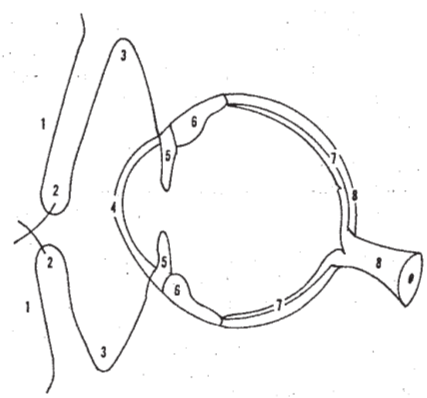

Fig 3. Modes of local therapy in ocular inflammation: *Ointment:* 1–5. *Drops:* 3–5. *Parenteral Injections*— subconjunctival: 4–6; deep subtenons: 6–8; retrobulbar: 8.[10]

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dient is low, ie, less than 2.5 to 3.0%, the drug can be dissolved directly in the isotonic vehicle. The finished solutions will be hypertonic somewhat but well within the comfort tolerance of the eye.

Typical stock solutions are as follows:

Isotonic Sodium Chloride Solution

Sodium Chloride USP	0.9 g
Benzalkonium Chloride	1:10,000
Sterile Distilled Water	qs 100 mL

Boric Acid Solution

Boric Acid USP	1.9 g
Benzalkonium Chloride	1:10,000
Sterile Distilled Water	qs 100 mL

Boric acid solution at pH 5 is an appropriate vehicle for the following:

Cocaine	Tetracaine
Neostigmine	Zinc salts
Phenacaine	Piperocaine
Procaine	

Boric acid solution with an antioxidant is useful for oxygen sensitive drugs such as epinephrine, phenylephrine or physostigmine. The following solutions are suggested. Phenylmercuric nitrate replaces benzalkonium chloride as the preservative in the first solution.

Boric Acid	1.9 g
Sodium Sulfite Anhydrous	0.1 g
Phenylmercuric nitrate	1:50,000
Sterile Purified Water	qs 100 mL
Sodium Acid Phosphate (NaH_2PO_4) anhydrous	0.56 g
Disodium Phosphate (Na_2HPO_4) anhydrous	0.284 g
Sodium Chloride	0.5 g
Disodium Edetate	0.1 g
Benzalkonium Chloride	1:10,000
Sterile Purified Water	qs 100 mL

These vehicles are suitable for salts of

Atropine	Homatropine
Ephedrine	Pilocarpine

Sterilization Procedures—Those procedures suited best for the extemporaneous preparation of ophthalmic solutions are:

1. Solutions in Final Container
   a. Place the filtered solution in containers that have been washed and rinsed with distilled water.
   b. Seal dropper bottles with regular screw caps. The dropper assembly should be stapled into a paper envelope.
   c. Sterilize 20 minutes at 15 psi (121°).
   d. Do not assemble until ready to use.
2. Dropper Bottles
   a. Wash container thoroughly and rinse with distilled water.
   b. Loosen caps and place bottles in autoclave.
   c. Autoclave 15 minutes at 15 psi (121°).
   d. Partially cool autoclave.
   e. Remove bottles from autoclave and secure caps.
   f. Store sterilized bottles in a clean, dustproof cabinet.
3. Glassware and Equipment
   a. Wrap adapters (containing filter), syringes, glassware, spatulas, etc, in autoclave paper and secure with masking tape.
   b. Place articles in autoclave and sterilize in the manner described in Section 2 above.
   c. Store in separate cabinet until ready to use.
4. Microbiological Filtration
   a. All equipment and glassware as well as stock solutions should be sterile. The prescription should be dispensed in a sterile container.
   b. Unwrap sterile syringe and draw prepared solution into syringe.
   c. Unwrap sterile adapter containing bacterial filter and attach to syringe. These are available as single-filtration, presterilized disposable units and should be utilized whenever possible.
   d. Force solution through filter directly into sterile container (dropper or plastic *Drop-Tainer* (Alcon) type).
   e. By employing an automatic filling outfit, more than one container of the same prescription can be prepared.
   f. Cap container immediately.

The procedures outlined above should be carried out in a clean area equipped with ultraviolet lighting and preferably in a laminar-flow hood.

Laminar-Flow Principles—A laminar-flow work area is a particularly convenient means of preparing sterile, particulate-free solutions. Laminar flow is defined as air flow in which the total body of air moves with uniform velocity along parallel lines with a minimum of eddies. Laminar flow minimizes the possibility of airborne microbial contamination by providing air free of viable particles and free of practically all inert particulates. Laminar-flow units are available in a variety of shapes and sizes and in two broad categories, horizontal and vertical laminar flow. It should be noted that laminar flow *per se* is not a guarantee of sterility. Correct procedures and sterile techniques remain necessary. See Chapter 84.

General Considerations

A number of requirements must be considered in the preparation of ophthalmic solutions, suspensions or ointments. These include sterility, clarity, buffer, buffer capacity and pH, tonicity, viscosity, stability, comfort, additives, particle size, packaging and preservatives. Many of these requirements are interrelated and must be considered collectively in the preparation of an ophthalmic product. The buffer system must be considered with tonicity and comfort in mind. Stability can be related to the pH, buffer system and packaging. Sterilization must be considered in terms of stability and packaging.

Ophthalmic solutions are formulated to be sterile, isotonic and buffered for stability and comfort. A viscosity-imparting agent may or may not be present. Solutions must be free from foreign particles. Solution pH must be selected for optimum drug stability. The pH then should be maintained by the inclusion of a buffer system of sufficient capacity to maintain pH throughout the extent of the shelf life of the product.

The proper pH, buffer and buffer capacity often represent a compromise between stability of the drug and comfort in the eye, since optimum patient comfort usually is found at the pH of the tear fluid, or about 7.4, while optimum stability for many drugs is generally lower, perhaps as low as 4.0–5.0. Buffer capacity should be sufficient to maintain pH, but minimized to the point where tear fluid can overcome capacity and readjust to pH to 7.4 immediately after instillation in the eye.

Sterilization represents the major requirement of eye products and the method, or methods, employed depend on the active ingredient and product resistance to heat and to the packaging used. More than one means of sterilization may be used. The sterile solution or suspension usually will contain an antimicrobial preservative to deal with inadvertent contamination during use. The preservative should not be relied upon to produce a sterile product and should not be considered as a substitute for sterile techniques and procedures.

Sterilization

Common methods of sterilization include moist heat under pressure (autoclave), dry heat, filtration, gas sterilization and ionizing radiation.

Dangers of Nonsterile Medications—The possibility of serious ocular infection resulting from the use of contaminated ophthalmic solutions has been documented amply in the literature. Such solutions repeatedly have been the cause of corneal ulcers and loss of eyesight. Contaminated solutions have been found in use in physicians' offices, eye clinics and industrial infirmaries, and dispensed on prescription in community and hospital pharmacies. The microbe most frequently found as a contaminant is the *Staphylococcus* group. *Pseudomonas aeruginosa* is a less frequent contaminant and the solution most often found contaminated is that of sodium fluorescein.

Pseudomonas aeruginosa (*B pyocyaneus; Pseudomonas pyocyanea*; Blue pus bacillus)—This is a very dangerous and

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opportunistic organism that grows well on most culture media and produces both toxins and antibacterial products. The latter tend to kill off other contaminants and allow the *P aeruginosa* to grow in pure culture. This gram-negative bacillus also grows readily in ophthalmic solutions, which may become the source of extremely serious infections of the cornea. It can cause complete loss of sight in 24–48 hours. In concentrations tolerated by tissues of the eye, it seems that all the antimicrobial agents discussed in the following sections may be ineffective against some strains of this organism.

A sterile ophthalmic solution in a multiple-dose container can be contaminated in a number of ways unless precautions are taken. For example, if a dropper bottle is used, the tip of the dropper while out of the bottle can touch the surface of a table or shelf if laid down, or it can touch the eyelid or eyelash of the patient during administration. If the *Drop-Tainer* (Alcon) type of bottle is used, the dropper tip can touch an eyelash, or the cap while removed to permit administration, or its edge may touch a table or finger and that edge can touch the dropper tip as the cap is replaced.

The solution may contain an effective antimicrobial but the next use of the contaminated solution may occur before enough time has elapsed for all of the organisms to be killed, and living organisms can find their way through an abrasion into the corneal stroma. Once in the corneal stroma, any residual traces of antimicrobial agents are neutralized by tissue components and the organisms find an excellent culture medium for rapid growth and dissemination through the cornea and the anterior segment of the eye.

Other Organisms—*Bacillus subtilis* may produce a serious abscess when it infects the vitreous humor. The pathogenic fungus considered of particular importance in eye solutions is *Aspergillus fumigatus*. Other fungi or molds may be harmful by accelerating deterioration of the active drugs.

With regard to viruses, as many as 42 cases of epidemic keratoconjunctivitis were caused by one bottle of virus-contaminated tetracaine solution. Virus contamination is particularly difficult to control because none of the preservatives now available is virucidal. Moreover, viruses are not removable by filtration. However, they are destroyed by autoclaving. The pharmacist and physician have not been made adequately aware of the dangers of transmitting virus infection via contaminated solutions. This is particularly pertinent to the adenoviruses (Types III and VIII) which are now believed to be the causative agents of viral conjunctivitis such as epidemic keratoconjunctivitis.

Methods

Steam under Pressure—Terminal sterilization by autoclaving is an acceptable, effective method of sterilization; however, the solution or suspension components must be sufficiently heat-resistant to survive the procedure. If sterilization is carried out in the final container, the container also must be able to survive the heat and pressure. A recent addition to this technique is the so-called air over steam autoclave. This combination allows pressure adjustments to be made during the autoclave cycle. Pressure manipulations permit the autoclave sterilization of materials which, while heat-resistant, tend to deform (ie, polypropylene containers).

Filtration—The USP states that sterile membrane filtration under aseptic conditions is the preferred method of sterilization. Membrane filtration offers the substantial advantage of room temperature operation with none of the deleterious effects of exposure to heat or sterilizing gas.

Sterilization by filtration does involve the transfer of the finished sterile product into previously sterilized containers using aseptic techniques. The membrane filtration equipment itself usually is sterilized as an assembly by autoclaving.

The application of filtration procedures to the extemporaneous preparation of sterile ophthalmic solutions has been proposed by several workers. Several types of equipment are available for small-scale work, as described in Chapter 37. Particular interest has been shown in the Swinny adapter fitted on a syringe and in the Millipore *Swinnex* disposable filter units. Empty sterile plastic "squeeze" containers and sterile plastic filtration units can be purchased directly from the manufacturers, eg, Wheaton (polyethylene containers) and Millipore (*Swinnex* filter units). They permit extemporaneous preparation of ophthalmic solutions which have a high probability of being sterile if the work is carried out under aseptic conditions. A supplementary device can permit automatic refilling of the syringe. The filter unit must be replaced after use.

Gas—Gas sterilization of heat-sensitive materials may be carried out by exposure to ethylene oxide gas in the presence of moisture. Ethylene oxide gas for sterilization use is available commercially diluted either with carbon dioxide or halogenated hydrocarbons. Ethylene oxide sterilization requires careful consideration of conditions required to effect sterility. Temperature and pressure conditions are quite nominal in contrast to wet or dry heat, however, careful control of exposure time, ethylene oxide concentration and moisture is essential.

Gas sterilization requires the use of specialized but not necessarily elaborate equipment. Gas autoclaves may range from very large walk-in units to small laboratory bench-scale units suitable for small hospitals, laboratories or pharmacies.

In using gas sterilization the possibility of human toxicity must be kept in mind. Care should be taken to restrict exposure to ethylene oxide during the loading, venting and unloading of the sterilizer. Ethylene oxide sterilization produces irritating byproducts which remain as residues in or on the articles sterilized. Residues include ethylene glycol and ethylene chlorohydrin (when in contact with chloride ions) in addition to ethylene oxide itself. To minimize such residues the sterilized articles should be aerated for at least 72 hours, preferably at 40 to 50°.

Ambient aeration time for sterilized polyethylene bottles should be about 48 hours. Ethylene oxide is recommended for the sterilization of solid materials which will not withstand heat sterilization. The FDA has recommended maximum residues in the parts per million range for ethylene oxide, ethylene glycol and ethylene chlorohydrin.

Radiation—Sterilization by exposure to ionizing radiation is an acceptable procedure for components of ophthalmic preparations or indeed for the total product as in certain ophthalmic ointments. Sources of radiation are twofold and include linear electron accelerators and radioisotopes. The linear accelerators produce high-energy electrons with very little penetrating power. Radioisotopes, particularly ^{60}Co, are employed more widely for sterilization. Sterilization by radiation may produce untoward effects such as chemical changes in product components, as well as changes in color or physical characteristics of package components.

Ophthalmic Preparation Characteristics

Clarity—Ophthalmic solutions are by definition free from foreign particles and clarity normally is achieved by filtration. It is, of course, essential that the filtration equipment be clean and well-rinsed so that particulate matter is not contributed to the solution by equipment designed to remove it. Operations performed in clean surroundings, the use of laminar-flow hoods and proper nonshedding garments will contribute collectively to the preparation of brilliantly clear solutions free from foreign particles. In many instances clarity and sterility may be achieved in the same filtration step. It is essential to realize that solution clarity is equally a function of the cleanliness of the intended container and closure. Both container and closure must be thoroughly clean, sterile and nonshedding. That is, the container or closure must not contribute particles to the solution during prolonged contact such as shelf-life storage. This normally is established by thorough stability testing.

Stability—The stability of a drug in solution, ie, an ophthalmic product, depends on the chemical nature of the drug substance, product pH, method of preparation (particularly

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temperature exposure), solution additives and type of packaging. Until two or three decades ago the stability of ophthalmic solutions was an exceedingly short-term concept; generally, it was the time required for a patient to complete the use of 15 or 30 mL of solution. Now, of course, the stability of ophthalmic products is expressed in terms of years. However, 2- to 3-year stability often is achieved only by virtue of compromise.

Drugs such as pilocarpine and physostigmine are both active and comfortable in the eye at a pH of 6.8; however, at this pH chemical stability (or instability) can be measured in days or months. With either drug, a substantial loss in chemical stability will occur in less than 1 year. On the other hand, at pH 5 both drugs are stable for a period of several years.

In addition to optimal pH, if oxygen sensitivity is a factor, adequate stability may require the inclusion of an antioxidant. Plastic packaging, ie, the low-density polyethylene *Drop-Tainer* (Alcon) that represents a patient convenience, may prove detrimental to stability by permitting oxygen permeation resulting in oxidative decomposition of the drug substance.

The attainment of optimum stability most often imposes a series of compromises on the formulator. The optimum pH may be lower than preferable for product comfort, although this effect may be minimized by adjusting pH with a buffer of minimum capacity. Additives such as chelating agents and antioxidants may be required and convenience packaging may diminish shelf life of the product.

It should be stressed that stability refers to total product stability not just the chemical stability of a single product component. That is an oversimplification. A well-planned stability program will consider and evaluate the chemical stability of the active ingredient, chemical stability of the preservative substance, continuing preservative efficacy against selected test organisms and adequacy of the package as a function of time (ie, does the package protect sterility in addition to various physical measures such as pH, clarity, resuspendability of suspensions and the like). One also must support the thesis that the material on test is representative of all lots of a given product.

Buffer and pH—Ideally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4. Practically, this seldom is achieved. The large majority of active ingredients used in ophthalmology are salts of weak bases and are most stable at an acid pH. This generally can be extended to suspensions of insoluble corticosteroids. Such suspensions usually are most stable at an acid pH.

Optimum pH adjustment generally requires a compromise on the part of the formulator. The pH selected should be optimum for stability. The buffer system selected should have a capacity adequate to maintain pH within the stability range for the duration of the product shelf life. Buffer capacity is the key in this situation.

It generally is accepted that a low (acid) pH *per se* necessarily will not cause stinging or discomfort on instillation. If the overall pH of the tears, after instillation, reverts rapidly to pH 7.4, discomfort is minimal. On the other hand, if the buffer capacity is sufficient to resist adjustment by tear fluid and the overall eye pH remains acid for an appreciable period of time, then stinging and discomfort may result. Consequently, buffer capacity should be adequate for stability, but minimized so far as possible, to allow the overall pH of the tear fluid to be disrupted only momentarily.

Tonicity—Tonicity refers to the osmotic pressure exerted by salts in aqueous solution. An ophthalmic solution is isotonic with another solution when the magnitudes of the colligative properties of the solutions are equal. An ophthalmic solution is considered isotonic when its tonicity is equal to that of an 0.9% sodium chloride solution.

The calculation of tonicity at one time was stressed rather heavily. The fledging pharmacist was taught in great detail the requirements of and means of achieving exact tonicity, sometimes to the detriment of other factors such as sterility and stability.

In actuality the eye is much more tolerant of tonicity variations than was at one time suggested. The eye usually can tolerate solutions equivalent to a range of 0.5% to 1.8% sodium chloride. Given a choice, isotonicity always is desirable and particularly is important in intraocular solutions. It need not, however, be an overriding concern when total product stability is to be considered.

The tonicity of ophthalmic (and parenteral) solutions has been investigated intensively over the years. These studies have resulted in the accumulation and publication of a large number of sodium chloride equivalents which are useful in calculating tonicity values. See Chapter 36.

Viscosity—The USP permits the use of viscosity-increasing agents to prolong contact time in the eye and thus enhance drug absorption and activity. Substances such as 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 in number. 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, that class of such compounds which 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, that readily may leach out of the plastic and into the contained solution. Label glues, inks and dyes also may penetrate poly-

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ethylene 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 should 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. The pharmacist should not fail to discourage such use just as he or she should take the time to instruct the patient 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 1566 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 it is 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 to further challenge and verify preservative activity.

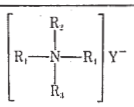
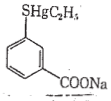
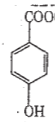
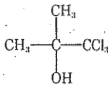
In addition to preservative effectiveness as an immediate measure, its adequacy or stability as a function of time also must be ascertained. This often is done by measuring both chemical stability and preservative effectiveness over a given period of time and under varying conditions.

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 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 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 prod-

Table 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

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ucts 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 preservatives. Refer to RPS-14, page 1571 for a summary of quaternary germicides in ophthalmic drugs.

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% of 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, in 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 pseudomonal organisms 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 (approximately 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 used in a concentration of 0.5%. One of the products of hydrolysis is hydrochloric acid, which causes a decrease in the pH of aqueous solutions. This decomposition occurs rapidly at high temperatures and slowly at room temperature, in unbuffered solutions that were originally neutral or alkaline. Therefore, ophthalmic solutions that contain chlorobutanol should be buffered between pH 5.0 and 5.5. At room temperature it dissolves slowly in water and, although it dissolves more rapidly on heating, loss by vaporization and decomposition is accelerated.

A combination of chlorobutanol and phenylethyl alcohol (0.5% of each) has been reported to be more effective against *P aeruginosa*, *S aureus* and *P vulgaris* than either antimicrobial singly. Also, preliminary solution of the chlorobutanol in phenylethyl alcohol effects solution of the former in water without the use of heat.

Ophthalmic Preparations for OTC Use

A comprehensive review of over-the-counter ophthalmic preparations recently has been completed by an expert panel approved by the FDA. The panel review extended over the period 1973 through 1979. The finding of this panel, in the form of a tentative final monograph, appeared in the *Federal Register*.[14]

In a comprehensive assessment the panel considered the following conditions amenable to OTC drug therapy.

Tear Insufficiency—Rational formulations used to treat tear insufficiency are aqueous solutions containing demulcent agents, tonicity agents and pH and buffering agents. Tear insufficiency includes:

1. Keratoconjunctivitis sicca
2. Sjogren's syndrome
3. Dry eye in the elderly

Corneal Edema—Increased water content in the cornea usually is treated with hypertonic solutions of sodium chloride, either 2 or 5%.

Inflammation and Irritation of the Eye—

1. Presence of loose foreign material in the eye. Commonly treated with an isotonic eyewash properly buffered and preserved.
2. Irritation from airborne pollutants and chlorinated water. Management consists of avoiding the offending allergens and the use of vasoconstrictors, astringents, demulcents and emollients for symptomatic relief.
3. Allergic conjunctivitis. Treatment by topically applied vasoconstrictors and astringents, demulcents, emollients and cold compresses. Only in mild cases, where edema and congestion are slight, is OTC treatment alone adequate.

In providing such OTC medications the pharmacist should take the opportunity to point out that unsupervised use of these products should be limited to 72 hours, when based on self-diagnosis. If the condition persists or worsens at any time, treatment should be discontinued and a physician consulted at once.

Contact Lenses

Contact lenses are optical and/or therapeutic ophthalmic devices divisible into four general categories. The rigid, hydrophobic, so-called hard contact lenses, principally PMMA (polymethyl methacrylate); rigid, semihydrophobic; flexible hydrophilic; flexible hydrophobic and rigid-gas-permeable. Each lens class is accompanied by its support solution products and devices. Solutions used with hard contact lenses are rather conventional compositions, usually regarded as OTC products. Conversely, solutions ancillary to the hydrophilic lenses may be classed as new drugs or devices from a regulatory standpoint. Such preparations require great care and considerable pharmaceutical skill to formulate. Lens materials and support products are further classified and identified in Table 2.

Hard Contact Lens—Some evidence is available to show that contact lenses were visualized by Leonardo da Vinci in

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Table 2—Contact Lens Classes, Characteristics and Support Products

Lens type	Chemical classification	Major characteristics	Typical support products
"Hard," rigid, hydrophobic	PMMA (polymethyl methacrylate)	Negligible gas permeability, low water content, medium wettability	Wetting solutions Soaking solutions Cleaning solutions Combination Artificial tears
"Soft," flexible, hydrophilic	HEMA (hydroxyethyl methylmethacrylate)	High water content, low gas permeability, good wettability	Cleaning solutions Disinfection solutions
Flexible hydrophobic	Silicone rubber	Good gas permeability Poor wettability	Wetting solutions Cleaning solutions Soaking solutions
	Silicone vinylpyrollidone	Good gas permeability Good wettability	
Rigid, hydrophilic	CAB (cellulose acetate butyrate)	Good gas permeability Good wettability	Wetting solutions Cleaning solutions Soaking solutions Rewetting solutions

1508 and later, in 1637, by Rene Descartes. In 1827 the British astronomer, Sir John Herschel, described the mathematics of these devices. He speculated on the possibility of filling a glass contact lens with transparent gelatin to correct for corneal irregularities. Not until 1888 was the original concept executed by the artificial eye maker, Albert Muller. He made a glass protective shell for the cornea of a lagophthalmic patient who had carcinoma of the upper lid. The patient wore the device for 20 years, and corneal clarity was maintained. Other cases were reported in Europe of glass shells placed on the eye as corneal protective devices.

Until the latter part of the 1940s almost all contact lenses had a portion resting directly on, or arching over, the cornea with a supporting flange resting beyond the limbus on the sclera. Thus, they were scleral lenses. However, contact lenses without scleral portions (corneal lenses) were in existence at least as early as 1912, when they were being manufactured by Carl Zeiss.

The glass scleral contact lenses that were made from 1888 to 1938 were fitted by a tedious method of trial and error using a fitting set that might contain more than 1000 lenses. The lenses were heavy and adjustments on them by the fitter were impossible. Their life in the eye was short, because the glass was attacked vigorously by lacrimal fluid; in about 6 months the lenses became too rough to wear or to see through. However, they had the advantage that tears readily wet glass. In 1922 Dallos, in Budapest, perfected a molding technique by which a glass shell could be fabricated to approximate closely the curvature of the globe. With the introduction of the methyl methacrylate plastic molded scleral contact lens in 1938 by Obrig and Muller, the feasibility of using plastic for lens fabrication was demonstrated. Although the optical properties of glass are superior to those of plastic, the relative gain in ruggedness and the reduction in weight to one-third that of glass far offset this disadvantage. Not until PMMA became available was a flush-fitting shell possible. The concept was developed by Ridley, in England, in 1954. The protective effect is very useful in various conditions characterized by corneal epithelial fragility and for cosmetic effects.

The "hard" plastic corneal contact lens was introduced by Tuohy in 1948. This was a major development. He specified a lens of smaller diameter that rested within the limbal area of the cornea. The results were poor. Development of a corneal lens was hindered by the fear of traumatizing the cornea with an appliance that fitted directly onto it. The first corneal lens to have any measure of success was developed in the early 1950s by Dickinson, Sohnges and Neill. Its thickness was about 0.2 mm and was considered to be a fairly thick lens. Thinner lenses, about 0.1 mm, were introduced in the early 1960s.

Scleral bifocal lenses were developed initially in 1936 and the corneal type in 1958. Bifocal contact lenses are more difficult to fit, more costly and, in many cases, more uncomfortable than single-vision lenses.

Lens-Care Products

Wetting Solutions—These are preparations designed to furnish an hydrophilic coating over the characteristically hydrophobic surface of PMMA, silicon, acrylate and other rigid lens surfaces. Typically, wetting solutions include an acceptable viscosity-imparting agent, a surfactant and a preservative. The surface-activity and viscosity effect may be obtained from a single compound. Agents commonly used include cellulose derivatives, polyvinyl pyrollidone, polyvinyl alcohol and polyethylene glycol derivatives. Preservatives include those acceptable for ophthalmic use. Such solutions are sterile.

Cleaning Solutions—Cleaning solutions commonly are used to remove surface contaminants—lipids, protein and the like. Cleaning is accomplished by the use of surfactants which preferably are nonionic or amphoteric. Solutions are sterile and properly preserved. Viscosity-imparting agents generally are not included.

Adequate cleaning of hydrophilic lenses is a far more complex and challenging problem than hard-lens cleaning. Because of their permeability characteristics, contaminants penetrate into the lens structure and easily may bind chemically or physically to the HEMA lens material. Contaminants may be surface films or crystals, amorphous aggregates of protein material, cellular debris or insoluble inorganic salts.

Cleaning products generally are specific to the lens material and require FDA approval, with proof of cleaning efficacy and safety. Cleaners are based on surface activity, enzyme action or even abradant action, in which case the abradant material is softer than the lens itself. Adequate cleaning of hydrophilic lens material daily is a necessary prelude to disinfection. Most recently the use of extended-wear lenses has found wide acceptance. Successful use usually depends on the use of an enzyme for cleaning, together with special disinfectants.

Disinfecting Systems—Disinfection of the first hydrophilic lens approved by the FDA was accomplished using a heating device which generated steam from a saline solution. The latter was prepared either by the user or available from the manufacturer. Subsequent to the so-called thermal systems, disinfection solutions were developed which met the requirements necessary for FDA approval. Because of the sorption characteristics of hydrophilic lens materials, many of the accepted ophthalmic preservatives are unsatisfactory for use in soft-lens disinfecting systems, including the ubiquitous benzalkonium chloride. Once again, however, the use of a quaternary disinfectant covalently bonded to a soluble, relatively high-molecular-weight polymer has met with some success.

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In addition to possessing satisfactory disinfecting activity, such a preparation must be isotonic, in an acceptable pH range, nonreactive (nonbinding) with lens materials and, over a normal use period, induce or bring about no physical, chemical or optical changes in the lens. It is of course sterile and safe for use in the eye even though direct instillation into the eye is not intended.

Soaking Solutions—Soaking or storage solutions, as the name suggests, are used to store and hydrate hard lenses but, most importantly, to disinfect such lenses. Disinfection should be rapid and as complete as possible making use, once again, of acceptable ophthalmic preservative substances. Soaking solutions typically contain chlorhexidine (gluconate), benzalkonium or quaternary/polymer compounds enhanced by sodium edetate.

Artificial Tears—Solutions intended to rewet hard lenses *in situ* are referred to as rewetting solutions or artificial tears. Such preparations are intended to reinforce the wetting capacity of the normal tear film. Early products of this type tended to be somewhat viscous wetting solutions acceptable for direct installation into the eye. More recent preparations mimic tears more accurately and their viscosity is rather low, thus, user acceptability is improved.

Guidelines for Safety and Efficacy Testing—The FDA periodically issues or updates guidelines describing recommended test procedures for contact lens-care products, other than those used with PMMA lenses and, also, for typical OTC products used with hard lenses. The reader is advised to review the most recent guidelines for appropriate protocols for non-PMMA products.

Tests for OTC (hard) lens products are divided into those appropriate for products intended for direct instillation in the eye and those not so intended. Products intended for direct instillation require multiple-application safety tests in the rabbit eye, preservative efficacy tests and sterility testing, in addition to adequate efficacy tests.

Products not intended for direct instillation require short term evaluation in the rabbit eye and, of course, preservative efficacy and sterility testing.

Soft Contact Lens—In 1960 Wichterle and Lim introduced a new, soft, hydrophilic gel lens synthesized by copolymerization of HEMA with ethylene glycol dimethacrylate (EGDM). Its hydrophilic nature was in marked contrast to the hydrophobic properties of PMMA; its increased permeability to water, oxygen and other constituents of tears having low molecular weight appears to offer metabolic advantages.

Hydrophilic (gel, hydrogel, soft or flexible) lenses are made of polymerized or copolymerized hydrophilic monomers with a cross-linking agent, such as EGDM. The cross-links add stability to the gel lenses and act to decrease the water saturation. The most widely used monomer is HEMA which may be copolymerized with lesser amounts of polyvinylpyrrolidone (PVP), a more hydrophilic polymer. The copolymer acts to increase the hydration level beyond the maximum 40% potential of homogenous poly-HEMA. Gel lenses of even higher water content can be formed by combining a hydrophilic monomer or polymer (usually PVP) with a relatively hydrophobic monomer (usually methyl methacrylate). Lenses of this type are available with as much as 85% water at equilibrium. In addition, these cross-linked polymers cannot be formed by heat or pressure and thus usually are not harmed by boiling in aqueous solution or by autoclaving.

Hydrophilic lenses are elastic and flexible when hydrated, yet brittle when dry. They can absorb and concentrate tear-film constituents as well as environmental pollutants, vapors, cosmetic ingredients, water impurities and antimicrobial preservatives, as well as active ingredients, in ophthalmic preparations. The refractive index for HEMA is 1.43 when hydrated in normal saline; hydrophilic lenses of greater hydration level have a correspondingly lower refractive index. Depending on the amount of cross-linking and the amount and type of additives, the dimensions can be influenced by such factors as pH, tonicity and molecular or ionic species of dissolved substances.

Advantages and Disadvantages of Soft Contact Lenses—Soft contact lenses have the major advantage of wearer comfort and easy adaptability, particularly for the first-time lens wearer. Soft lenses are misplaced or lost less easily and allow an easier transition to eye glasses. The typical vision blurring associated with a transition from hard lenses to eye glasses is absent.

Because of the flexibility of soft contact lenses an accurate fit to the eye is more difficult than is the case with hard lenses. Visual clarity usually is less with soft lenses; indeed, the long-time hard-lens wearer may find visual clarity or acuity of soft lenses unacceptable at first wearing.

Soft lenses require far more care than their hard counterparts. The soft polymers will allow penetration of contaminants deep into the lens body where even simple removal become difficult. Soft lenses may become more or less permanently contaminated by sorption of drug product components, in addition to protein fragments or various other debris.

Even with reasonable care, soft lenses can be expected to have a wearer life substantially shorter than hard lenses. Eye corrective changes requiring refitting and lens replacement may occur well before hard lenses require replacing because of wear.

Despite the obvious practical disparities the popularity of soft contact lenses is immense, and increasing as durability and wearing time are increased. Wearer comfort, easy adaptability and adequacy for most relatively minor visual corrections contribute to soft-lens acceptability and popularity.

Therapeutic Uses

The majority of contact lenses are used for reasons of optical acuity, convenience and/or cosmetic value. However, so far as is known, the first use of such a device, in 1888, was to protect a cornea, and therapeutic usefulness has continued since that time. A major therapeutic advance was made by Ridley, in 1954, using PMMA, at the time that it was replacing glass as the principal material used in making lenses. Currently, there is evidence of contact-lens development of major therapeutic importance in the use of soft lenses in the treatment of very serious pathological conditions. They are of value in several ways, which are interrelated to the extent it is difficult to give an example which illustrates only one point. The several functions can be listed as:

1. As "bandages" (through which one can see) to protect the epithelium of the cornea.
2. While in use as bandages, to permit movement of medicinal fluids through the lens to the eye, as well as under the lens (see below).
3. When so used, to increase the duration of the effect from a given quantity of drug.
4. When so used, to increase the degree of effect from a given amount of drug (see below).

The first two functions have become rather well-established in the past few years; the last two have been of less therapeutic value.

Bullous keratopathy is the most severe form of corneal edema. Its treatment is presented as an example of the first two functions of soft contact lenses. The lens acts basically as a simple bandage, but has the added valuable quality that the ophthalmic solutions, used as drops, can pass through the lenses and act on the eye. The pain of bullous keratopathy usually is relieved dramatically by the use of the lens as a protective shield, as similarly accomplished by the earlier hard scleral lenses. Vision may be improved slightly. The pain results mainly from the lids rubbing on the bullae, rupturing them and exposing corneal nerves. The lenses can be worn fulltime, 24 hours a day for months, except for removal for cleaning. They may need to be cleaned only when protein deposits build up on them. They should be removed and inserted only by a physician. New lenses will be needed as the cornea changes in shape.

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Compared with hard lenses, use of the soft lens is much simpler. No moldings of the eye or keratometer readings are needed. The iatrogenic aspects of the hard lens have, to a great extent, been alleviated by the soft lens. Few problems occur on over-wearing the lenses. Usually, no abrasions are found. The eyes are white and usually free of conjunctival infection. As to medicinal agents, because of the concomitant iritis, pupils must be dilated with cycloplegics for the first few days, as by use of atropine. Eyelid hygiene techniques are needed. Antibiotics, such as chloramphenicol drops, are used if secondary infection or blepharitis is present. A 5% hypertonic saline solution may be used to improve vision; the patient can use it as often as it is helpful.

The conditions for which the use of soft lenses is apparently very helpful and well established are

1. Edema
   a. Bullous keratopathy
   b. Aphakic
   c. Secondary to glaucoma
   d. Fuchs' dystrophy
   e. Uveitis, etc
2. Epithelial erosion and defects
   a. Ulcers
   b. Chemical burns
   c. Post-graft
3. Exposure
   a. Neurotropic keratitis
   b. Lid abnormalities
4. Irregular cornea
   a. Scars
   b. Dystrophy
5. Dry eye
   a. Nonprogressive conjunctival cicatrization (Stevens-Johnson syndrome)
   b. Sjögren's syndrome
   c. Trachoma
   d. Pemphigoid

Summary

The progress in ophthalmic pharmaceutics and in lens care pharmaceutics during the last decade must be considered as striking. Very substantial advances have been made in ophthalmic bioavailability and the factors influencing ophthalmic drug absorption. New approaches and new techniques have confirmed (or refuted) many long held tenets of ophthalmic formulation technology. Continuing studies in the general field of ophthalmic pharmaceutics and pharmacokinetics should continue to advance the frontiers of ophthalmic drug therapy and ophthalmic drug delivery.

In the contact-lens and lens-care field one is confronted with a plethora of new lenses and lens polymers. Wearing time has been lengthened substantially, comfort improved and correctable visual defects increased. By the same token the requirements for lens hygiene also have increased. Advances in this broad field also show no signs of abating.

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