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Chapter 43 Ophthalmic Preparations

Masood Chowhan, PhD; John C. Lang, PhD and Paul Missel, PhD

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INTRODUCTION¹

Ophthalmic preparations are specialized dosage forms designed to be instilled onto the external surface of the eye (topical), administered inside the eye (intraocular) or adjacent to it (periocular, e.g., juxtasceral or subtenon), or used in conjunction with an ophthalmic device. The latter include preparations used in conjunction with surgical implantation (such as an intraocular lens) and dry eye formulations compatible with a punctal appliance (e.g., a punctal plug), and extends to a variety of solutions used in the maintenance of contact lenses. The preparations may have any of several purposes (e.g., therapeutic, prophylactic, or palliative for topically administered agents) but include mechanical, chemical, and biochemical actions of agents used in the care of ocular appliances and tissue prophylaxis during or following surgery. Because of the dangers associated with the administration or repetitive administration of intraocular and periocular preparations, their suitability is restricted to therapeutic applications or surgical adjuncts.

The versatility of dosage forms of ophthalmic preparations allows the clinician to choose the form most suitable for the function desired. Therapeutically active formulations can be designed to provide extended action for convenience or for reduction in risk of repetitive administration, improved bioavailability of the agent, or improved delivery to a targeted tissue. The residence of an ocular preparation can range from the few seconds needed for tears to clear an irritating substance; to hours for a gel, a gel-forming solution, or an ointment; to months or years for an intraocular or periocular dosage form. A preparation may be strictly therapeutic or may serve in prophylaxis. The latter includes surgical adjuncts to maintain the health of fragile cells, and postsurgical or post-trauma preparations designed to prevent or reduce the likelihood of infection. Another form of prophylaxis, one for a device, is the antisoiling function provided by some contact lens solutions.

Ophthalmic preparations are similar to parenteral dosage forms in their requirement for sterility as well as considerations for osmotic pressure (tonicity), preservation, tissue compatibility, the avoidance of pyrogens in intraocular dosage forms, particulate matter, and suitable packaging.

Topical therapeutic dosage forms have customarily been restricted to solutions, suspensions, and ointments. But with advances in materials science, the range of ophthalmic dosage forms has expanded significantly to include gels, either preformed or spontaneous gels responsive to the ocular environment, and ocular inserts, both forms reducing dosage frequency. These are most often multidose products, containing suitable preservative(s) to meet compendial preservative effectiveness test [e.g., *US Pharmacopeia* (USP),² *European Pharmacopoeia*,³ or *Japanese Pharmacopoeia*⁴] requirements. Now, however, single-dose units (also referred to as unit-dose products) that are preservative-free preparations have become available, generally packaged in form-fill-seal plastic containers with 0.25 mL to up to 0.8 mL, have become available. These unit-dose containers are designed to be discarded after a single use or after a single day's use if the container has a reclosable feature and the product is so labeled.

Injections and implants have been developed for intraocular drug delivery. Irrigating solutions and viscoelastic gels are available specifically for adjunctive use in ophthalmic surgery. Specialized formulations are now available for use in the care of contact lenses. The designs of these preparations, meeting all of the requirements for safety, efficacy, component compatibility, tissue acceptability, storage, shipping, and shelf-life, are beyond the scope of this review. Nonetheless, a description of the requirements and the designs for some of these formulations should be illustrative and didactic.

From a historical perspective, preparations intended for treatment of eye disorders can be traced to the writings of the Egyptians, Greeks, and Romans. In the Middle Ages, *collyria* were referred to as materials that were dissolved in water, milk, or egg white and used as eyedrops. One such collyrium contained the mydriatic substance belladonna to dilate the pupils of milady's eyes for cosmetic purpose.

From the time of belladonna collyria, ophthalmic technology progressed at a pharmaceutical snail's pace until after World War II. Before World War II and into the 1950s, ophthalmic preparations were mostly compounded by the pharmacist for immediate use. Not until 1953 was there a legal requirement by the US Food and Drug Administration (FDA) that all manufactured ophthalmic solutions be sterile. The range of medicinal

agents to treat eye disorders was limited, as was the state of eye surgery and vision correction, which was limited to eyeglasses. In the past 50 years, a modern pharmaceutical industry specializing in ophthalmic preparations has developed to support the advances in diagnosis and treatment of eye diseases, in eye surgery, and in contact lens design and use. Because of the variety of ophthalmic products readily available commercially, the pharmacist now is rarely required to compound a patient's ophthalmic prescription. More important, however, is that the pharmacist appreciate even subtle differences in formulations that may impact efficacy, comfort, compatibility, or suitability of a preparation for particular patients.

Currently and in the future, in addition to the advances in dosage-form technology, drug molecules will be designed and optimized specifically for ophthalmic application. New therapies may become available for preventing blindness caused by degenerative disease – including age-related macular degeneration (AMD), macular edema, and diabetic retinopathy. Biotechnological products may also become available to treat causes of multifactorial eye disorders like glaucoma. Such specialized therapeutic agents also will require carefully designed and compatible dosage forms.

Because dosage forms are fashioned to complement the requirements of the therapeutic agent, and the latter are selected for their action upon particular tissues so as to modify their function, we will now turn to a description of ocular tissues and their physiology.

ANATOMY AND PHYSIOLOGY OF THE EYE

In many ways the human eye is an ideal organ for studying drug administration and disposition, organ physiology, and function. Unlike many bodily organs, most of its structure can be inspected without surgical intervention. Its macroscopic responses can be investigated by direct observation. Its miraculous function, so intricate and complex, converting a physical electromagnetic stimulus into a chemical signal that is coupled to distant neurons for signal processing by an electrochemical wave, is detectable by sensitive instruments attached to external tissues. The basis for the function and protection of this important organ that links humans to

their external environment is the tissues composing it. The structures to be described are illustrated in Figures 43-1 to 43-3. Figure 43-1 provides a horizontal section of the eyeball identifying the major structures and their interrelationships.⁵ Figure 43-2 shows in greater detail the anterior portion of the eye and eyelids, in vertical section, emphasizing some of the structures associated with tear apparatus.⁶ Figure 43-3 emphasizes the flow of tears into the nasal structures.⁶ This brief introduction will focus on the anatomical structures composing the eye and their function.

EYELIDS

Eyelids serve two purposes: mechanical protection of the globe and creation of an optimum milieu for the cornea. The inner surfaces of the eyelids and the outermost surfaces of the eye are lubricated by the tears, a composite of secretions from both lacrimal glands and specialized cells residing in both the bulbar (covering the sclera) and palpebral (covering the inner surface of the lids) 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 conjunctival cul-de-sac. The elliptical opening between the eyelids is called the palpebral fissure, and the corner of the eyes where the eyelids meet are the canthi.

OVERVIEW OF STRUCTURE AND FUNCTION OF THE EYEBALL

Structure

The eyeball is housed in the bones of the skull, joined to form an approximately pyramid-shaped housing for the eyeball, called the orbit. The wall of the human eyeball (bulbus, globe) is composed of three concentric layers that envelop the fluid and lenticular core.⁷⁻⁹

OUTER FIBROUS LAYER

The outer scleral layer is tough and pliable but only slightly elastic. The anterior third is covered by the conjunctiva, a clear, transparent, mucous surface. The most anterior portion of the outer layer forms the cornea, a structure so regular and the

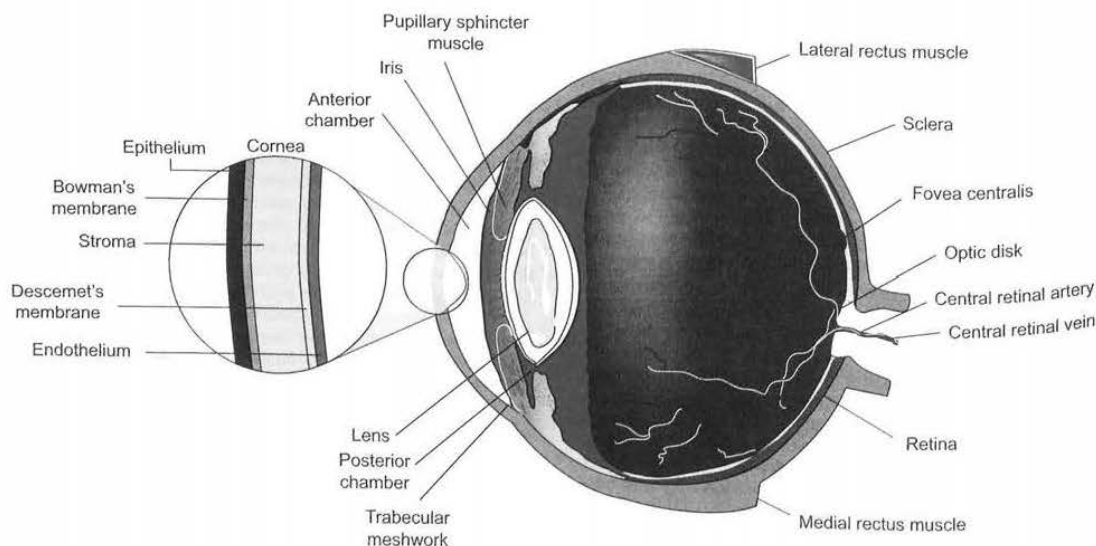


Figure 43-1. A cutaway horizontal section of the eyeball, illustrating the important anatomic structures and their interrelationships diagrammatically. The different layers of the cornea are illustrated in the magnified view. Relative sizes are suggestive and not proportional. The diameter of a mature eyeball is generally slightly greater than one inch. (Courtesy, Alcon Laboratories, Inc., Fort Worth, TX).

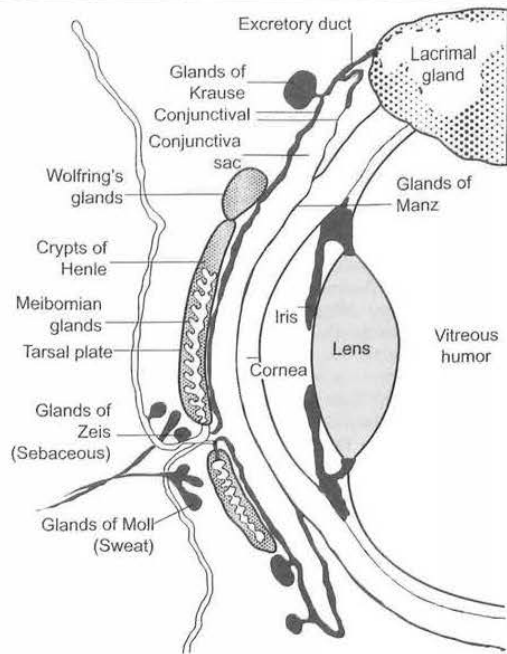


Figure 43-2. The front half of the eye, in vertical section, identifying the important structures associated with cornea and the front of the eye, including the eyelids and the glands associated with tears.

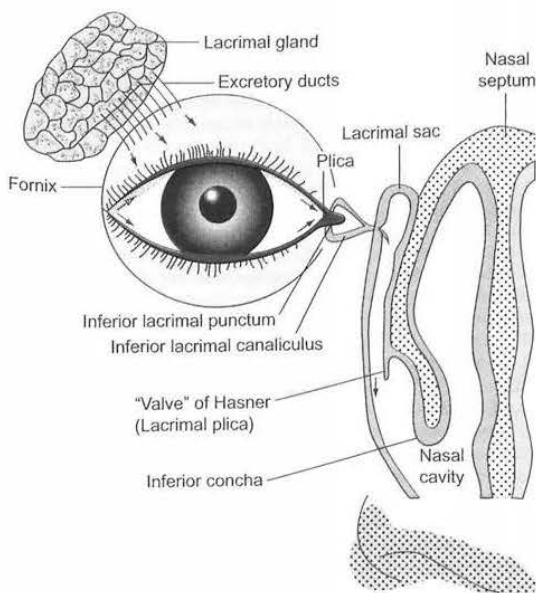


Figure 43-3. The structures associated with the tears and lacrimal flow and access to the nasolacrimal system.

water content so carefully adjusted that it acts as a transparent window. It is devoid of blood vessels. Over the remaining two thirds of the globe, the fibrous collagen-rich 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 vessels become dilated.

The cornea, slightly thicker than the sclera and ranging in thickness from 500 micrometers to 1 mm, consists of five identifiable layers. Proceeding from the most anterior layer, these are the hydrophobic stratified squamous epithelium, which is underlaid by the Bowman membrane, then the stroma and the Descemet membrane, and then the innermost layer, the endothelium. The stroma is a hydrophilic elastic network of highly organized connective tissue and is the thickest layer of the cornea. The fibrous collagen-rich Descemet membrane separates the stroma from the single squamous-cell layer of endothelium, the location of the pump that keeps the cornea in its relatively dehydrated, transparent state. The cornea functions as a bilayer barrier, with the hydrophobic epithelium as the primary barrier to hydrophilic molecules and the hydrophilic stroma as the primary barrier to hydrophobic molecules. A schematic drawing of the cornea is provided in Figure 43-1 and its relation to other anterior tissues in Figure 43-2.

MIDDLE VASCULAR LAYER

The middle vascular layer, or uvea, provides nourishment to the eye and consists (from the back of the eye to the front) of the choroid, the ciliary body, and the iris. The choroid consists of a pigmented vascular layer, colored by melanocytes and traversed by medium-sized arteries and veins, with the chorioecapillaris containing a network of small vessels that nourish the neural retina. The ciliary body contains muscles that control the extension of the lens, allowing visual accommodation, as well as the ciliary processes that secrete aqueous humor into the posterior chamber to maintain the intraocular pressure (IOP) that, in turn, keeps the eyeball fully expanded. The pigmented iris is a ring of muscular tissue around the pupil, a round centric hole that acts as a variable aperture to control pupil diameter and, thereby, the level of light entering the eye. The canal of Schlemm, one of the important paths for outflow of the aqueous humor, resides in the angle of the iris. Bruch's membrane separates the choroid from the retina.

NEURAL RETINA

This innermost layer of the eyeball is a complex tissue that supports the harvesting of light through the collective action of photoreceptors and nerve cells specialized for distinguishing white from black (rods) or for discerning color (cones). In addition, the retina consists of cells that support metabolism (like the heavily pigmented retinal pigmented epithelium, which purges photoreceptors of spent molecules and metabolites, and regenerates the *cis*-retinal), provide structure (astrocytes and Müller cells), or contribute to the primary function of photo-detection/signal processing (the ganglion cells that begin to process the electrochemical information transmitted from the photoreceptors).

OCULAR CORE

Within the globe, the crystalline lens spans the interior fluid-filled center close to the iris and is anchored by zonule fibers to the ciliary body. The lens is composed of a single layer of replicating epithelial cells that, with age, flatten into layers of long, thin crystalline-filled lamellar fibers. The lens is the only tissue in the body that retains all cells ever produced, a fact that contributes to age-related alterations in size, clarity, and extensibility. A tough, thin transparent membrane called the capsule covers the outermost layer of the lens.

The aqueous and vitreous humors are interposed between the solid structures of the eye. The clear, fluid aqueous humor fills the globe anterior to the lens and is primarily responsible for maintaining correct IOP. The gel-like vitreous humor accounts for most of the weight of the eye and resides posterior to the lens, in direct contact with the retina.

FUNCTION

The eyeball houses the optical apparatus that causes the formation on the neural retina of inverted, reduced images of the outside world.

Dimensional Stability

DIMENSIONAL STABILITY

The optical function of the eye calls for stability of its dimensions, which is provided partly by the fibrous outer coat but more effectively by the intra ocular pressure (IOP), which exceeds the pressure prevailing in the surrounding tissues. This IOP is the result of a steady production of specific fluid, the aqueous humor, which originates from the ciliary processes anterior to the lens and exits the eye by an intricate system of outflow channels. The resistance encountered during this passage and the rate of aqueous production are the principal factors determining the level of the IOP. In addition to this hydro-mechanical function, the aqueous humor acts as a carrier of nutrients, substrates, and metabolites for the avascular tissues of the eye.¹⁰

OPTICAL PATHWAY

The optical pathway consists, in sequence, of the precorneal tear film, the cornea, the aqueous humor, the pupil, the crystalline lens, the vitreous humor, and the retina. 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). After traversing the cornea, light passes through the clear aqueous humor to the pupil, where the amount of light entering the eye is regulated by the pupillary diameter, and to the second refractive element of the eye, the lens, whose variable focal length allows objects both near and far to be brought into focus (accommodation). The shape of the lens, controlled by the muscles of the ciliary body, refracts and focuses the reduced inverted image on the retina. That image is sharp and clear, in part because of the high transparency of the vitreous humor, which, because of its gel-like state, keeps debris and cells from entering the pathway for the light. The image formed by the electromagnetic light signal on the neural retina is converted to a chemical signal, changing *cis*-retinal to *trans*-retinal, which in turn is processed by neural cells into an electrochemical signal transported through axons to central nerve cell bodies. Continuous maintenance of the photoreceptors and neural tissues in a state capable of supporting the conversion of the excitation associated with a retinal image to processable information is integral to the functioning of the retina and is the reason retinal tissue is among the most rapidly metabolizing tissues in the body. The dependence of the neural retina on the metabolic support provided by the underlying cell layer, the retinal pigmented epithelium, explains why damage to the tissue—such as detachment of the retina or diminished blood supply—can result in nearly immediate and permanent loss of vision.¹¹

TISSUES RESPONSIBLE FOR REFRACTION

Any alteration in the shape or transparency of the cornea 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. Transparency of the cornea is largely attributable to its organized laminar arrangement of cells and fibers, and the absence of blood vessels. The normal cornea possesses no blood vessels except at the sclero-corneal junction, the limbus. The cornea must therefore 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. That the normal cornea is devoid of blood vessels is an important feature in surgical grafting.

Cloudiness of the cornea may occur as a result of disease (e.g., excess pressure in the eyeball, a symptom associated with

glaucoma); the presence of scar tissue due to injury or 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 may heal as an opaque patch that can be a permanent impairment of vision unless it is located in the periphery of the cornea.

The corneal nerves do not supply all forms of sensation to the cornea, but 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 that the cornea possesses a true sense of touch; nerve endings supplying the sensation of heat appear to be 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 that occur exogenously. A means of detecting abrasions on the corneal surface is afforded by staining the cornea with sodium fluorescein. Any corneal abrasion is subject to infection.

As with the cornea, any change in the transparency of the lens as a result of age or disease can significantly affect visual clarity. Loss of flexibility of the lens can reduce visual accommodation and cause difficulty in focusing on near objects. Also, upon aging or as a result of trauma, the lens may generate opacities caused by the oxidation and crosslinking of lens proteins. When cataract surgery is required to restore clarity to cloudy vision, the natural lens is removed and replaced by an artificial one. The capsule, though, is preserved so that it can provide scaffolding for the implanted synthetic intraocular lens.

Lacrimal System

The conjunctival and corneal surfaces are covered and lubricated by a precorneal tear film, a fluid secreted by the conjunctival and lacrimal glands.¹¹ The clear, watery secretion of the lacrimal gland, delivered through a number of fine ducts into the conjunctival fornix, contains numerous salts, glucose, other organic compounds, and approximately 0.7 percent protein, including the enzyme lysozyme. Small accessory lacrimal glands are situated in the conjunctival fornices. The tear 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 blinking and, when blinking is suppressed, may dry in patches. It seems to be unaffected by the addition of concentrations of up to 2 percent sodium chloride to conjunctival fluid. A pH below 4.0 or above 9.0 causes derangement of the film. The film affects the movement of contact lenses and forms more easily on hydrophilic than on hydrophobic prostheses.

The innermost mucin protein layer of the film is especially important in maintaining the stability of the film and is postulated to be held in place by the microvilli of the corneal epithelial cells. Sebaceous meibomian glands of the eyelids secrete an oily fluid that forms the outer layer of the tears, helps to prevent overflow at the lid margin, and reduces evaporation from the exposed surfaces of the eye.

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, at velocities of tens of centimeters per second. The movement of the eyelids includes a narrowing of the palpebral fissures in a zipper-like action from lateral to medial canthus. This aids transport or movement of fluid toward the lacrimal lake and elimination of unwanted contaminants.

Tears are drained from the lacrimal lake through two small openings, the superior and inferior puncta, which drain into connecting small tubes, the lacrimal canaliculi, which

themselves join at the common canaliculus that leads into the upper part of the nasolacrimal duct, the beginning of which is the lacrimal sac, as shown in Figure 43-3. The drainage of tears into the nose does not depend merely on gravity. Fluid enters and passes along the lacrimal canaliculi by capillary action, aided by aspiration resulting from contraction of muscles embedded in the eyelids, and by peristalsis in the muscles near the canaliculi. 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 aspirated into the sac 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 reflexively by stimulation of nerve endings of the cornea or conjunctiva. This reflex is abolished by anesthetization of the surface of the eye and by disorders affecting its nerve function.

The normal cul-de-sac is maintained free of pathogenic organisms in part by the chemical action of enzymes, such as lysozyme, which normally destroy saprophytic organisms with limited action against pathogens, and in part by the continuous physical flow of normally sterile secretions, which constantly wash the bacteria, dust, etc., away from the eye down into the nose. In certain diseases or upon aging, the lacrimal gland, like other glandular structures in the body, may undergo involution, with the result that the lacrimal fluid becomes scanty. 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 can lead to symptoms of dryness, burning, and general discomfort, and ultimately may interfere with visual acuity.

Summary

This brief overview of the structure and function of the eye should provide a basis for understanding the highly integrated tissues comprising this miraculous organ and suggest the importance of providing medications that in no way impair the balance of functions required for maintaining normal functioning of the eye.

BIOAVAILABILITY

THERAPEUTIC TARGETS

Bioavailability of pharmacological agents is dictated by the ocular structure and physiology just discussed. But bioavailability also is controlled by physical constraints and tissue biochemistry (to be discussed in the next subsections), by physical and chemical characteristics of the therapeutic agents, and by the preparations by which they are presented. The bioavailability and potential efficacy of an agent also are determined by the therapeutic targets, which are governed by disease etiology.

For example, treatment of a superficial infection of the cornea, while possibly requiring sustained delivery to enable less frequent administration of antimicrobial therapy, does not involve special considerations of corneal permeation or access to the target tissue. In this circumstance, product design might be directed toward the reduction of any corneal or scleral transport, in that these would be regarded as drug lost from the target site. On the other hand, a recalcitrant case of uveitis may require both topical and systemic administration of anti-inflammatory agents so as to eliminate the condition. In this case, however, transport to the uvea, an internal tissue, is desirable.

Chronic diseases associated with aging, like glaucoma, may be amenable to routine administration of a topical medication. The target, however, may be determined by the particular mechanism for treating the disease. For instance, a drug influencing the generation of aqueous humor may target the iris

ciliary body, whereas a drug influencing the outflow of aqueous humor might target the trabecular meshwork that opens into the canal of Schlemm. The inherent characteristics of the drug also will determine, in part, any need for sustained delivery. In general, a lipophilic agent will be absorbed readily into the lipophilic corneal epithelium, whereas an ionic or hydrophilic agent will be absorbed more slowly. But corneal permeation may still be a significant barrier to delivery at the target tissue even for a lipophilic drug, because transport through the largely aqueous stroma is still required. The capacity of the epithelium for the drug, in part controlled by its partitioning characteristics, may govern any need for sustained administration as well as the dosing regimen. The solubility of the drug, especially for often relatively insoluble hydrophobic lipophilic agents, can limit the size of the reservoir of drug administered, or the exposure to the drug, where the latter is defined as the area under the curve in a concentration-vs.-time plot of drug residence.

Recently, treatments for ocular diseases of the deep tissues have invoked techniques more commonly utilized in targeted systemic delivery. For example, the treatment of retinal cytomegalovirus infection, accompanying end-stage HIV infections, has engendered treatments delivering drug directly to the vitreous humor, with either intracameral injection or an implant. Photodynamic therapy utilizes a radiation (generally light) to activate a drug delivered systemically. Angiostatic agents for the treatment of wet AMD are delivered from an implant. As Higuchi, years ago, and others more recently have described, the rate of delivery from such devices can be controlled by the design of the device, by drug characteristics (primarily solubility), or by a balance of both.¹²

Nonetheless, eyedrops remain the most common modality for administration of therapeutic agents, and so considerations of the quantitative relationships governing the balance of effects controlling access of these agents to their target tissues are of significance and will be summarized in the next few sections. The approach will be primarily hydrodynamic,^{13,14} though molecular theories are now available to give rationale for the macroscopic transport laws.¹⁵ More intricate transport characteristics, such as those occurring when membranes actively transport the therapeutic agent, are less common than simple passive diffusion and therefore will be neglected here. The approach highlights the interrelationships of phenomena whose subtle control in commercial products improves their efficacy. While transmembrane transport is most relevant to transcorneal delivery, some of the same considerations apply to active drugs delivered from implants, because these drug reservoirs serve only as a source for the agents that must traverse tissues or tissue boundaries to reach their target sites.¹⁶

CORNEAL ABSORPTION AND DRUG ACCESS

Physical and Chemical Considerations

Under normal conditions the human tear volume averages about 7 microliters.¹⁷ The estimated maximum volume of the cul-de-sac is about 30 microliters, 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 25 to 50 microliters in volume.

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. Patton¹⁸ has shown that approximately equal tear film concentrations result from the instillation of 5 microliters of 1.61×10^{-2} M pilocarpine nitrate or from 25 microliters of 1.0×10^{-2} M solution. The 5 microliters contains only 38 percent as much pilocarpine, yet its bioavailability is greater because of decreased drainage loss. Human responses can be expected to be similar, and this is supported by studies of gamma scintigraphy.¹⁹ However, human tear responses are

much more significant, and variable, than those in some *in vivo* models. When the therapeutic agents themselves are irritating, excess tearing may occur that may influence bioavailability in affected individuals. There is a practical limit to the concept of minimum dosage volume. There is a difficulty in designing and producing a dropper configuration that will deliver small volumes reproducibly.²⁰ 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- to 7.5-microliter dose-volume range.

The concept of dosage-volume drainage and cul-de-sac capacity directly affects 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.

Though this is generally not a major concern, an instilled drug can be subject to protein binding in the tear fluid and metabolic degradation by enzymes such as lysozyme. Stability, however, is always a primary consideration, both in the bottle and in the tissues. Rapid conversion of a drug to a metabolite is generally to be avoided unless by design (prodrugs).

Corneal Absorption

Penetration of drugs administered topically occurs primarily through the cornea. Drugs administered by instillation must penetrate the eye and do so primarily through the cornea. Corneal absorption is generally more effective than scleral or conjunctival absorption, in which drug is removed by circulatory flow into the general circulation. This is also true because most therapeutic agents tend to be reasonably lipophilic. In the case of more hydrophilic materials, which as mentioned earlier are more slowly absorbed into the corneal epithelium, there is evidence to suggest that a scleral route may be more common. A practical example comes from studies of carbonic anhydrase inhibitors,²¹ a class of drug used in the treatment of glaucoma.

Many ophthalmic drugs are weak bases and are conveniently applied to the eye as aqueous solutions of their salts. If the molecule is maintained in an ionized state, for example, by employing a weakly acidic buffered vehicle, stability of the drug often can be prolonged. If the buffer is weak, little discomfort is generally experienced at the time of instillation. Once neutralized by the tears, the fraction of free base may increase, and this may be the form of the drug most readily absorbed by the corneal epithelium. Nonetheless, during transport through the hydrophilic stroma, an important fraction of the agent may be ionized. Similarly, the form transported through the endothelium may be the free base, and that presented to the ciliary body (one of the sites of pharmacological action) in transport from the aqueous humor may be the ionized salt. This scenario is described simply to suggest the complexity that can be exploited in targeting an ophthalmic drug, as well as complementary considerations involved in providing a preparation capable of the requisite stability for a conventional two-year shelf-life.

The cornea can be penetrated by ions to a small but measurable degree. Under comparable conditions, the permeabilities are similar for all ions of low molecular weight, which suggests that the passage is through extracellular spaces. The diameter of the largest particles that can pass across the cellular layers seems to be in the range of 10 to 25 Å. Some effort has been directed toward increasing the upper molecular-weight limit for water-soluble therapeutic agents by utilizing a class of molecules referred to as penetration, or permeation, enhancers. These molecules are selected for their capacity to increase transiently permeation of larger molecules while producing minimal discomfort or toxicity.

Because highly water-soluble drugs generally penetrate the cornea less readily and the cornea is known to be a membrane including both hydrophilic and lipophilic barrier layers, most

effective penetration is obtained with drugs having both lipophilic and hydrophilic properties. As an 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.

Work on transport of drugs through the cornea, dating from the work of Edelhauser *et al.* in 1965,¹³ and Lee and Robinson in 1979,²² and Lee in 1990,²³ has indicated the interplay of physical properties that regulate access of drugs to ophthalmic tissues. The hydrodynamic principles are well known and will be outlined here. From the physical chemistry of passive diffusion across a simple membrane capable of sustaining a concentration difference (and discussed in other chapters of this volume), the main mechanism of entry into the eye,

$$J = -D dC_m/dx \quad (1)$$

according to Fick's first law of diffusion, where J is the flux of drug across the membrane (amount per area per time), D is the diffusion coefficient, and the derivative of C_m is the spatial concentration gradient in the membrane (at steady state, constant across the membrane).²⁴ Even from this simple relationship, the consequences of the physical properties of the drug can be inferred. As the solubility of the drug increases the gradient will increase, so the driving force for entry of the agent into the aqueous humor will be increased. Experiment similarly has shown specific characteristics of the diffusion coefficient; namely, the diffusion coefficient decreases with increasing molecular size (and hence molecular weight of the compound). So all else being equal, we need to balance the increased specificity and targeting of a larger active molecule against the loss in rate of membrane transport. The equation also makes clear that any means for maintaining the concentration on the donor side of the membrane, thereby sustaining the gradient term for a longer period of time, will increase the mean total flux.

To perceive the consequences of partitioning in a more complicated bilayer membrane (a good model for the cornea in that the major layers serving as barriers to drug entry are the epithelium and stroma), we need to look at the diffusion equation for a bilayer:

$$J = \frac{PC_w}{\frac{Pl_s}{D_s} + \frac{l_e}{D_e}} \quad (2)$$

where P is the distribution coefficient (e.g., the octanol:water partition coefficient, wherein it is a good approximation of the partitioning into the epithelium), the subscripts designate either stroma (s) or epithelium (e), l is the length representing the thickness of the layer, and C_w is the concentration of drug at the donor side of the membrane, i.e., in the concentration of drug in the tears.²⁵ This equation is an approximation to the differential equation. One source of approximation is that it presumes that the concentration on the donor side (in the eye, the concentration of active ingredient in the tears) is much higher than on the receiver side of the membrane (the concentration in the aqueous humor). From this equation we can observe that as the partitioning increases, the effectiveness of the epithelium as a barrier diminishes and is replaced nearly exclusively by the stroma. Similarly, as the partitioning decreases, the epithelium becomes the dominant barrier. Of course, this is just a mathematical representation of an anticipated phenomenon. Clearly there is an advantage to increasing the lipophilicity of the agent so as to improve absorption and transport. A precaution to be kept in mind, however, is that ordinarily when the lipophilicity is increased, the aqueous solubility (which C_w may approach) generally decreases. This is an example of the need to balance a number of characteristics, as mentioned earlier.

There are circumstances when sustaining the presence and concentration of the drug in the tear volume is important, especially when the drug is sufficiently hydrophilic to severely limit absorption directly into the corneal epithelium. From the equations for a stirred-tank chemical reactor, which is undergoing a

steady-state flow of fluid with a solvent entering and a solution of mixed chemicals flowing from it, we expect:

$$C_{\infty}(t) = C_1 \cdot \exp\left(\frac{-V_T \cdot t}{V_T}\right) \quad (3)$$

where the time dependence of C_{∞} is explicitly indicated, C_1 is the initial concentration, V_T is the volume of the reactor (here the tear volume), and its derivative is the rate of flow through the reactor, essentially the rate of tear generation. A number of characteristics of drug delivery are apparent from this equation. One is that if the drug causes discomfort and increases the rate of tearing (V_T in the equation), then the concentration in the tears is depleted more rapidly. Analogously, if the preparation includes a means for retaining a drug carrier in the cul-de-sac, then only a fraction of the drug present is released free into the tears, and $C_{\infty}(t)$ no longer changes with time and, until the reservoir is depleted, may be approximately constant. Because what is important is the total amount of drug reaching the target tissue over a time period,

$$N_{\text{off}} = A \cdot \int dt J(t) \quad (4)$$

the effect of reducing the loss rate from tear flow may counterbalance the consequence of reducing the total level in the tears. Note, for situations in which there is a means for sustaining drug release, Equations 2 and 3 have to be modified in any event, because C_1 is no longer the total initial concentration but the fraction in the tears that is transportable through the cornea. This introduction should provide some notion of the types of complexity involved in achieving improved delivery of a therapeutic agent. When more is known about the details of ocular function, characteristics of the therapeutic agents, and vehicles, it is possible to solve the differential equations numerically so as to improve the design of topically applied medications.²⁶⁻²⁸

DELIVERY TO THE OCULAR POSTERIOR

Optimizing drug delivery to the ocular posterior requires understanding the mechanisms by which substances are cleared by diffusion, by physiological processes of hydraulic, vascular, and lymphatic flows.^{29,30} Computational fluid dynamics can be a useful tool for predicting the influences of processes on the clearance of intravitreally injected substances³⁰ and delivery from devices implanted into the vitreous³¹ or immediately outside the globe in the juxtasclear space.³² This entails construction of an anatomically accurate model for the eye, which enables simulation of diffusion of drug in physiological flow fields with clearance mechanisms engaged. An example of such a simulation exercise modeling clearance of an intravitreal depot of triamcinolone suspension particles is illustrated in Figures 43.4 and 43.5. The significance of these activities, a subject of ongoing research, is difficult to overstate since the diseases being addressed—AMD, macular edema, and diabetic retinopathy—are sight-threatening. The current standard of treatment for AMD requires monthly injections of an antibody against vascular endothelial growth factor. Significant efforts are under way to develop alternate therapies to reduce the frequency of administration or implantation, providing durations of delivery ranging from months to years. A practical consequence is that the testing period for an implanted device is extended appreciably.

Finally, though the approach described in this section has been primarily macroscopic and phenomenological, microscopic models and calculations of transport based on them have provided additional detail about the molecular features of ocular drug transport. For example, it is generally believed that lipophilic drugs permeate the corneal epithelium by transcellular transport, whereas more hydrophilic drugs permeate the corneal epithelium by paracellular transport. A model of these different mechanisms has indicated that the transcellular transport probably is along the lipophilic bilayers of the cell outer membranes, whereas the paracellular transport is probably along

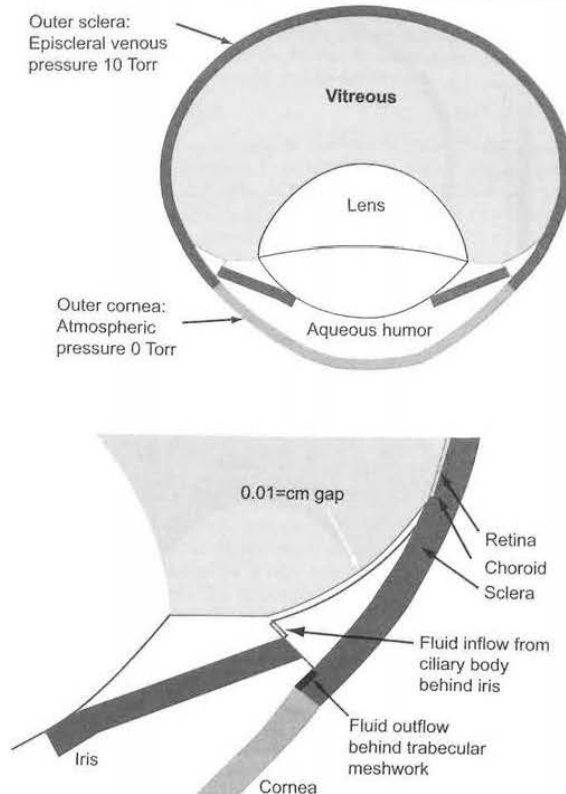


Figure 43-4. Ocular geometry used for computational fluid dynamic simulation of clearance of intravitreally injected substances. All tissue regions are treated as porous media except for the aqueous humor, which is treated as a simple liquid. The small gap between the ciliary body represents the Canal of Petit, a feature which becomes important for accurate simulation of the clearance of slowly diffusing materials. Aqueous fluid is produced at a rate of 3 μL / minute on the blue boundary of the iris as shown. Most of the fluid is eliminated on the outflow boundary behind the trabecular meshwork, simulating conventional outflow. A small amount of the fluid percolates throughout the remaining ocular structure. (From Missel PJ et al. Simulating dissolution of intravitreal triamcinolone acetate suspensions in an anatomically accurate rabbit eye model. *Pharm Res* 2010; 27: 1530–1546.)

the extracellular space, the “pores” of a macroscopic model.²⁴ These models provide insight into mechanisms of transport and how these may be manipulated to improve drug delivery while maintaining safety.

TYPES OF OPHTHALMIC DOSAGE FORMS

Ophthalmic products include prescription and over-the-counter (OTC) drugs, products for the care of contact lenses, and products used in conjunction with ocular surgery. This section will focus on the pharmaceutical aspects of the various ophthalmic dosage forms encompassed by these types of products. The therapeutic uses of individual products can be found in several reference books along with the individual product's labeling.^{33,34}

OPHTHALMIC SOLUTIONS

These are by far the most common dosage forms for delivering drugs to the eye. By definition, ingredients are completely soluble such that dose uniformity is not an issue, and there is little physical interference with vision. The principal disadvantage of solutions is their relatively brief contact time with the

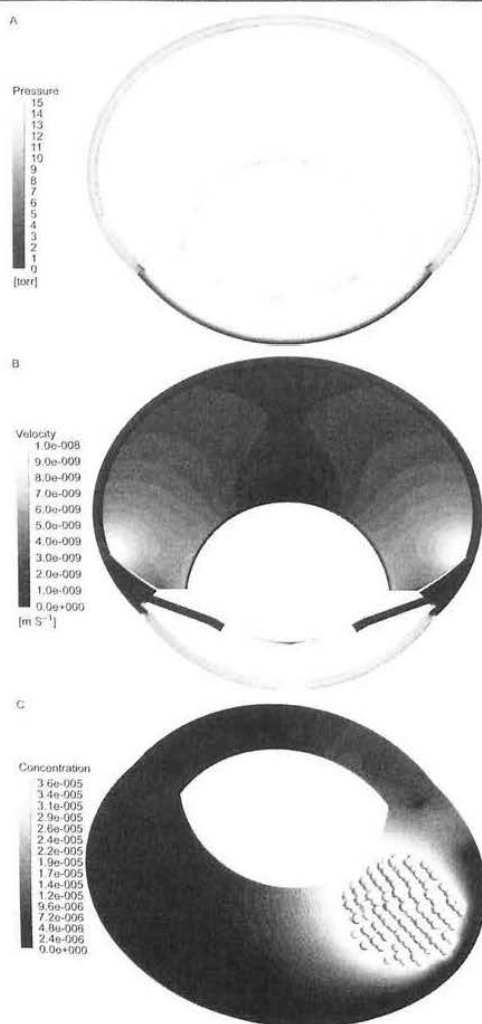


Figure 43-5. Computational fluid dynamic simulation results in the model for the rabbit eye. (a) Pressure distribution within a normotensive eye (Torr). (b) Velocity, clipped to a maximum value of 10^{-8} m/s to illustrate contours in the vitreous. (c) Dissolved triamcinolone acetonide concentration (grams/mL) after the dissolution process has achieved steady state for a suspension of 16 mg triamcinolone acetonide divided into 276 particles confined to a 100 microliter intravitreal depot. (From Missel PJ *et al.* Simulating dissolution of intravitreal triamcinolone acetonide suspensions in an anatomically accurate rabbit eye model. *Pharm Res* 2010; 27: 1530–1546.)

drug and the absorbing tissues of the external eye. Contact time can be increased by the inclusion of viscosity-imparting agents; however, their use is limited to relatively low viscosities so as to allow dispensing of the eyedrop from the container or eyedropper and to minimize excessive blurring of vision. A residue can be produced on the eyelashes and around the eye when any excess of a viscous solution spills out of the eye and dries. The residue usually can be removed easily by careful wiping with a moist towel to the closed eye.

GEL-FORMING SOLUTIONS

Ophthalmic solutions (usually water-based), which contain a polymer system that is a low-viscosity liquid in the container

but gels on contact with the tear fluid, have increased contact time and can provide increased drug absorption and prolonged duration of therapeutic effect. The liquid-to-gel phase transition can be triggered by a change in temperature, pH, ionic strength, or presence of tear proteins, depending on the particular polymer system employed. Timolol maleate gel-forming solutions formulated with specific patented gellan or xanthan gums have clinically demonstrated prolonged duration of IOP lowering, such that their dosing frequency can be reduced from twice to once a day.^{35,36} Review the labeling for commercial gel-forming solutions before dispensing for current instructions related to patient administration.

POWDERS FOR SOLUTIONS

Drugs that have very limited stability in aqueous solution can sometimes be prepared as sterile powders for reconstitution by the pharmacist before dispensing to the patient. The sterile powder should be aseptically reconstituted with the accompanying sterile diluent that has been optimized for dissolution, preservation, and stability. The pharmacist must convey to the patient any special storage instructions, including the expiration date.

OPHTHALMIC SUSPENSIONS

Suspensions are dispersions of finely divided, relatively insoluble drug substances in an aqueous vehicle containing suitable suspending and dispersing agents. 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 could theoretically exceed 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 dissolution 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, because irritation produces excessive tearing and rapid drainage of the instilled dose, as discussed earlier. It has been recommended that particles be smaller than 10 microns 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 might cause the smallest particles to dissolve and the largest particles to become larger.

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 not only 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 use a “Shake Well” label and counsel the patient whenever an ophthalmic suspension is dispensed. An improved ophthalmic suspension has been developed for insoluble drugs such as steroids, which tend to cake upon settling.³⁷ The improved suspension controls the flocculation of the drug particles such that they remain substantially resuspended for months and provides for easy resuspension of any settled particles. Nonetheless, the pharmacist also should be aware of the possibility of crystal growth over time. This potential stability problem is especially problematic for drug substances whose solubility is significantly dependent on temperature. The majority of suspension products have a “Do Not Freeze” warning on the label, because they are likely to agglomerate on freezing and will not be resuspended by simple shaking.

A second and infrequently occurring 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. Manufacturers of commercial suspensions take these possibilities into account in the development and testing of the final formulation and the labeled storage conditions.

In some cases a water-soluble drug has been converted to an insoluble form and formulated as a suspension to improve the drug's stability, compatibility, bioavailability, or patient tolerance. The insoluble forms of steroids such as prednisolone and dexamethasone have better ocular bioavailability and are considered more potent anti-inflammatories for topical ocular use. A resin-bound form of the β -blocker betaxolol has been formulated as a suspension and is prepared *in situ* using a carbomer polymer.³⁸ The novel suspension formulation improves both comfort and ocular bioavailability of betaxolol, the 0.25 percent suspension therapeutically equivalent to a 0.5 percent solution.

OPHTHALMIC OINTMENTS

Ophthalmic ointments are primarily anhydrous and contain mineral oil and white petrolatum as the base ingredients, the proportions of which can be varied to adjust consistency and the melting temperature. Dosage variability probably is greater than with solutions (though probably no greater than that with suspensions). Ointments will interfere with vision, and their use is usually limited to bedtime instillation. They remain popular as a pediatric dosage form and for postoperative use. The anhydrous nature of the base enables its use as a carrier for moisture-sensitive drugs. The petrolatum base can be made more miscible with aqueous components by the addition of liquid lanolins.

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,³⁹ 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.

OPHTHALMIC EMULSIONS

An emulsion dosage form offers the advantage of the ability to deliver a poorly water-soluble drug in a solubilized form as an eyedrop. The drug is dissolved in a nonaqueous vehicle, such as castor oil, and emulsified with water, using a nonionic surfactant and, if needed, an emulsion stabilizer. An emulsion with

water as the external phase can be less irritating and better tolerated by the patient than use of a purely nonaqueous vehicle. Such an emulsion is used to deliver cyclosporine topically for the treatment of chronic dry eye conditions.⁴⁰

OPHTHALMIC GELS

Gel-forming polymers, such as carbomer, have been used to develop aqueous, semisolid dosage forms, which are packaged and administered the same as ointments. The viscous gels have significantly increased topical residence time and can increase drug bioavailability and decrease dosage frequency, compared to solutions. Although they contain a large proportion of water, they can still cause blurring of vision. A carbomer gel of pilocarpine administered at bedtime has been shown to prolong the IOP-lowering effect in patients for up to 24 hours.⁴¹

OCULAR INSERTS

Ocular inserts have been developed in which the drug is delivered on the basis of diffusional mechanisms. Such a solid dosage form delivers an ophthalmic drug at a near-constant known rate, minimizing side effects by avoiding excessive absorption peaks. The delivery of pilocarpine by such an insert was commercialized in 1975 (Ocuser Pilo) by *Alca Corporation*. The Ocuser is designed to be placed in the lower cul-de-sac to provide a weekly dose of pilocarpine, at which time the system is removed and replaced by a new one. The near zero-order rate delivery is based on the selection of a non-eroding co-polymer membrane enclosing the drug reservoir.⁴²

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 must be removed from the eye when exhausted of its drug content. Such manipulations can be difficult for the elderly patient. Nonetheless, such therapeutic inserts represent a notable commercialized scientific achievement in pharmaceutical sciences. The Ocuser Pilo product is no longer marketed, because the drug has largely been replaced in glaucoma therapy by topical β -blockers.

Ocular inserts that gradually erode in the tear fluid have been studied but not commercially developed as ocular drug delivery systems.⁴³ In theory, an erodible insert would be advantageous, because it would not require removal at the end of its therapeutic cycle, would provide precise unit dosing, and, if anhydrous, would not require a preservative. It may also increase ocular bioavailability and reduce the therapeutic dosage and possible systemic effects. The chief disadvantages may be related to patient use issues, control of erosion and drug release rates, and sterilization.

An erodible insert is available (LACRISERT) for treatment of dry eye. It is molded in the shape of a rod from a hydroxypropyl cellulose polymer, which is the active ingredient. When inserted into the lower cul-de-sac, the polymer imbibes tear fluid and forms a gel-like mass that gradually erodes while thickening the tear film over a period of several hours. The unit-dose insert is anhydrous, and no preservative is required, which is beneficial for some sensitive patients.

DRUG ADMINISTRATION

TOPICAL ADMINISTRATION

The instillation of eyedrops remains one of the less precise, yet 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, most 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.

METHODS OF USE FOR TOPICAL ADMINISTRATION

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.

PRECAUTIONS WHEN USING EYEDROPS

- If dropper is separate, always hold it with the 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 (i.e., when supplied by a pharmaceutical manufacturer to the pharmacist), the same rules apply to avoid contamination.
- Never use eyedrops that have changed color.
- If you are using more than one kind of drop at the same time, wait several minutes before using other drops.
- 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/GELS

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 $\frac{1}{4}$ to $\frac{1}{2}$ inch) 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.

PRECAUTIONS WHEN USING OPHTHALMIC OINTMENTS/GELS

- Take care to avoid contaminating cap when removed.
- When opening ointment tube for the first time, squeeze out the first $\frac{1}{4}$ inch of ointment and discard, as it may be too dry.
- It may be helpful to practice ointment use by positioning yourself in front of a mirror.
- 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 using another ointment.
- To improve flow of ointment, hold tube in hand several minutes to warm before use.

NASALACRIMAL OCCLUSION

To limit absorption of topically applied drugs directly into the bloodstream from the highly vascular areas of the nasal cavity, the patient should be instructed to close the eye immediately after eyedrop instillation, place a finger between the eyeball and the nose, and apply pressure for several minutes. This will temporarily occlude both superior and inferior canaliculi, preventing nasolacrimal drainage.

INTRAOCULAR PREPARATIONS

Ophthalmic products introduced into the anterior chamber or vitreous chamber of the internal eye structure are specialized dosage forms, requiring additional pharmaceutical considerations in their formulation, packaging, and manufacture. They are essentially parenteral-type products requiring both sterility and nonpyrogenicity as well as strict control of particulate matter, to ensure that they are compatible with sensitive internal tissues critical to visual acuity. In some cases in which the product may be introduced into the sterile field during surgery, sterility of the exterior of the primary package is required. Because preservatives commonly used in topical ophthalmic products can be toxic to sensitive intraocular tissues, such as the corneal endothelium, intraocular products are designed and packaged as preservative-free single-use products.

Present technologies are summarized in the next subsections, but many novel technologies can be expected in the next several years with the advent of new therapeutics and approaches to delivery for such devastating diseases as AMD, diabetic retinopathy, and cystoid macular edema, diseases of the back of the eye.

IRRIGATING SOLUTIONS

During ocular surgery an irrigating solution is used to maintain hydration, ocular volume, and clarity of the cornea, providing the surgeon a clear view of the surgical field. The irrigating solution also provides a physiological medium for removing blood and cellular debris, and for replacing the natural aqueous intraocular fluid. A balanced salt solution (BSS) is the primary intraocular irrigating solution, which includes the key ionic components to maintain corneal endothelial integrity: sodium, potassium, calcium, magnesium, and chloride, as well as a neutral to slightly alkaline pH and osmolality of about 305 mOsm.⁴⁴ An enriched balanced salt solution (BSS Plus) is also available to provide enhanced physiological compatibility when required in an irrigating solution. The enriched solution contains oxidized glutathione, dextrose, and bicarbonate in addition to the critical ionic components.⁴⁵ The additional ingredients in the enriched solution require, for maximum shelf-life stability, that the product be packaged in a two-part system to be aseptically reconstituted just before use. Intraocular solutions do not contain a preservative and should be discarded after initial use. These irrigating solutions are also designed to be used without additional additives, because there is potential for intraocular toxicity. An acidic epinephrine injection containing sodium bisulfite antioxidant, when added to an intraocular irrigating solution and diluted as much as 500-fold, has been reported to produce intraocular toxicity.⁴⁶

INTRAOCULAR INJECTIONS

Products approved for direct injection into the eye include miotics and viscoelastics for ocular surgery, and two antiviral agents to treat cytomegalovirus retinitis. The miotics carbachol and acetylcholine are used at the end of cataract surgery to constrict the pupil, allowing the iris to cover the implanted intraocular lens. Both products are specially packaged such that the exterior of the primary vial is sterile. This is accomplished by use of a special outer container that is permeable to sterilant gas and prevents contamination of the exterior of the vial.

Solutions with viscoelastic properties are injected into the eye during surgery to provide a mechanical barrier between tissues and allow the eye surgeon more space for manipulation with less potential for trauma to very sensitive intraocular tissues. The primary viscoelastic substance is a highly purified fraction of sodium hyaluronate. Purification is required to remove foreign proteins to be non-antigenic and noninflammatory for intraocular use. The viscoelasticity can be varied by use of fractions and concentrations of different molecular weights. Chondroitin sulfate and purified hydroxypropyl

methylecellulose are also utilized as viscoelastic and viscoadherent surgical adjuncts. The viscoelastic products are packaged and sterilized such that the primary package can be placed in the sterile surgical field before use. Sodium hyaluronate viscoelastic products usually require refrigeration during storage to maintain their integrity.

INTRAVITREAL INJECTIONS/IMPLANTS

Two antivirals have been approved for treatment of the ocular sequelae of AIDS with direct emplacement in the vitreous cavity so as to provide high localized ocular therapeutic concentrations. A polymer-coated sterile tablet containing ganciclovir, called a Vitrasert,⁴⁷ is implanted by the surgeon in the vitreous cavity, where it releases drug over a period of several months and then is removed and replaced with a new tablet. The tablet is formulated with magnesium stearate as the drug carrier and coated with polymers that provide the prolonged drug release. It is important that, during handling, this polymer coating is not damaged and the special sterile packaging not be compromised. A sterile solution of fomivirsen is also available for intravitreal injection to treat cytomegalovirus retinitis. It is supplied in single-use vials and is injected intravitreally without requiring surgery but must be repeated every 2 to 4 weeks.

JUXTASCLERAL INJECTIONS

Certain disease conditions in the back of the eye are usually untreatable through topical administration to the eye. For example, cystoid macular edema (associated with trauma, chronic inflammation, and diabetes) results in swelling of the macula and, if left untreated, loss of vision. At present there is no effective treatment available for AMD, whose incidence and severity increase with age, resulting in progression from accumulation of proteins and glycosaminoglycans (drusen) to leakage of blood vessels (hemorrhage) and eventual blindness. For such conditions, localized intravitreal or juxtascleral injections may be preferable to systemic administration of drugs (either alone or accompanied by laser-initiated events, such as photodynamic therapy).

OTHER MODES OF ADMINISTRATION

Packs

These sometimes are used to give prolonged contact of a drug solution with the eye to maximize absorption. Sterile cotton pledgets, placed in the lower cul-de-sac, have been used in this manner, but more recently corneal shields and soft contact lenses, developed as bandages, have been utilized to protect the cornea during healing.⁴⁸ Corneal shields are made of collagen that is crosslinked to control the rate of erosion, usually 12 to 72 hours. Hydrophilic polymers used for soft contact lenses without vision correction have also been utilized as a drug reservoir. The soft lenses remain intact and therefore require removal.

INTRACAMERAL INJECTIONS

Injections may be directly into the anterior chamber (e.g., acetylcholine chloride, alpha-chymotrypsin, carbamylcholine chloride, certain antibiotics, and steroids) or directly into the vitreous chamber (e.g., amphotericin B, gentamicin sulfate, and certain steroids).

IONTOPHORESIS

This procedure keeps the solution in contact with the cornea by means of an eyecup bearing an electrode. An ionic drug thus is subjected to a current generated by a difference in electrical potential, which acts as an electrochemical driving force to transport the drug in the direction of the potential gradient.⁴⁹

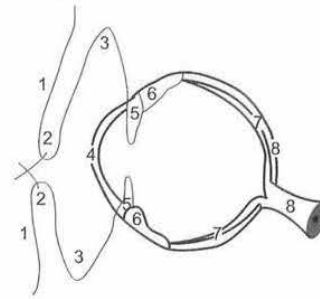


Figure 43-6. The locations for administration and target of therapy. Ointment: regions 1–5. Drops: regions 3–5. Parenteral injections—subconjunctival: regions 5–6, deep subtenons: regions 6–8, retrobulbar: region 9.

SUBCONJUNCTIVAL INJECTIONS

Subconjunctival injections (Figure 43-6)⁵⁰ are used frequently to introduce medications that, 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 mydriatics 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 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 (Figure 43-6) 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 removal via bloodstream effects from these injections is remote. In general, such injections are given for the purpose of targeting medications (e.g., antibiotics, local anesthetics, enzymes with local anesthetics, steroids, and vasodilators) to the posterior segment of the globe and affecting the nerves and other structures in that space for a sustained period of time.

PREPARATION

COMMERICAL MANUFACTURE

Pharmaceutical manufacturers provide finished ophthalmic products, manufactured and tested for quality according to stringent industrial and governmental standards. The products' sterility and, where required, their nonpyrogenicity, as well as other important quality standards, are assured by end-product testing of each batch and also by the use of validated manufacturing processes developed for each individual product. The products' manufacturing and quality control are governed largely by the current Good Manufacturing Practice (GMP) regulations⁵¹ promulgated and enforced by the FDA. If the product is a new or generic drug or medical device and has received FDA marketing approval, the manufacturer must also meet the requirements specified in the approved application for chemistry, microbiology, manufacturing, and quality control. Significant changes to the approved requirements must be submitted and approved by the FDA. For products not requiring prior FDA approval to market, such as monographed OTC drug products,⁵² the manufacturer must meet the quality standards of applicable

USP or NF compendial monographs in addition to the current GMP regulations.

The manufacturer is subject to pre-approval inspections and periodic GMP postapproval inspections by the FDA. The FDA also conducts inspections of the suppliers of active ingredients, both foreign and domestic, and certain inactive ingredients and packaging operations. The manufacture is subject to recalls of batches of product that do not meet quality requirements. In some cases a recall may result, not from actual failed test results, but from a lack of assurance that the product will continue to meet quality requirements through its shelf-life.

PHARMACY COMPOUNDING

Compounding of individual patient prescriptions by pharmacists has been and continues in some areas to be an integral part of pharmacy practice. The routine need to compound sterile ophthalmic products is no longer required with the broad range of commercially manufactured products available today. Most of the new and generic prescription ophthalmic products marketed today have been subjected to the FDA's rigorous requirements for proof of safety and efficacy or bioequivalence, as well as the manufacturing and quality requirements already described.

If the pharmacist is asked to compound a prescription for a noncommercial product, such as a preservative-free version or pediatric strength, he or she should be well versed in the preparation of sterile products, have the proper equipment and facilities, and be knowledgeable about the special requirements for ophthalmic formulations and packaging. Reference information on the standards and technology for pharmacy compounding, with special emphasis on preparation of sterile products, should be consulted.^{53,54} The pharmacist must also consult the rules and regulations of the applicable state board of pharmacy concerning sterile pharmacy compounding as well as any federal regulatory requirements promulgated by the FDA. Congress included in the 1997 FDA Modernization Act certain legal conditions for which compounding, as defined in the Act, would be exempt from FDA regulation. The pharmacy compounding section of the Act was subsequently litigated and overturned in its entirety, because it contained unconstitutional restrictions on commercial speech. The FDA may seek new legislation to address its concerns regarding manufacturing in the guise of compounding. In the meantime, the FDA has issued a guidance document on how the agency intends to regulate pharmacy compounding of human drugs considered to be outside the bounds of traditional pharmacy practice and in violation of the US Food, Drug, and Cosmetic Act of 1938 (FDCA; www.fda.gov/cder/pharmcomp), and has provided a Pharmacy Compounding Compliance Policy Guide (2002).

STERILIZATION

Common methods of sterilization include moist heat under pressure (autoclave), dry heat, filtration, gas sterilization, and ionizing radiation. Please refer to Chapter 40, where these sterilization procedures are described in detail.

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 have repeatedly been the cause of corneal ulcers and even loss of eyesight. Contaminated solutions have been found to be in use in physicians' offices, eye clinics, and industrial infirmaries, and have been dispensed on prescription in community and hospital pharmacies. The microbes most frequently found as contaminants are staphylococci group. *Pseudomonas aeruginosa* is a less common contaminant, and the solution most often found contaminated is sodium fluorescein.

Ps. aeruginosa (*Bacillus pyocyaneus*; *Pseudomonas pyocyanea*; blue pus bacillus) is a very dangerous and 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 *Ps. 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 to 48 hours. At concentrations tolerated by tissues of the eye, most of the antimicrobial agents discussed in the following sections may be ineffective against some strains of *Ps. aeruginosa*.

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 (Alecon) 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 cause harm 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 viral infection via contaminated solutions. This is particularly pertinent to the adenoviruses (types III and VIII), now believed to be the causative agents of viral conjunctivitis, such as epidemic keratoconjunctivitis.

The danger of nonsterile preparations is exponentially increased for products intended for injection within the eyeball. Endophthalmitis and loss of vision can occur within a short time of onset of a bacterial infection.

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 withstand 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 that, while heat-resistant, tend to deform (i.e., polypropylene containers). The sterilization cycle for a product should be carefully validated, and one must assure that sterilization temperature and time are monitored at the coldest spot of the autoclave load to assure sterility of the product.

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.

Several types of membrane filtration equipment are available for small-scale processing, as described in Chapter 40.⁵⁴ Particular interest has been shown in the Swinney 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, including 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. To avoid contamination, the pharmacist should fill sterile filtered solutions into presterilized containers closed with appropriate fitments and closed under laminar flow, using aseptic techniques. The Parenteral Drug Association has produced several audiovisual teaching materials for aseptic techniques and processing. The reader should refer to these guidelines for reference.

Gas

Gas sterilization of heat-sensitive materials may be carried out by exposure to ethylene oxide (EtO) gas in the presence of moisture. EtO gas for sterilization use is available commercially, diluted with either carbon dioxide or halogenated hydrocarbons. EtO 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, EtO concentration, and moisture is essential.

Gas sterilization requires that specialized, but not necessarily elaborate, equipment be used. Gas autoclaves may range from very large walk-in units to small units on the scale of a laboratory bench that are suitable for small hospitals, laboratories, or pharmacies. Users of gas autoclaves must keep in mind the possibility of human toxicity and take care to restrict exposure to EtO during the loading, venting, and unloading of the sterilizer. EtO sterilization produces irritating by-products that 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 EtO itself. Aeration of the sterilized articles for at least 72 hours, preferably at 40°C to 50°C, will minimize such residues.

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

Extreme caution is necessary when using EtO gas sterilization. The previously accepted 12:88 mixture of EtO to Freon has been replaced with 100 percent EtO for environmental reasons. This gas is explosive, and all workers also should be protected from accidental exposure because of concern for carcinogenicity and other toxic reactions to EtO. This method at present is used as a last resort when no other methods can be used.

Radiation

Sterilization by exposure to ionizing radiation is an acceptable procedure for components of ophthalmic preparations or,

indeed, for the total product, such as 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 ⁶⁰Co (a source for gamma irradiation), are employed more widely than linear electron accelerators 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. Gamma sterilization is currently the method used in place of EtO for sterilizing most of the packaging components. Gamma sterilization of containers may alter the surface characteristics, and this can increase degradation of drug molecules and/or some of the excipients used in the formulation. Some plastic manufacturers have developed special grades of polypropylene resin that are stabilized to withstand gamma irradiation.

OPHTHALMIC PREPARATION CHARACTERISTICS

CLARITY

Ophthalmic solutions, by definition, contain no undissolved ingredients and are essentially free from foreign particles. Filtration can enhance clarity in some cases. It is essential that the filtration equipment be clean and well rinsed to avoid introduction of particulate matter into 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 clear solutions essentially free from foreign particles. In many instances the same filtration step can produce both clarity and sterility. If viscosity-imparting polymers are used, a polish-filtering step may be necessary before the final filtration.

Both container and closure must be thoroughly clean, sterile, and non-shedding, so that neither one introduces particulate matter to the solution during prolonged contact for the duration of the shelf-life. Normally this is established by thorough stability testing, which also will indicate whether insoluble particles (by-products of drug degradation) have been generated. Solution formulations may also contain viscosity-imparting polymers that can diminish clarity. In these situations it may be important to both define the visual clarity of the product and monitor its stability. The *European Pharmacopoeia* describes visual clarity and recommends standards that can be used for clarity specifications.⁵

STABILITY

The stability of a drug in an ophthalmic product depends on a number of factors, including the chemical nature of the drug substance, whether it is in solution or suspension, product pH, method of preparation (particularly temperature exposure), solution additives, and type of packaging. A pharmaceutical manufacturer strives for a shelf-life measured in years at controlled room-temperature conditions, whereas the compounding pharmacist often is uncertain about the shelf-life of his or her preparation and thus provides relatively small quantities at one time, assigns a shelf-life in terms of days or weeks, and may specify refrigerated storage as a further precaution. The attainment of optimum stability often requires some compromises in the formulation, packaging, and preparation of the final product.

The product's pH is often the stability-controlling factor for many drugs. 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. Either drug will lose a substantial amount of chemical stability in less than a year. On the other hand, at a pH of 5.0, both drugs are stable for a period of several years. (With regard to eye comfort at acidic pH, see the later discussion under Buffer and pH.)

In addition to optimal pH, if oxygen sensitivity is a factor, adequate stability may require inclusion of an antioxidant or special packaging. Plastic packaging, such as the low-density polyethylene containers (e.g., the DropTainer from Alcon) that are convenient for patient use, may prove detrimental to stability by permitting oxygen permeation, resulting in oxidative decomposition of the drug substance. Development of an epinephrine solution with 2 to 3 years' stability in a plastic package requires the use of a pH of about 3.0 for protection from oxidation, whereas an epinephrine borate solution formulated at a pH of about 7.0, which is more comfortable to the patient, requires an antioxidant system and the use of glass packaging. The prodrug of epinephrine, dipivefrin, significantly increases ocular bioavailability and is effective at one-tenth the concentration of epinephrine. The structure of the chemical derivative protects the active epinephrine portion from oxidation, so that it can be packaged in plastic. However, the labile ester linkage introduced in the prodrug requires that it be formulated at a pH of about 3.0 to minimize hydrolysis; even with this precaution, the shelf-life of dipivefrin stored at room temperature can be extended to no longer than 18 months.

Pharmaceutical manufacturers conduct comprehensive stability programs to assure the assigned expiration dating for each product. In addition to monitoring the standard chemical and physical stability of the pharmaceutical, they test the stability of the preservative by chemical means or by actual challenge of its efficacy with appropriate test organisms. Sterility is not a stability parameter *per se*, but each container-closure system can be tested by microbial challenge to assure integrity of the package against environmental contamination before opening.

Some of the newer classes of ophthalmic drugs, like prostaglandins, are very hydrophobic and have very low concentrations. For example, in the product Xalatan, latanoprost is present at 0.005 percent, and in the product Travatan, travoprost is present at 0.004 percent. Active agents at such low concentrations present a challenge for formulators, because the loss of even small amounts of drug (e.g., from adsorption losses to packaging) can become significant. Pharmacia's Xalatan requires refrigerated storage, and as indicated earlier, temperature cycling also can reduce the concentration of active drug. It is important that the pharmacist knows the properties of the drug substance, in order to maintain product quality throughout the shelf-life of the product.

BUFFER AND PH

Ideally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4. Practically, formulators seldom achieve this. Most active ingredients used in ophthalmology are salts of weak bases and are most stable at an acid pH. This property generally holds for suspensions of insoluble corticosteroids.

Optimum pH adjustment generally requires a compromise on the part of the formulator, who should select not only a pH that is optimal for stability but a buffer system that has adequate capacity 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 only momentary disruption of the overall pH of the tear fluid. Special care in formulating intraocular products is required regarding their pH and buffer capacity. The corneal endothelium can tolerate much less deviation from physiological conditions, compared to the external corneal epithelium.⁵⁵

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 a 0.9 percent sodium chloride solution (290 mOsm). However, the osmotic pressure of the aqueous intraocular fluid is slightly higher than that of normal tears, measuring about 305 mOsm.

In actuality the *external* eye is much more tolerant of tonicity variations than was at one time suggested and usually can tolerate solutions equivalent to a range of 0.5 to 1.8 percent sodium chloride. Given a choice, one will find that isotonicity is desirable and is particularly important in intraocular solutions.⁵⁶ However, in certain cases a nonisotonic topical product is desirable. Tear fluid in some cases of dry eye (keratoconjunctivitis sicca) is reported to be hypertonic, and a hypotonic artificial-tear product is used to counteract this condition. Hypertonic ophthalmic products are used to relieve corneal edema, and solutions and ointments containing 2 or 5 percent sodium chloride are available for this use.

The tonicity of ophthalmic (and parenteral) solutions has been the subject of intensive investigation over the years. These studies have resulted in the accumulation and publication of a large number of sodium chloride equivalents that are useful in calculating tonicity values. See Chapter 31 for a thorough discussion of the measurement and calculation of tonicity values.

VISCOSITY

Ophthalmic solution and suspension eyedrops may contain viscosity-imparting polymers to thicken the tear film and increase corneal contact time (i.e., reduce the rate of tear fluid drainage). For suspensions, the increased viscosity also retards the settling of particles between uses and at the same time maintains their suspension for uniform dosing. However, added viscosity may impede initial resuspension, particularly in a suspension that has a tendency to cake during storage. The hydrophilic polymers most often used for these purposes are methylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, and polyvinyl alcohol—at concentrations that produce viscosities in the range of about 5 to 100 Centipoise. These polymers also themselves appear as the active ingredients in artificial-tear solutions for dry eye therapy because of their lubrication and moisturizing. Viscosity agents can have several disadvantages, in that they sometimes produce blurring of vision and can leave a residue on the eyelids. These effects are most often seen at the higher end of the viscosity range. The added viscosity can make filtration more difficult, particularly for the small pore-size filters used to sterilize solutions.

Newer ophthalmic dosage forms, such as gel-forming solutions and semisolid aqueous gels with their increased viscosity and gel elasticity, significantly improve drug bioavailability and duration of effect. With these advances, the frequency of dosing can be reduced and patient compliance improved. These newer dosage forms incorporate novel polymer systems with special rheological properties to enhance their effect. Their complex rheology and intricate dependence on environment, however, increase the complexity of the sterile manufacturing process.

ADDITIVES

Most ophthalmic dosage forms contain additives or pharmaceutical excipients as inactive ingredients. Because of the need for tissue compatibility in ophthalmics, particularly in intraocular products, however, the use of additives is perhaps less common.

The most common inactive ingredient is the product's vehicle. For topical dosage forms, Purified Water USP is used. Because of the requirement for nonpyrogenicity, Water for Injection USP is used for intraocular products. While a mineral oil and petrolatum combination is the vehicle used for ophthalmic

ointments, nonaqueous liquids are rarely used in topical eye drops because of their potential for ocular irritation and poor patient tolerance. Some mineral and vegetable oils have served as vehicles for very moisture-sensitive or poorly water-soluble drugs. Use of the purest grade of oil, such as that used for parenteral products, is a requirement.

Multiple-dose topical ophthalmic products commonly contain microbiological preservatives, which will be discussed in a later section. Other commonly used additives in topical eye products are ingredients to adjust pH and tonicity, and to buffer pH, in addition to the viscosity agents previously discussed. Ingredients to adjust pH and tonicity and to buffer pH are essentially the same as those used in parenteral products. Less commonly used additives are antioxidants, such as sodium bisulfite, ascorbic acid, and acetylcysteine.

Topical eye products sometimes incorporate surfactants to disperse insoluble ingredients or to aid in solubilization. Formulators use them in the smallest concentration possible to achieve the desired function, because they can be irritating to sensitive ocular tissues. Nonionic surfactants are preferable, because they are generally less irritating than ionic surfactants. Polysorbate 80 is the surfactant used to prepare an ophthalmic emulsion. Polyoxyl 40 stearate and polyethylene glycol function to solubilize a drug in an anhydrous ointment so that it can be filter-sterilized. Formulators often add surfactants to stabilize more hydrophobic drugs, for example, preventing loss to adsorption on the container walls. For example, the nonionic surfactant like polyoxyl 40 hydrogenated castor oil (HCO-40) stabilizes travoprost, a prostaglandin derivative.⁵⁷ Similarly, Cremophore EL stabilizes diclofenac in the Voltaren formulation marketed by Novartis.

The FDA has published a list of all inactive ingredients used in approved drug products on its Internet website at www.fda.gov/ocder. The list includes dosage forms and concentration ranges.

PACKAGING

Currently, almost all commercially available ophthalmic products are packaged in plastic containers. Obvious advantages—ease of use, little breakage, less spillage—have led to universal acceptance of these plastic packaging components, consisting of bottle, fitment, and closure. Alcon was the first company to introduce these packaging components, identified as a DropTainer for ophthalmic products, in the late 1940s and then saw them adopted by the industry as the standard for packaging topical ophthalmic products. These bottles are generally of low-density polyethylene, either without any colorants or with opacifying agents or other colorants for light protection. Polypropylene or high-density polyethylene resins are also used to meet specific product requirements. The fitments determine drop size of the product and may contain additional features to prevent streaming of product at the time of use. Caps or closures are generally made from polypropylene and basically seal the container to prevent contamination or leakage of the product.

The FDA and other health authorities are also concerned about leachable impurities extracted either from the packaging components themselves or even occasionally from the label adhesives or ink used in printing the labels. Normally, as a part of a stability program, actual package-formulation compatibility studies are required, including monitoring any extractables that come out in the product as a function of the duration of storage. Selection of compatible packaging material has become a critical issue for newer drug products, especially those in which the concentration of active is extremely low, like prostaglandins, described earlier. The prostaglandin travoprost, the active ingredient in Travatan, required reengineering of the total packaging, starting with the resin (syndiotactic polypropylene) to stabilize the drug, as well as altering size and shape to maintain squeezability of the bottle.⁵⁸ Travoprost was found not to be stable when stored in low-density polyethylene containers, the compound being lost to adsorption onto and into surfaces,

even at room temperature. Consequently, chemical assay of marketed product must be conducted in a manner that does not deplete the concentration.

Specialized containers, like those developed by Merck for their timolol/pilocarpine combination product, maintain two solutions in different chambers, adjusted separately to provide optimal chemical stability. At the time of dispensing the product, fractions of both solutions are combined and reconstituted by the pharmacist. For example, the final timolol/pilocarpine product, once reconstituted, would be at a nearly physiological pH, would provide pilocarpine as stable for one month at room temperature, and will be found comfortable to patients. Alcon also has developed a proprietary package⁵⁹ that can keep unstable or reactive components separate during storage, and that permits the pharmacist, at the time of dispensing to the patient, to rupture a diaphragm, allowing the disparate fractions to be mixed. After mixing, the product is expected to remain stable for a month at room temperature. This container is designed to handle either liquid/liquid two-part or solid/liquid two-part components.

Pharmacists also should be aware of unit-dose products currently available in form-fill-seal containers that are preservative free. These products are discarded after single use. These products are most suited for patients who are sensitive or allergic to common preservatives and require chronic administration of a product. Specialized manufacturing technology involves melting a plastic resin to form the container walls, filling with the drug solution (usually 0.2 to 0.8 mL), and then sealing to maintain sterility. At the time of use the tip is broken off, the solution is dosed, and then the package is discarded. For technical reasons relating to manufacturing and filling capabilities, as well as for the need to minimize evaporation rate, these containers contain an excess volume of the product. The disadvantage is that patients may desire to use the entire volume and risk using an accidentally contaminated product. Recently, some unit-dose containers have been modified to allow the product to be recapped after use. These containers are designed and labeled to be discarded after a single day's use (12 hours) in order to reduce the risk of significant contamination, yet make them more economical for the patient.

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 or flexible bags. Type 1 glass vials with appropriate stoppers are used for intraocular ophthalmic products administered by injection. These packaging components should meet the same requirements as parenteral products. Products injected intraocularly also are required to meet endotoxin limits. Readers should refer to Chapter 41, Parenteral Preparations, and Chapter 42, Pharmaceutical Compounding – USP <797> Sterile Preparations for more details.

Plastic packaging, usually low-density polyethylene, is by no means interchangeable with glass, however. Plastic packaging is permeable to a variety of substances, including light and air. The plastic package may contain a variety of extraneous substances such as mold-release agents, antioxidants, reaction quenchers, and the like, which may leach out of the plastic and into the contained solution. Label glues, inks, and dyes also may penetrate polyethylene. Conversely, confined volatile or lipophilic materials may permeate from solution into or through plastic walls. Sterilization, depending on the method, may influence the resin properties; for example, gamma irradiation may increase acid extractables or generate sites that may degrade certain drugs. For these products EtO gas sterilization may be the only remaining option. However, gas sterilization also may degrade active molecules or leave harmful residuals, and certainly requires aeration under forced air to remove the traces of the gas and volatile residues. Whatever process is selected will need to be validated and monitored, assuring the process neither degrades the active ingredient nor generates toxic residues.

Teaching
away?

Table 43-1. Ophthalmic Cap Color Coding

Color	Pharmaceutical Class
Yellow or blue	β -blockers
Gray	Nonsteroids
Pink	Steroids
Brown or tan	Anti-infectives
Orange	Carbonic anhydrase inhibitors
Turquoise	Prostaglandins
Red	Mydriatics
Green	Miotics

Patients may be prescribed more than one ophthalmic medication for the same or different conditions, and this can lead to confusion as to which medication is for which use. Historically, red caps have been used for mydriatic drops and green caps for miotic drops, such as pilocarpine. The FDA now requires the use of certain colored caps on several additional types of ophthalmic drugs as a result of a cooperative effort between the FDA, the ophthalmic industry, and the Academy of Ophthalmology. The intent is to help patients prevent medication errors and improve patient compliance. The pharmacist should counsel the patient or caregiver about the purpose of the cap color coding and the importance of opening only one container at a time so that the cap is replaced on the correct container. A listing of the current coding is provided in Table 43-1.

Glass containers (using type 1 glass) remain a convenient package material for extemporaneous preparation of ophthalmic solutions. Type 1 glass should be used. The container, well rinsed with sterile distilled water, can also be sterilized by autoclaving. Presterilized droppers normally are available, presterilized and packaged in a convenient blister pack.

Invariably, packaging of ophthalmic ointments consists of metal tubes with an ophthalmic tip. Autoclaving with either heat or EtO can conveniently sterilize such tubes. In rare cases of metal reactivity or incompatibility, it may be necessary to package ointments in tubes lined with epoxy or vinyl plastic.

Regardless of the form of packaging, consumer protection requires that some type of tamper-evident feature be included. The common tamper-evident feature used on most ophthalmic preparations is the moisture- or heat-sensitive shrink band. Some form of identification on the band should be present, so that its disruption or absence constitutes 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. Use of an eyecup will inevitably spread or aggravate eye infections. Pharmacists should discourage their use, just as they should take the time to instruct patients in the proper use and care of eye medications. While ophthalmic administration may seem simple enough, it can be a foreign and difficult task for many people. The suggestions and precautions given earlier (under Types of Ophthalmic Dosage Forms) may be useful in instructing patients.

ANTIMICROBIAL PRESERVATIVES⁶⁰

A preservative is a substance or mixture of substances added to a product formulation to prevent the growth of, or to destroy, microorganisms introduced accidentally once the container is opened for use.^{61,62} Addition of the preservative is not intended to be a means of preparing a sterile solution, for which other appropriate techniques exist (discussed elsewhere).

Preservatives are used for topical ophthalmic products packaged in multiple-dose containers unless the formulation itself is self-preserving, as is the case with some antimicrobial products, like the ophthalmic solution Vigamox (moxifloxacin). FDA regulations (21 CFR 200.50) allow unpreserved ophthalmic liquid

products to be packaged in multiple-dose containers only if they are packaged and labeled in a manner that affords adequate protection and minimizes the hazards resulting from accidental contamination during patient use. This can be accomplished by using a reclosable container with a minimum number of doses, which is to be discarded after 12 hours from initial opening and which should be labeled appropriately.

Solutions intended for intraocular use should not contain preservatives because of the risk of irritation and damage to these delicate tissues. Medicines intended for chronic topical applications in patients who cannot tolerate preservatives should also be free of preservatives. Unit-dose ophthalmic solutions are especially useful for patients with sensitivity to preservatives who nevertheless require daily medication, such as glaucoma patients or individuals requiring chronic application of palliatives for dry eye. Ophthalmic solutions prepared and packaged for a single application (i.e., a unit dose) need not contain a preservative, because they are not intended for reuse.

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

The selection of an ophthalmic preservative can be difficult 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, being 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 *Ps. aeruginosa* strains.
2. The agent should be stable over a wide range of conditions, including autoclaving temperatures and pH range.
3. Other components of the preparation as well package systems should be compatible with the agent.
4. The preservative should cause neither toxicity nor irritation, within a reasonable margin of safety.

Only through evaluating preservative substances can as a part of the total ophthalmic preparation in the proposed package can producers establish the adequacy of the preservative. Criteria for preservative effectiveness in ophthalmic products are official compendial requirements in the *US Pharmacopeia*, *European Pharmacopoeia*, and the *Japanese Pharmacopoeia*. Health authorities expect that products will meet these preservative effectiveness criteria throughout their approved shelf-lives, in the final packaging, and at the recommended storage conditions.²⁻⁴

In addition to its effectiveness as an immediate measure, formulators must also ascertain a preservative's adequacy or stability as a function of time. They often accomplish this by measuring both chemical stability and preservative effectiveness over a given period of time and under varying conditions.

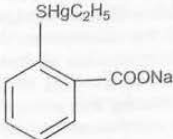
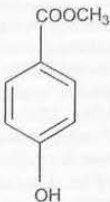
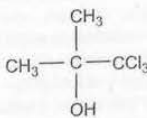
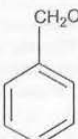
Many of these test procedures are not totally applicable to the preparation of an extemporaneous ophthalmic solution. In such a situation the pharmacist must make selections based upon known conditions and physical and chemical characteristics, guided by those used in commercial ophthalmic preparations. In these circumstances it would be prudent to prepare only minimum volumes for short-term patient use.

The choice of preservatives suitable for ophthalmic use is surprisingly narrow. The classes of compounds available for such use are described in Table 43-2.⁶³ In each case or category there are specific limitations and shortcomings.

QUATERNARY AMMONIUM COMPOUNDS

Benzalkonium chloride (BAC) is a typical quaternary ammonium compound and is the most common preservative used in ophthalmic preparations, being present in over 65 percent of commercial ophthalmic products. Note the structure of BAC is

Table 43-2. Ophthalmic Preservatives⁶³

Type	Typical Structure	Concentration Range	Incompatibilities
Quaternary ammonium compounds	$\left[\begin{array}{c} R_2 \\ \\ R_1 - N^+ - R_1 \\ \\ R_1 \end{array} \right] Y^-$	0.004–0.02 %, 0.01% most common	Soaps Anionic materials Salicylates Nitrates
Organic mercurials (thimerosal example)		0.001–0.01%	Certain halides with phenylmercuric salts
Parahydroxy benzoates (methyl ester example)		Maximum 0.1%	Adsorption by macromolecules; marginal activity
Chlorobutanol		0.5 %	Stability is pH-dependent; activity concentration is near solubility
Aromatic alcohols		0.5–0.9 %	Low solubility in water; marginal activity

a slight departure from the general one provided in Table 43-2 in which there are three small alkyl chains on one longer alkyl chain (the R's). For BAC one of the R1's is a benzyl group. Despite its widespread 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, BAC has excellent chemical stability and very good antimicrobial characteristics. Given the alternatives, it is often better to modify a formulation to eliminate the incompatibility than to include a compatible but less effective preservative. The presence of a surfactant, for example, may require higher levels of BAC to achieve an adequate level of preservation.

The literature on BAC is somewhat mixed; however, this is to be expected given the wide variation in test methods and, indeed, the chemical variability of BAC itself. The official substance is defined as a mixture of alkyl benzyldimethylammonium chlorides, including all or some of the group ranging from $n\text{-C}_8\text{H}_{17}$ through $n\text{-C}_{16}\text{H}_{33}$. The $n\text{-C}_{12}\text{H}_{25}$ homologue content is at least 40 percent on an anhydrous basis.

Reviews⁶⁴ of BAC indicate that it is well suited for use as an ophthalmic preservative. Certain early negative reports have been shown to be erroneous; in some cases adverse tissue reactions were attributed to BAC when, in fact, a totally different compound was used as the test material. Although BAC is the most common quaternary preservative, others occasionally mentioned include benzethonium chloride and cetyl pyridinium chloride. All are official compounds. More recently,

quaternary ammonium functionality has been attached to soluble, reasonably high-molecular-weight polymers. These agents possess good antimicrobial effectiveness with fewer compatibility problems than the official quaternary preservatives.

Search for milder, safer, gentler preservatives for ophthalmic products, specifically artificial-tear and chronic-use products, has been a challenge for many companies. As a result of this research, some commercial products now incorporate these improved agents as preservatives. Alcon has introduced many lens care and ophthalmic products preserved with polyquaternium-1 (polyquad), a newer preservative of the same class as BAC but with less cytotoxicity. More effective than BAC, these agents also are effective at a lower concentration. Their concentration in the product can range from 0.005 percent to 0.0005 percent and yet still meet compendial preservative efficacy requirements. Polyquad has been used widely in many lens care and artificial-tear products.

OXIDIZING AGENTS

Systems based on either sodium perborate or a stabilized oxychloro complex are being used as preservatives based on their ability to generate a mild oxidative and cytotoxic effect in aqueous media. Sodium perborate produces hydrogen peroxide as the oxidative species, and the stabilized oxychloro complex is a mixture of oxychloro species but primarily comprises chlorite and a trace of chlorine dioxide. Once in the eye, the active agents in either system are spontaneously reduced to harmless by-products and have been marketed as so-called disappearing preservatives in OTC products for dry eye treatment.

ORGANIC MERCURIALS

It is generally stated that phenylmercuric nitrate or phenylmercuric acetate, in 0.002 percent concentration, should replace BAC as a preservative for salicylates and nitrates, and in solutions of salts of physostigmine and epinephrine that contain 0.1 percent sodium sulfite. The preferred range of concentrations employed is 0.002 to 0.004 percent. Phenylmercuric borate sometimes is used in place of the nitrate or acetate.

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

The effectiveness of phenylmercuric nitrate against *Ps. aeruginosa* is questionable; researchers have found that pseudomonads survive after exposure to a concentration of 0.004 percent for longer than a week.

Development of iatrogenic mercury deposits in the crystalline lens has occurred, resulting from use of miotic eyedrops containing 0.004 percent phenylmercuric nitrate, three times daily, for periods of 3 to 6 years. Although there was no impairment of vision, the yellowish brown discoloration of the lens capsule is reportedly permanent.

Thimerosal (Merthiolate; Lilly) is an organomercurial with bacteriostatic and antifungal activity that functions as an antimicrobial preservative in concentrations of 0.005 to 0.02 percent. Its action, as with other mercurials, has been reportedly slow.

PARAHYDROXYBENZOIC ACID ESTERS

Mixtures of methylparaben and propylparaben are sometimes used, as antimicrobial preservatives, mostly in ophthalmic ointments; the preferred maximum concentration of methylparaben is in the range of 0.1 percent, its NOEL, while that of propylparaben approaches its solubility in water (>0.04 percent). 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.

SUBSTITUTED ALCOHOLS AND PHENOLS

Chlorobutanol is reportedly effective against both Gram-positive and Gram-negative organisms, including *Ps. aeruginosa* and some fungi. It is broadly compatible with other ingredients, and manufacturers normally choose a concentration of 0.5 percent. 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, and generally packaged in glass containers. At room temperature it dissolves slowly in water, and although heat dissolves it more rapidly, loss by vaporization and decomposition is accelerated.

A combination of chlorobutanol and phenylethyl alcohol (0.5 percent of each) has been reported to be more effective against *Ps. aeruginosa*, *Staphylococcus aureus*, and *Proteus vulgaris* than either antimicrobial singly. In addition, dissolving chlorobutanol in phenylethyl alcohol before dissolution in water eliminates the need to heat the solution.

OTC PRODUCTS FOR DRY EYE

Dry eye is a condition that can be either an annoying irritation in its mild form or a painful and destructive pathology in its severe form, damaging the corneal surface and interfering with vision. Possible causes of dry eye include decreased tear production, increased tear evaporation rate, or an abnormality of the tear film that decreases its natural capacity to protect and lubricate the epithelial tissues. It is one of the most common

complaints of patients seeking treatment from their eye-care doctor. This condition is somewhat unique in that it is largely treated with OTC monograph drug products, and the pharmacist is often asked to assist in its selection.⁶⁵ These products are variously known as artificial tears, ocular lubricants, demulcents, or emollients, and are available as solutions, gels, or ointments. Also unique is that these dry eye products are often the essential viscous-vehicle component of therapeutic ophthalmic products. Several reference books include the compositions of the various commercial dry eye products.^{33,34}

OTC dry eye products contain water-soluble polymers as active ingredients that protect and lubricate the mucous membrane surfaces of the conjunctiva and cornea, providing temporary relief of the symptoms of dryness and irritation. The polymers thicken the tear film and decrease the rate of tear loss in addition to lubricating and protecting the tissues. Mucin is a natural lubricating component of tears, and thus, dry eye products are expected to provide a mucomimetic effect. The active-ingredient demulcent (lubricant) polymers in these products, along with their permitted concentrations and labeling, are defined in an OTC monograph issued by the FDA.⁶⁶ The monograph does not specify viscosity grades, and therefore, a wide range of product viscosities is available. The more viscous products can provide longer duration of relief; however, they are also more likely to blur vision and leave a residue of polymer on the eyelids. The OTC products vary in their choice of polymer or combination of polymers, concentrations, and viscosity. The majority of OTC dry eye products contain one or more of the following permitted polymers: celluloses such as hydroxypropyl methylcellulose (hypromellose) or carboxymethylcellulose sodium; polyol liquids such as glycerin, polyethylene glycol, or polysorbate 80; polyvinyl alcohol; or povidone. Dextran 70 can be used only in combination with another permitted demulcent polymer.

The inactive components of OTC dry eye products are similar to those used in therapeutic ophthalmic products and require equally careful selection, keeping in mind that the monograph products are labeled for use as often as needed and thus must be nonirritating and physiologically compatible. In the moderate to severe forms of dry eye, the product may be dosed as often as every hour, and in the especially severe cases, as often as every 15 minutes. The preferred vehicle is aqueous for replenishing natural tears and dissolving the active and inactive ingredients. The vehicle is usually adjusted to be isotonic with sodium chloride, and in some cases other salts are used as well as nonionic ingredients, such as dextrose and mannitol. Some cases of dry eye have been reported to produce tears that are hypertonic, and several products feature a slightly hypotonic formula to restore the natural tear osmotic pressure. The products generally are adjusted or buffered to provide a pH of about 7.4, but rarely outside of the range of about 7.0 to 8.0.

Storage of solutions of some polymers, notably polyvinyl alcohol, can lead to a more acidic pH. The preservative chlorobutanol also produces an acidic pH as it degrades in solution. The bicarbonate included in some products is a more physiologically compatible buffer that requires a hermetically sealed secondary package for stability. Some products include both monovalent and divalent chloride salts in their vehicles in an attempt to mimic the electrolyte composition of natural tears.

The majority of dry eye products contain a preservative and are packaged in multiple-dose plastic ophthalmic containers. As in therapeutic products, BAC is the most widely used preservative. Newer preservatives having improved compatibility with ocular tissues, such as Polyquad, are increasingly in use, as well as the "disappearing" preservatives sodium perborate and Purite. Sodium perborate forms hydrogen peroxide, which can be irritating in the eye but quickly degrades to oxygen and water. Purite is a stabilized oxychloro complex that degrades to sodium chloride and water when exposed to long-wavelength ultraviolet light.

Preservative-free products are also available and are gaining popularity, particularly for patients with chronic dry eye

conditions and those who are sensitive to preservatives. These products are packaged in form-fill-seal unit-dose containers, but manufacturing considerations dictate that they contain enough product for several doses while bearing labels indicating that they are to be discarded after a single dose. This problem has led to the introduction of a modified package with a reclosable cap allowing its use as a small-volume multiple-dose container for preservative-free products when for safety reasons they are labeled to be discarded no longer than 12 hours after first opening.

The large majority of dry eye products are solution dosage forms administered as eyedrops, but gel-like and ointment dosage forms are also available. People who suffer with dry eye or who have a defect in lid closing that causes increased tear evaporation benefit from the these ointments, which consist primarily of a mixture of petrolatum and mineral oil that imparts emollient properties. Lanolin is sometimes added to the base to provide some water miscibility. The ratio of oils can be varied for consistency and melting temperature. Patients primarily use the ointments as a night-time medication, because they usually cause a blurring of vision. Several products bearing labels identifying them as gels or liquid gels are aqueous-based dosage forms containing one or more of the permitted lubricant polymers. The gel dosage form identifier is used to designate a more viscous product; however, the dosage directions read the same as for the eyedrop products (instill one or two drops as needed), as this dosage statement is the only one permitted for dry eye products marketed using the permitted lubricant polymers under the OTC monograph.

One disadvantage of most OTC dry eye products is their relatively short duration of effect. Several products have become available that incorporate novel delivery system technology into these products to prolong the duration of the lubricant and protectant effects of the monograph active ingredients. One product, AquaSite,⁶⁷ incorporates the polymer polycarboxyl, and in a more recent product, Systane,⁶⁸ a modified hydroxypropyl guar polymer forms a gel-like matrix when the product components interact with the tear fluid.

CONTACT LENSES AND THEIR CARE

HISTORICAL BACKGROUND⁶⁹⁻⁷¹

Evidence suggests that the concept of altering corneal power was first envisioned by Leonardo da Vinci early in the sixteenth century. In the next century, more than a hundred years later, René Descartes described a device, a glass-filled tube in direct contact with the cornea, capable of implementing this concept, though it prohibited blinking and so was not a practical solution. In the early nineteenth century the British astronomer Sir John Herschel described the mathematics of these devices and proposed a means of treating very irregular corneas by using a glass capsule filled with a gelatin solution. Not until 1888 was the original concept executed by the artificial-eye maker, Albert Müller. 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.

But perhaps the first contact lenses, scleral lenses resting on the bulbar conjunctiva beyond the limbal ring, were fabricated and fit by the German ophthalmologist A.E. Fick, working in Zurich late in the nineteenth century. Contact lenses without scleral portions (corneal lenses) were in existence at least as early as 1912, when they were manufactured by Carl Zeiss. Glass prostheses produced by Fick and others, while conceptually a step forward, suffer from reasonably rapid deterioration in the tear fluid. However, they had the advantage that the glass was readily wetted by tears.

Experimentation in the twentieth century led J. Dallos, working in Budapest, to perceive the importance of tear flow underneath the contact lens. Dallos also took impressions of

human eyes to improve the fidelity of the ground lens to the shape of the cornea. The first contact lenses, scleral lenses made of plastic in the late 1930s with polymethyl methacrylate (PMMA) from Rohm and Haas, are attributed to W. Mullen and T. Obrig. The advantages of durability and weight reduction far outweighed the slight differences in optical properties. And in 1948, K. Tuohy filed a patent for a plastic corneal contact lens. With the advent of PMMA, a flush-fitting shell became possible, a concept developed in England in the 1950s by Ridley. The first corneal lenses to have any measure of commercial success were developed in the early 1950s by F. Dickinson and W. Sohnges. Its thickness was about 0.2 mm, considered to be fairly thick. Thinner lenses, of about 0.1 mm, were introduced in the early 1960s.

The first soft contact lenses consisted of silicone, an elastomer nearly devoid of water but with good permeability to oxygen and carbon dioxide. However, the first soft contact lenses to be commercialized were of hydroxyethyl methacrylate hydrogels, developed by O. Wichterle and D. Lim in Czechoslovakia in the early 1960s. Continuous improvements have progressed to the present day, including milestones such as silicone acrylate rigid gas-permeable (RGP) lenses in the 1970s, disposable inexpensive lenses in the 1980s, and daily disposable and silicone hydrogel lenses in the 1990s.

With the advent of commercialized, relatively comfortable, inexpensive corneal contact lenses, the need for lens care products developed beginning in the 1950s and, as summarized below, a great variety of functionality now exists, depending on the requirements of the individual products.

From a regulatory perspective, during the period from their approval by the FDCA of 1938 until the US Medical Device Amendments to the FDCA of 1976, contact lenses and contact lens care products were regulated as drugs. Although during this period a device was defined in the FDCA, many medical devices were thought to be "used for the cure, mitigation, or prevention of disease," leading to their classification as drugs. With increased activity in industry and significance of biomedical devices in maintaining health, congressional awareness arose regarding the advantages for greater regulation. The amendments made provision for three classes of device, with different requirements for each. Those with least risk were assigned to class I, and those associated with increasing risk, to a progressively higher class. If safety and efficacy of a device could be reasonably assured by "general controls" (including restrictions on design, production, storage, maintenance, and use), then the device was assigned to class I, which may be exempted from the requirement for a 510(k) (the section of the FDCA that allows for clearance of class II medical devices; see later) but still require company or product registrations. Under the 1976 amendments to the FDCA, contact lenses and lens care products were reclassified as class III devices, requiring a premarket approval application and approval by the FDA before marketing.

However, by 1990, following years of experience with certain devices in the marketplace and recognition that little purpose was being served duplicating regulatory investigation of substantially equivalent safe and effective devices, Congress passed new legislation. The US Safe Medical Devices Act of 1990 authorized reclassification of certain contact lens and lens care products as class II devices, requiring special controls in the form of a 510(k) submission and clearance. The products covered by this reclassification include solutions, dry products, tablets, and disinfecting units used in caring for and disinfecting soft (hydrophilic) and RGP contact lenses. In March 1994, the down-classification of two types of daily-wear contact lenses, from class III to class II, was implemented by a rule in the *Federal Register*. In July of 1997 a similar down-classification of certain contact lens care products, including multipurpose solutions and in-eye contact lens solutions, was implemented by a rule in the *Federal Register*. Extended-wear contact lenses remain governed by class III regulations.

Table 43-3. 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 methacrylate)	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
	Silicone vinylpyrrolidone	Good gas permeability; good wettability	Soaking solutions
Rigid, hydrophilic	CAB (cellulose acetate butyrate)	Good gas permeability; good wettability	Wetting solutions Cleaning solutions Soaking solutions Rewetting solutions

CONTACT LENSES, CURRENT ART

As a consequence of these years of development, the consumer currently can choose from an enormous selection of contact lenses and lens materials. There are basically four classes of lenses, and the identification of these classes is both by polymer type and lens characteristics: hard contact lenses, RGP contact lenses, soft hydrophilic contact lenses, and silicone-based flexible hydrophobic lenses. These classes are summarized in Table 43-3. Hard contact lenses are generally fabricated from PMMA or polysilicone acrylate polymers or co-polymer blends containing one of these materials. RGP contact lenses are generally consist of more polarizable and oxygen-permeable materials such as cellulose acetate butyrate, *t*-butyl styrene, or silicone polymers or co-polymers. These lenses generally provide visual acuity superior to that of the more flexible soft contact lenses. The US Adopted Names (USAN) designates these hydrophobic lens types with less than 10 percent water by the suffix *focon*. However, RGP lenses have a low oxygen permeability and so should be removed and cleaned after a day's wear; moreover, because of greater lens awareness, especially a new wearer, should wear them routinely (i.e., not intermittently). They are durable, however, and so may be preferred because the replacement schedule is extended. RGP lenses with higher oxygen transmissibility tend to be preferred, especially in comparison with hard contact lenses, because the improved exchange of gases assists in maintaining the health of the cornea.

The third class of contact lenses, soft hydrophilic lenses, is fabricated from such a wide variety of materials and their blends that the FDA has grouped them according to two parameters, ionicity and water content (either low or high, less than or greater than 50 percent water):

- Group I includes the nonionic polymers of low water content, such as polyacon, a simple poly(hydroxyethyl methacrylate) (HEMA),
- Group II includes the nonionic polymers of high water content, such as alphafileon A (a co-polymer of five monomeric units: HEMA, vinyl pyrrolidone, ethylene dimethacrylate, hydroxycyclohexyl methacrylate, and a substituted vinyl carbonate),
- Group III includes ionic polymers of low water content, such as bufileon (a terpolymer of HEMA, dimethyl oxobutyl acrylamide, and the trimethacrylate ester of ethyl *t*-butane triol with some level of hydrolysis of the esters to the free acid) or ocufilcon A (a terpolymer with HEMA, methacrylic acid, and ethylene dimethacrylate), and
- Group IV includes ionic polymers of high water content, such as a higher water content ocufilcon B/C or etafileon (a terpolymer of HEMA, the salt of methacrylic acid, and the trimethacrylate ester of ethyl *t*-butane triol).

The final class of contact lenses, considered either a group of harder soft lenses or a group of softer RGP lenses with high oxygen solubility and transmission, is that of the silicone hydrogel lenses. These silicone and fluorosilicone materials are candidates for continuous extended-wear applications.

Such diverse functionalities provide distinct properties in addition to water content, ranging from oxygen and metabolite transport, hardness, and flexibility, through processability, to durability and stability. More complete lists of the materials used in contact lens manufacture are available, but in general the USAN Council designates these hydrophilic lens types with greater than 10 percent water by the suffix *filcon*.⁷²⁻⁷⁴ While the nomenclature adequately distinguishes monomer components, and the alphabetical trailing designation indicates differences in ratios of monomer units, one must remember that differences in crosslinker (often ethylene glycol dimethacrylate), initiator, catalyst, filler, or color additive are not delineated.

While this is a reasonable overview of the categories of choices for the materials composing contact lenses, it is still an incomplete list with regard to the properties that concern both the consumer and his or her practitioner in selecting a contact lens. In addition to the chemical composition, the following choices are necessary: (1) duration of wear (daily vs. continuous), (2) lens replacement schedule (daily vs. biweekly vs. monthly vs. quarterly), (3) lens design (spherical, toric, orbifocal), (4) colored or clear, (5) means of manufacture (lathe-cut or cast-molded), (5) edge design (which can affect lens motion, overall fit, comfort, and acuity) and lens thickness, (6) fitting characteristics, like the selection available for base curves and lens diameter, and (7) any surface treatment or conditioning. With this multiplicity of choices and the subtlety of competing requirements, the recommendation of the practitioner is vital.

But ultimately, the consumer's personal metrics—comfort, convenience, and cost—also remain significant factors in lens selection rates. For example, patients with drier eyes are more likely to prefer group I lenses.

In addition to their use in vision correction, soft contact lenses, like collagen shields, find occasional use for therapeutic purposes, serving as bandages providing protection in treatment of bullous keratopathy (or other forms of corneal edema or other corneal irregularities or sources of cicatrization) or for lid abnormalities, and with ulcers, chemical burns, grafts, or dry eye. They are also efficacious in sustaining the delivery of therapeutic agents, as discussed previously. Patients will have to care for lenses that are used for these therapeutic purposes with the same preparations as those needed for lenses prescribed for refractive correction.

In summary, both doctors and consumers of contact lenses have a broad range of alternatives. Current lens materials and

the solutions to maintain them (next section) provide a wide selection of properties suitable for individual ocular health requirements and preferences.

CONTACT LENS CARE PRODUCTS

General Considerations

With the previous two sections for background, we are ready to discuss those preparations produced for the care of contact lenses. For all of the specialized solutions to be discussed, it is generally necessary (1) to adjust pH, tonicity (osmolality), surface and interfacial tensions, and viscosity; (2) preserve and maintain sterility; (3) assure stability and shelf-life; and (4) package and sterilize appropriately. In the United States these solutions are class II medical devices.⁷¹

Wetting Solutions

These are lubricating and cushioning preparations designed to furnish a 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 effects may be obtained from a single compound. Agents commonly used include cellulose derivatives, polyvinyl pyrrolidone, polyvinyl alcohol, and polyethylene glycol derivatives. The need for surface-active agents, which facilitate wetting of lenses and spreading of tears, is greater for hard contact lenses because of their hydrophobic surface characteristics. Preservatives include those acceptable for ophthalmic use, including polyquad and a polyhexyl-methylene biguanide, called PHMB or DYMED.

Cleaning Solutions

Cleaning solutions commonly are used to remove surface contaminants—lipids, protein, organic salts, and the like. Cleaning is accomplished by the use of surfactants that preferably are nonionic or amphoteric. Viscosity-imparting agents generally are not included. Some cleaning agents also include a mild abrasive: silica for RGPs or plastic particles for soft lenses.

Adequate cleaning of hydrophilic lenses is a far more complex and challenging problem than for hard-lens cleaning. Because of their permeability characteristics, contaminants penetrate into the lens structure and may bind chemically or physically to the HEMA or ionic portions of the 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 clearance, 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 must be softer than the lens itself. Adequate daily cleaning of hydrophilic lens material can enhance disinfection but in some cases may not be necessary, given the choices of today's powerful disinfecting solutions and enzymatic cleaners, available in either a tableted or liquid form. Most recently, daily-wear planned-replacement lenses have found wide acceptance. Conventionally their successful use is reliant on enzymatic cleaning together with special disinfectants. However, extended-wear lenses, soiling at a lower rate, require only rewetting drops.

The significance of adequate cleaning cannot be overstated. Improperly or inadequately cleaned and maintained lenses are perhaps the most important contributors to complications associated with the wear of contact lenses such as discomfort, loss of visual acuity, conjunctivitis, and keratitis.

There are two types of cleaning solutions, daily and weekly cleaners. Weekly-cleaning solutions may include proteolytic enzymes like subtilisin, or a broad-spectrum less toxic enzyme like pancreatin (which contains protease, lipase, and amylase activity), or concentrated surfactants. Daily-cleaning solutions achieve cleaning using less aggressive surface-active agents and polymers, often nonionic but nonsolubilizing agents that will be

less toxic if carried over into the eye. Examples include Tween 20 or 80 (types of polysorbate detergents) and tyloxapols (surfactants). A daily cleaning solution even containing a nontoxic enzyme is available (SupraClens).

The goal is to provide thorough cleaning of the lenses for the benefits described previous without causing any degradation of the lenses.

Disinfecting Systems

Disinfection of the first hydrophilic lens approved by the FDA was accomplished using a heating device that generated steam from a saline solution. The latter was either prepared by the user or available from the manufacturer. Subsequent to the so-called thermal systems, requiring heating at 80°C for 10 minutes, disinfection solutions were developed that met the requirements for FDA approval while not damaging the more delicate soft lens materials. 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 BAC. Once again, however, the use of a quaternary disinfectant covalently bonded to a soluble, relatively high-molecular-weight polymer has met with some success. These have to a large extent replaced chemical antimicrobial agents like sorbic acid, thimerosal (containing mercury), and hydrogen peroxide, among many others. Perhaps the most common in current use are a cationic polymer, polyquad, and a polyhexylmethylene biguanide.

In addition to possessing satisfactory disinfecting activity, such a preparation must be isotonic, be in an acceptable pH range, be 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, serve in storage and hydration of hard or RGP lenses but, most importantly, in disinfection of 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. Soaking solutions are intended to be rinsed off lenses before insertion.

Rewetting Solutions

Solutions intended to rewet hard or RGP lenses *in situ* are referred to as rewetting solutions or lubricating drops. 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 instillation into the eye. More recent preparations mimic tears more accurately, and their viscosity may be rather low, to improve user acceptability, or adjusted to be responsive and to improve retention and duration of the wetting characteristics.

Multipurpose Solutions

By combining the actions of two or more of the solutions just described, these products simplify regimens, improve compliance, generally increase the comfort of contact lens products, and greatly increase the convenience of using contact lenses. For soft contact lenses, multipurpose solutions have to combine only the functions of cleaning and disinfection, whereas a complete multipurpose solution for a hard or RGP lens must also provide some level of wetting. Suffice it to say that these solutions, which contain an intricate balance of ingredients, have grown in popularity significantly because of the greatly increased level of convenience they provide. Their efficacy often precludes the need for separate cleaning solutions for many patients.

GUIDELINES FOR SAFETY AND EFFICACY TESTING

The FDA periodically issues or updates guidelines describing recommended test procedures for contact lens care products. The reader is advised to review the most recent guidelines for appropriate requirements.

Current guidelines cover all lens care products. Applicable guidelines are determined by the type of product (e.g., saline solution, cleaning solution, multipurpose solution, and rewetting drops) and the claim (e.g., disinfection in a regimen as opposed to a stand-alone process). Safety testing includes determinations of cytotoxicity, oral toxicity, potential for sensitization, and single to multiple exposure in an animal (rabbit) eye. The tests designated depend on the active ingredient (e.g., if it is a new entity or has been in previous products) and its concentration (e.g., if it is the same or different from that used in a currently approved product). Efficacy of preservation, disinfection, and cleaning, compatibility with lens or lens types, and clinical trials are also required, with their type and scope dependent on product type, characteristics, ingredients, and claims.

SUMMARY

There has been considerable progress in ophthalmic pharmaceuticals and in lens care products during the last decade. Very substantial advances have occurred in designing vehicles and packaging for highly potent active ingredients presented at very low concentrations; in increasing ophthalmic bioavailability and controlling factors influencing ophthalmic drug absorption; in the design of implants and means of delivering them for providing therapeutic agents to the retina and other deep ophthalmic tissues; and in devising robust yet delicately balanced multipurpose solutions for contact lens wearers. Continuing advances in the general field of ophthalmic pharmaceuticals and pharmacokinetics can be expected to assist in maintaining and improving ocular health.

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