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Chapter 13

Design and Evaluation of Ophthalmic Pharmaceutical Products

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I. INTRODUCTION

Any modern text on the design and evaluation of therapeutic products must place into unique perspective the nature of the eye and requirements of ophthalmic dosage forms. The eye, perhaps better than any other bodily organ, serves as a model structure for the evaluation of drug activity. In no other organ can a practitioner, without surgical or mechanical intervention, so well observe the activity of an administered drug. With such modern instrumentation as the biomicroscope (Fig. 1), the specular microscope (Fig. 2), the confocal microscope capable of viewing the single-layered corneal endothelium, and various devices for measuring intraocular pressure, blood flow, and electroretinal response, the ophthalmologist can readily track changes in ocular structures from the cornea to the retina and monitor their function and physiology. In so doing, the ophthalmologist and diagnostic scientist often detect signs of ocular or systemic disease long before sight-threatening or certain general health-threatening disease states become intractable. With such specialized instrumentation, the practitioner can view the activity of the drug product on the entire eye or, for those products administered to the internal structure of the eye, the activity or effect of the drug product on a cell, a group of cells, or entire tissues.

Ophthalmic pharmaceutical dosage forms serve as delivery vehicles for a wide range of drugs with pharmacological activity in the eye. The most commonly employed ophthalmic dosage forms are solutions, suspensions, and ointments. The characteristics essential for each of these dosage forms have been generally defined in the United States Pharmacopeia (USP) and will be expanded upon in this chapter. Also included are the newest dosage forms for ophthalmic drug delivery—gels, gel-forming solutions, ocular inserts or systems, intravitreal injections, and implants. Common to all ophthalmic dosage forms is the critical requirement for sterility of the finished product as well as appreciation for the sensitivity of ocular tissue to irritation and toxicity and the inherent limitations in topical ocular absorption of most drugs. As will be seen, these are primary factors in the design and evaluation of all ophthalmic pharmaceutical products.

The USP has numerous requirements, e.g., "ophthalmic solutions [need be] essentially free from foreign particles, suitably compounded and packaged for instillation into the eye," or "ophthalmic suspensions [need contain] solid particles dispersed in liquid vehicle intended for application to the eye" [1]. Ophthalmic suspensions are required to be made with the insoluble drug in a micronized form to prevent irritation or scratching of the cornea. A finished ophthalmic ointment must be free from large particles and must meet the requirements for "leakage" and for "metal particles" under "ophthalmic ointments". These and other requirements will be discussed further in subsequent sections.

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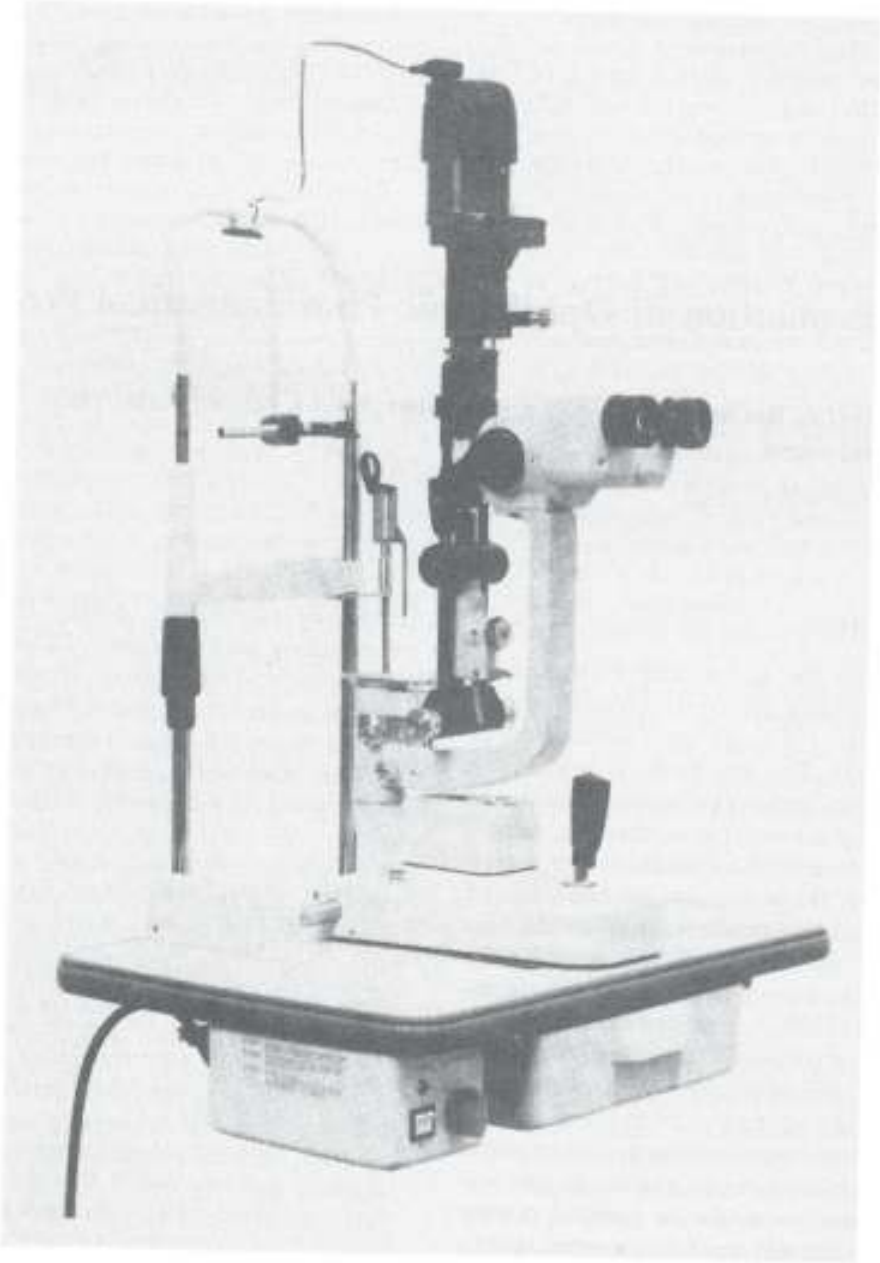

Fig. 1 Topcon slit-lamp biomicroscope.

Behind the relatively straightforward compositional nature of ophthalmic solutions, suspensions, and ointments, however, lie many of the same physicochemical parameters that affect drug stability, safety, and efficacy, as they do for most other drug products. But additionally, specialized dosage forms present the ophthalmic product designer with some extraordinary compositional and manufacturing challenges. These range from concerns for sterility and consistency of parenteral-type ophthalmic solutions for intraocular, subtenon, and retrobulbar use, to resuspendability of such insoluble substances as dexamethasone or fluorometholone, to reconstitution, creating for the patient an apparently conventional solution for compounds such as acetylcholine chloride and epinephrine bitartrate, whose shelf life depends on storage conditions.

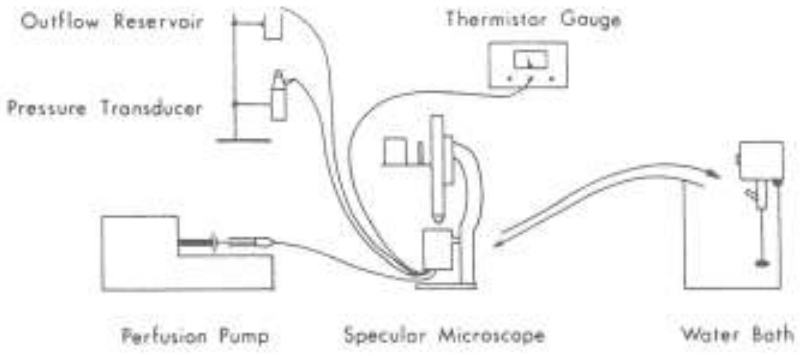

Fig. 2 Specular microscope setup for in vitro evaluation of effect of drugs on ocular tissue.

More recently, the challenge to formulate with consistency highly potent actives present in diminishingly low concentrations raised the bar for formulations another significant notch. Procedures and devices for safe intravitreal implantation of sustained antiviral medication have grown from the advent of new therapies for a life- and eye-threatening new disease, HIV-AIDS.

Like most other products in the medical armamentarium, ophthalmic products are currently undergoing *optimization*. New modes of delivering a drug to the eye are being actively explored, ranging from solid, hydrophobic, or hydrophilic devices that are inserted into the ophthalmic cul-de-sac, to conventionally applied dosage forms that, owing to their formulation characteristics, markedly increase the drug residence time in the fornix of the eye, thereby providing drug for absorption for prolonged periods and reducing the frequency that a given drug product must be administered. Intermediate between these alternatives, in both their physical state and effect on duration, are responsive polymeric systems that undergo transitions from liquid to gel or semisolid [2–7].

In as much as products for the diagnosis and treatment of ocular disease cover the spectrum of practically all dosage forms and, thus, require the same pharmaceutical sciences for their development, in this chapter we discuss the entire scope of considerations involved in the development of ophthalmic products, ranging from regulatory and compendial requirements, through physicochemical, safety, and efficacy considerations, to a discussion of types of dosage forms currently used by the medical practitioner.

The final consideration, but by no means a minor one, is the design and evaluation of contact lens care products, which are regulated by the U.S. Food and Drug Administration (FDA) as medical devices since they are accessory products necessary for the safe and effective use of contact lenses to correct visual acuity. These products include formulations for rinsing, storing, cleaning, and disinfecting contact lenses with specialized compositions for each major type of lens material, i.e., hard, soft hydrophilic, and rigid gas-permeable lenses. Also, lens care products for use in the eye as comfort drops while wearing contact lenses have been developed from similar products using lubricating polymers for treatment of minor eye irritation and tear deficiency (dry eye). The pharmaceutical scientist designing lens care products and improved ophthalmic drug dosage forms have taken advantage of advances in polymer and biomaterial sciences as is evident in the following sections.

II. HISTORICAL BACKGROUND

"If a physician performed a major operation on a seignior [a nobleman] with a bronze lancet and has saved the seignior's life, or he opened the eye socket of seignior with a bronze lancet and has saved the seignior's eye, he shall receive ten shekels of silver." But if the physician in so doing "has caused the seignior's death, or has destroyed the seignior's eye, they shall cut off his hand." The foregoing excerpts are from 2 of 282 laws of King Hammurabi's Code, engraved about 100 B.C. in a block of polished black igneous stone about 2.7 m high, now permanently preserved at the Louvre [8].

Mention is made of the Code of Hammurabi only to place in human history that period when reference to eye medicines or poultices was beginning to appear. The Sumerians, in southern Mesopotamia, are considered to be the first to record their history, beginning about 3100 B.C. The Egyptians used copper compounds, such as malachite and chrysocalla, as green

eye makeup with, no doubt, some beneficial effect against infection, owing to the antibacterial properties of copper [9]. The standard wound salve of the Smith Papyrus (approximately 1700 B.C.)—grease, honey and lint—probably served as one of the earliest ointments or ointment bases for the treatment of eye disease or wounds. The Greeks expanded on this basic salve to arrive at a typical enaimon (enheme), a drug for fresh wounds, which might have contained copper, lead, or alum, in addition to myrrh and frankincense [10]. The use of the aromatic substance myrrh in the form of sticks, blocks, or probes has been documented and attributed to the Romans and Greeks. Such sticks were called *collyria* and were dissolved in water, milk, or egg white for use as eyedrops. The Latin word *collyrium* is a derivative of the Greek word, *kollyrien* (in turn derived from *kollyra*, a roll of coarse bread), meaning a glutinous paste made from wheat and water that was rolled into thin cones, rods, or blocks. Often the physician's name was inscribed on these bodies [11]. Pliney the Elder (ca. A.D. 23–79) advocated the use of egg whites to "cool" inflamed eyes, and lycium, one of the most popular of the plant extracts of India, was recommended especially for "eye troubles" [12].

After having placed the origin of at least two dosage forms (solution and ointment) for treating disorders or wounds of the eye between approximately the first and second millennium B.C., we can readily reflect on the progress that the designers of dosage forms for eye products have made down through the ages—until relatively recently, little or none. Over the past two decades, however, we have begun to see new concepts emerging, some receiving the enthusiastic support of the ophthalmologist and optometrist, whereas others, not so fortunate, have been relegated to the status of little-used novelties.

III. ANATOMY OF THE EYE AND ADNEXA

In-depth discussions of the anatomy of the eye and adnexa have been adequately covered elsewhere in the pharmaceutical literature [13–17] and in recent texts on ocular anatomy. Here a brief overview is presented of the critical anatomical features that influence the nature and administration of ophthalmic preparations. In this discussion, consideration will be given primarily to drugs applied topically, that is, onto the cornea or conjunctiva or into the palpebral fornices. Increasingly, drugs are being developed for administration by parenteral-type dosage forms subconjunctivally, into the anterior and posterior chambers, the vitreous chamber, Tenon's capsule, or by retrobulbar injection.

Table 1 Anatomical Structures of the Eye

Conjunctiva	Iris
Inferior conjunctival sac	Uvea
Superior conjunctival sac	Posterior chamber
	Zonules of Zinn
Cornea	Lens
Epithelium	Vitreous humor
Bowman's membrane	
Stroma (substantia propria)	Tenon's capsule
Descemet's membrane	Retina
Endothelium	Ciliary body (zone)
	Meibomian glands
Anterior chamber	
Angle of anterior chamber	Posterior chamber
Schlemm's canal	Vitreous chamber
Spaces of fontana	
Retina	

Because some of the dosage forms described may be considered as adjunctive to ophthalmic surgical procedures, those procedures and the concomitant use of the drug are described in Sec. VIII.D. For orientation, readers are encouraged to familiarize themselves with the anatomical structures of the eye (Table 1), some of which are shown in Fig. 3.

The eye is essentially a globe suspended in the ocular orbit, specialized for sight through an arrangement of multiple tissues that function to focus, transmit, and detect incoming light. There is a central path that light travels to the retina, with all intervening tissues (cornea, aqueous humor, pupil, lens, and vitreous humor) being transparent. All surrounding tissues serve to nourish, support, and protect these essential structures.

The cornea composes only one sixth of the outer surface of the eye, yet it is the first and one of the most important barriers to external materials. The cornea is composed of three layers of varying structural and chemical properties that form barriers based on solubility, polarity and partitioning properties, molecular weight and geometry, and specific binding characteristics. The presence and type of intercellular junctions regulate molecular diffusion around the cells, while the hydrophilic or lipophilic characteristic of each layer controls diffusion across and along the cell membrane. The cornea itself has no blood vessels so it relies on passive diffusion of nutrients from surrounding tissues and aqueous humor.

The outermost layer, the epithelium, is composed of five to seven layers of stratified epithelial cells that makeup only 10% (50 μm) of the total corneal

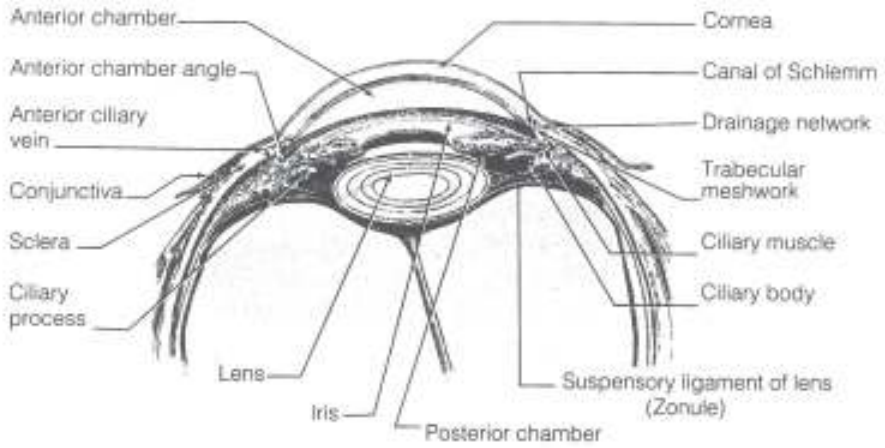

Fig. 3 Anatomical cross section of the human eye.

thickness. Basal cells of the epithelium are mitotically active, providing a regular supply of cells to replenish those lost through normal sloughing or injury. The tight junctions and lipophilic composition of the epithelium combine to form an effective barrier to molecules and foreign substances that are hydrophilic or of high molecular weight. The tears, composed of mucin, aqueous and lipid phases, serve to hydrate the epithelium, prevent adhesion of bacteria and other foreign materials, and influence the distribution and toxicity of foreign materials [18]. Finally, the epithelium is metabolically highly active against xenobiotics; while protective against toxic substances, this activity may also impact drug bioavailability and therapeutic index significantly. Bowman's membrane separates the epithelium from the stroma, the layer that comprises 90% of the cornea.

In contrast to the epithelium, the stroma is 76–80% water and composed mostly of collagen fibrils in a highly organized array with interstices filled with glucosaminoglycan ground substance and a scattering of keratocytes. No junctions are present, yet the hydrophilic composition presents a significant barrier to lipophilic molecules. The stroma is susceptible to swelling, and water content must be actively controlled to prevent opacification. This is a primary function of the endothelium, a single layer of hexagonally arranged cells separated from the stroma by Decemet's membrane. Since the corneal endothelial cells have discontinuous tight junctions, water readily passes from the aqueous humor across to the stroma. To counter this, cellular ion pumps maintain proper hydration of the stroma by active transport of ions out into the aqueous humor with water following the ionic gradient through passive diffusion. These "leaky" junctions may present a constant hazard of overhydration to the stroma and present little or no barrier to drug penetration, but are essential to the diffusion of nutrients from the aqueous humor into the cornea. The endothelium has an overall lipophilic nature that limits diffusion of hydrophilic molecules. It is important to note that the human endothelium has a fixed number of cells that are not mitotically active, instead compensating for cell loss only through migration and hypertrophy of individual cells to cover gaps in the layer. Inability to compensate for cell loss will result in loss of function and corneal opacification. Since endothelial cells are sensitive to chemical and mechanical insult, any ophthalmic preparation that could contact these cells must be carefully evaluated for biocompatibility.

The cornea is connected at the limbus to the opaque sclera, the tough fibroelastic capsule that encloses the eye and provides support and protection for the interior structures. The visible area of the sclera is generally referred to as the conjunctiva. The stroma has loosely packed collagen fibrils with scattered fibrocytes and few blood vessels except in the limbal area. No junctional complexes are present, so the sclera presents only a lipophilic barrier to foreign materials. The limbus is rich in blood vessels, and systemic absorption of topically applied drugs occurs here primarily. Within the interior of the eye, the limbal area contains the trabecular meshwork and canal of Schlemm at the junction of the iris and sclera. These structures drain aqueous humor from the anterior chamber, a function essential to prevent fluid accumulation, increased intraocular pressure, and glaucoma. The iris, a ring of

muscular tissue that regulates light entry into the back of the eye through the pupil, is located in front of the lens and physically forms the division between the anterior chamber and the posterior chamber. This structure is rich in blood vessels, which dilate when exposed to severe irritants resulting in iridial hyperemia and edema. The innervation of the iris provides the means by which the practitioner can control pupillary dilation.

The lens is essentially a flattened sphere that is held in place and connected to the ciliary body by fiber-like strands, the zonules of Zinn. Composed of concentric layers of crystalline fibers, the avascular lens has a single layer of epithelial cells on the anterior surface and is surrounded by a thin but tough capsule that conveniently provides the support for an intraocular lens (IOL) once a cataractous lens has been removed. The lens epithelial cells have some mitotic activity, and older cells progressively lose their cellular contents and migrate to form the crystalline fibers. The lens is flexible and changes shape in order to adjust focal length for near objects (accommodation), an ability that is lost with age. It is important to note that there is little exchange of materials in the lens and no loss of cells so that drug accumulation should be investigated for ophthalmic preparations that are absorbed into the eye. The ciliary body has two major functions. The ciliary muscle connects to the zonules of Zinn and controls lens accommodation. The anterior portion of the ciliary body facing the posterior chamber produces the aqueous humor that circulates across and through the pupil to the anterior chamber and out of the eye for a continual turnover of fluid.

Behind the lens is the vitreous chamber that contains vitreous humor, a transparent gelatinous material that has no turnover and is in direct contact with the retina. The retina is a bilayered highly metabolically active tissue that transforms light to an electrical signal, which is processed and transmitted as electronic images to the brain. The tissue is composed of a complex arrangement of photoreceptor cells (rods and cones) overlying the retinal pigmented epithelium (RPE) and is isolated from vascular fluids by the blood-retinal barrier, a combination of endothelial cell tight junctions lining the retinal blood vessels and tight junctions between the RPE cells that restricts diffusion from the systemic circulation. The choroid is a highly vascularized collagenous tissue lying between the retina and the sclera from the ciliary body to the optic nerve. The optic nerve connects to the retina at the optic disk, a highly vascularized area that is susceptible to ocular hypertension and drug effects. Finally, several accessory tissues (adnexa) are essential to proper functioning of the eye. Tenon's capsule, a thin membrane surrounding the sclera, separates the eye from the surrounding socket for freedom of movement. The lacrimal and Meibomian glands provide essential tear and lipid components while the eyelids assist in tear distribution and protect against mechanical injury.

From this discussion, the reader can appreciate the intricacy of the eye and the care required in devising ophthalmic preparations in order to provide safe and effective therapy.

IV. PHARMACOLOGY AND THERAPEUTICS OF OPHTHALMIC MEDICATION

It is not the purpose of this text to present an in-depth review of the pharmacology of ophthalmic drugs. For this purpose the reader is referred to one of the authoritative treatments of this subject [19–21]. However, since this topic is not commonly covered in pharmacy school curricula, a brief treatment is presented here. For the most part, drugs used in the eye fall into one of several categories, including miotics, mydriatics (with or without cycloplegic activity), cycloplegics, anti-inflammatories, anti-infectives (including antibiotics, antivirals, and antibacterials), antiglaucoma drugs, surgical adjuncts, diagnostics, and a category of drugs for miscellaneous uses. The intended ophthalmic use will define more precisely what drug or combination of drugs is to be used, the appropriate dosage form, and route of administration. For example, the practitioner will, with knowledge of certain contraindications, use mydriatic drugs specifically for their pupillary and accommodative effects, both in the process of refraction and in the management of iridocyclitis, iritis, accommodative exotropia, and so on. Atropine, homatropine, scopolamine, tropicamide, and cyclopentolate are examples of parasympathomimetic drugs possessing mydriatic and cycloplegic activity, whereas phenylephrine and epinephrine are examples of sympathomimetic drugs possessing only mydriatic activity.

Drugs that may be chosen for use in the management of glaucoma may be topically applied miotics, such as pilocarpine hydrochloride or nitrate, carbachol, echothiophate iodide, or demecarium bromide; epinephrine prodrugs like dipivefrin hydrochloride, nonselective β-adrenergic blocking agents such as timolol maleate and bunolol hydrochloride, and selective β-adrenergic blocking agents such as racemic- or the more potent *levo*-betaxolol hydrochloride, compounds devoid of pupillary effect; topically administered carbonic anhydrase inhibitors, such as

dorzolamide and brinzolamide; prostaglandin analogs of the class $PGF_{2\alpha}$, such as latanoprost and travoprost, capable of lowering intraocular pressure (IOP) significantly with little or no inflammatory or vasodilatory response; or they may be orally administered drugs to present an osmotic effect that will lower intraocular pressure, such as 50% glycerin or 45% isosorbide. Other drugs administered orally to lower intraocular pressure are the carbonic anhydrous inhibitors acetazolamide and methazolamide. Furthermore, the miotic drugs may be chosen to reverse the effect of mydriatics after refraction or during surgical procedures such as cataract removal. There is now available an antimydriatic drug devoid of pupillary activity, dapiprazole hydrochloride, which is gaining importance in the reversal of the effect of mydriatics.

Depending on the location of ocular inflammation, a specific corticosteroid in a specific dosage form may be chosen. For instance, a corticosteroid of high potency, such as prednisolone acetate, fluorometholone, dexamethasone, or rimexolone, may be chosen for deep-seated inflammation of the uveal tract. Further treatment of such inflammation may take the form of subtenon injections or oral (systemic) administration of selected corticosteroids, depending on the indication and the dosage forms available. For inflammation of a more superficial nature, the lower strengths of prednisolone acetate or the lower-potency corticosteroids, such as hydrocortisone or medrysone, will usually be chosen. It is now also possible to treat inflammation with nonsteroidal agents like diclofenac or keterolac, drugs not expected to raise IOP.

Drugs used for the treatment of ocular infection will generally be chosen based on the presumptive diagnosis of the causative agent by the ophthalmologist. Laboratory confirmation by microbial culture and identification is routinely conducted concurrently with the initiation of therapy. This is generally necessary because of the severity and sight-threatening nature of some types of infection. For example, if a patient has a foreign body lodged in the cornea originating from a potentially contaminated environment, the physician may choose to begin treatment of the eye, after foreign body removal, with a single or combination antibiotic, such as gentamicin, tobramycin, chloramphenicol, and a neomycin-polymyxin combination. Recent introduction of quinolone antibiotics like ciprofloxacin, ofloxacin, and norfloxacin have expanded the physician's choice of available products for ocular infections. The application of these agents is considered appropriate, since an infection with *Pseudomonas aeruginosa* can destroy a cornea in 24–48 hours, generally the time it takes to identify an infectious agent. Less fulminating, but no less dangerous, are infections caused by various staphylococcal and streptococcal organisms. For superficial bacterial infections of the conjunctiva and eyelids, sulfonamides, such as sodium sulfacetamide, are usually prescribed, as are yellow mercuric oxide and mild silver protein. Prophylactic therapy for ophthalmia neonaturnum is nearly universally required in the United States, with silver nitrate, penicillin G, or erythromycin being the primary anti-infectives used. Pre- and postsurgical prophylaxis is becoming more commonplace with the popularity of surgically corrected vision, and combinations of anti-infectives with anti-inflammatory agents are frequently used to reduce surgical trauma to the eye.

For fungal and viral infections, there are very few agents that the ophthalmologist can prescribe. These organisms' resistance and similarity to mammalian tissue make it difficult to find effective and safe therapies. For instance, idoxuridine, a selective metabolic inhibitor, has been shown to be useful against herpes simplex virus infection of the cornea. For the trachoma virus and viruses that cause inclusion conjunctivitis [i.e., TRIC (the single largest cause of blindness worldwide)], no specific antiviral agent has demonstrated satisfactory activity, and the secondary bacterial ramifications of this disease are managed by conventional antibiotics, such as tetracycline, chloramphenicol, and erythromycin. The trachoma virus itself seems to be somewhat susceptible to these antibiotics; however, up to 6 weeks of treatment three times per day are required to achieve an 80% cure rate [22,23].

A similar situation exists for the treatment of fungal keratitis. The antifungal antibiotic drugs nystatin and natamycin have been effective to varying degrees in superficial fungal infection, as have copper sulfate and sodium sulfacetamide [24,25]. For both of these drugs iontophoresis of the topically administered drug produces enhanced activities.

Drugs used as surgical adjuncts are primarily irrigating solutions, solutions of proteolytic enzymes, viscoelastics and miotics employed in cataract removal, intraocular lens placement, vitrectomy, and procedures to preserve retinal integrity. These drugs are considered true parenteral dosage forms, the design and evaluation of which are discussed in greater detail elsewhere in this chapter.

Diagnostic drugs, such as sodium fluorescein, are administered topically or intravenously to aid in the diagnosis of such conditions as corneal abrasions or ulceration and various retinopathies. This agent has become the most widely used diagnostic agent in the

practice of ophthalmology and optometry. Rose bengal has also been used topically, although to a far lesser degree than sodium fluorescein, which is available as well-preserved alkaline solutions in concentrations ranging from 0.5 to 2.0% [26,27], as fluorescein-impregnated absorbent sterile paper strips [28], or as unpreserved, terminally sterilized intravenous injections in concentrations ranging from 5 to 25% [29].

Several topically applied local anesthetics are routinely used by the eye care specialist in certain routine diagnostic procedures and for various relatively simple surgical procedures such as insertion of punctal plugs and surgical vision correction. The first of these to be used was cocaine, in concentrations ranging from 1 to 4% [30]. More modern local anesthetics, however, such as tetracaine hydrochloride and proparacaine hydrochloride, have replaced cocaine as drugs of choice in these procedures. For surgical procedures of a more complex nature, lidocaine hydrochloride and similar local anesthetics as retrobulbar injections have been used [31].

The foregoing overview has presented the major classes of ophthalmic drugs. One additional class of drugs that merits brief discussion includes drugs used for the treatment of various dry eye syndromes. The most severe of these, *keratoconjunctivitis sicca*, involves diminished secretion of mucins, consisting of glycoproteins and glycosaminoglycans and their complexes. These materials serve to coat the corneal epithelium with a hydrophilic layer that uniformly attracts water molecules, resulting in even hydration of the corneal surface. Diminished secretion of these substances causes dry spots to develop on the cornea, resulting in corneal dehydration, which can lead to ulceration, scarring, or corneal opacities [32]. Modern pharmaceutical products are available (Hypotears, Tears Naturale Forte) that contain mucomimetic high molecular weight polymers that serve to resurface the cornea temporarily, thereby preventing the aforementioned dehydration and affording the dry eye sufferer with a degree of relief previously unavailable [33,34]. These agents are not pharmacologically active, although recent research leads to the promise of drugs that will stimulate tear production for longer-term relief.

V. GENERAL SAFETY CONSIDERATIONS

A. Sterility

Every ophthalmic product must be manufactured under conditions validated to render it sterile in its final container for the shelf life of the product [35,36]. Sterility testing is conducted on each lot of ophthalmic product by suitable procedures, as set forth in the appropriate pharmacopeia and validated in each manufacturer's laboratory. While the majority of ophthalmic preparations contain preservatives for multiple-dose use, sterile preparations in special containers for individual use on a single patient must be made available. This availability is especially critical for every hospital, office, or other installation where accidentally or surgically traumatized eyes are treated, as well as for patients intolerant to preservatives.

The USP recognizes six methods of achieving a sterile product: (a) steam sterilization, (b) dry-heat sterilization, (c) gas sterilization, (d) sterilization by ionizing radiation, (e) sterilization by filtration, and (f) aseptic processing [37]. For ophthalmic products packaged in plastic containers, typical for ophthalmic products, a combination of two or more of these six methods is used routinely. For example, for a sterile ophthalmic suspension, bottles, dropper tips, and caps may be sterilized by ethylene oxide or gamma radiation; the suspended solid may be sterilized by dry heat, gamma radiation, or ethylene oxide; and the aqueous portion of the composition may be sterilized by filtration. The compounding is completed under aseptic conditions.

One can see by the complexity of these types of manufacturing procedures that much care and attention to detail must be maintained by the manufacturer. This sterile manufacturing procedure must then be validated to prove that no more than 3 containers in a lot of 3000 containers (0.1%) are nonsterile. Ultimately, it is the manufacturer's responsibility to ensure the safety and efficacy of the manufacturing process and the absence of any adverse effect on the product, such as the possible formation of substances toxic to the eye, an ever-present possibility with gas sterilization or when using ionizing radiation. For ophthalmic products sterilized by terminal sterilization (sterilization in the final sealed container, e.g., steam under pressure), the sterilization cycle must be validated to ensure sterility at a probability of 10^6 or greater.

Currently, the *British Pharmacopoeia* suggests five methods of sterilization: (a) sterilization by autoclaving, (b) dry-heat sterilization, usually to >60°C, (c) ethylene oxide, (d) ionizing radiation (electron accelerator or gamma radiation), and (e) sterilization by filtration. During the manufacture of an ophthalmic product, sterility may be checked while the finished product is in its bulk form before filling. It is then also tested on a random sampling basis in the finished package. Suggested guidelines for the number of

samples are dependent on whether or not sterilization has taken place in the sealed final container. While terminal sterilization (methods a–d) is preferred, sterilization by filtration and aseptic processing have been accepted for preparations that are incompatible with other methods. Class A products are those sterilized in bulk form and filled aseptically into sterile final containers without further sterilization. Class B products are those sterilized in sealed final containers. Class B is further subdivided according to method of sterilization: type 1 comprises those products sterilized by steam under pressure; type 2 comprises those products sterilized by any other means. Class A products require a minimum random sample number of no fewer than 30 items from each filling operation. Class B products require varying sample sizes, generally from 5 to 30 units per lot, depending on whether the sterilization occurs in a chamber or by a continuous process.

B. Ocular Toxicity and Irritation

Assessment of the potential for ocular irritation and toxicity of ophthalmic solutions represents an extremely important step in the development of both over-the-counter (OTC) and prescriptive pharmaceuticals. Excellent reviews of procedures describing these evaluations have been published [38–40,90]. Refinements in procedures, study design, use of objective measures, and standardization of noninvasive methods such as specular microscopy have resulted in greater reliability, detection, and predictability. In addition, the incorporation of structure-activity relationship (SAR) evaluations provides an early assessment of probable toxic effects of the chemical moieties under consideration. The historical evaluation of these procedures can be traced through the literature [41–50], as can an understanding of the mechanisms of ocular response to irritants, based on examination of the conjunctiva [51–54], the cornea [42,55–57], or the iris [42,58,120]. Advances in design and use of ophthalmic drugs and devices have brought ocular toxicity into sharper focus. Many interior structures of the eye adjacent to target tissues, or which are targets of newer therapies themselves, can suffer irreversible damage so safety evaluations must be comprehensive. In general, consideration must also be given to the use of various ophthalmic preparations with other drugs and devices. Testing, therefore, must be based on risk analysis to include both the intended uses of the product as well as reasonably foreseeable misuse.

Albino rabbits have been the primary species used to test ocular toxicity and irritation of ophthalmic formulations. While recent debate has centered on the use of rabbits or other species as predictors for human responses, there is consensus that there is no more reliable model that captures the full complexity of the eye and the ocular response of its intricate biochemical and physiological processes. In addition, the albino rabbit has obvious advantages due to its availability, ease of handling, ease of maintenance, and large prominent unpigmented eye. The ocular structures are easily observed and accessible, including the cornea, bulbar conjunctival iridial vessels, and posterior segment [39]. The primary differences between rabbits and humans in ophthalmic studies relate to decreased tearing in rabbits, decreased blinking rate, presence of lipid from a species-specific gland (Harderian gland), loosely attached eyelids, presence of a nictitating membrane [53,59–61], differences in the structure of Bowman's membrane, slower reepithelialization of the rabbit cornea [42], and regenerative endothelium of the rabbit. The corneal differences result in increased ocular response to irritants in the rabbit. The primate has gained in popularity as an ocular model for the evaluation of drugs and chemicals because it is more similar to human eye [59,60]. However, due to the difficulty and risk inherent in their care and handling, primates are used secondarily and in cases where other species may not provide an accurate assessment. This is especially true for drugs with melanin-binding characteristics that may accumulate in a pigmented iris.

Various governmental agencies have published guidelines for ocular irritancy studies [61,62,77]. These guidelines are directed toward ophthalmic formulations, chemicals, cosmetics, extractables from ophthalmic containers, and other materials that may intentionally or accidentally contact the eye during use. It is the manufacturer's responsibility to determine those studies specifically appropriate for testing the safety of the ophthalmic formulation, yet abiding by general governmental guidelines. The USP presents guidelines for a 72-hour ocular irritation test in rabbits using saline and cottonseed oil extracts of plastic containers used for packaging ophthalmic products. Containers are cleaned and sterilized as in the final packaged product to determine acceptability of the packaging system.

As a part of the Federal Hazardous Substances Act (FHSA), a modified Draize test was adopted [63–65] as the official method for evaluation of acute ocular irritancy [66]. It is a pass/fail determination that remains in effect today. Two refinements have been accepted as alternatives: (a) the test which uses a small volume more consistent with the capacity of the inferior con-

junctival sac [67], and (b) assessment of the degree, frequency, and duration of ocular changes using biomicroscopic slit-lamp examination and/or fluorescein staining [39,64,65]. While various in vitro tests have been proposed to replace this in vivo evaluation, none has yet been accepted or validated [68–70].

Current guidelines for toxicity evaluation of ophthalmic formulations involve both single and multiple applications, dependent on the proposed clinical use [39]. The multiple applications may extend over a 9-month period and incorporate evaluations of ocular irritation and toxicity, systemic toxicity, and determinations of systemic exposure (toxicokinetics). In many cases the systemic exposure from an ocular route is less than by parenteral administration, information that will assist in determining whether additional studies may be needed to establish systemic safety of the ophthalmic preparation. U.S. and international guidance documents are available [71,72], and regulations and tests have been summarized for ophthalmic preparations [39,73,74].

As mentioned previously (and discussed in detail in Sec. IX), contact lens products have specific guidelines that focus on compatibility with the contact lens and biocompatibility with the cornea and conjunctiva [75]. These solutions are viewed as new medical devices and require testing with the contact lenses with which they are to be used. Tests include a 21-day ocular study in rabbits and employ the appropriate types of contact lenses with which they are to be used and may include the other solutions that might be used with the lens. Additional tests to evaluate cytotoxicity potential, acute toxicity, sensitization potential (allergenicity), and risks specific to the preparation are also required [75–77]. These tests are sufficient to meet requirements in the majority of countries, though testing requirements for Japan are currently much more extensive.

While systemic exposure is rarely encountered in intraocularly administered drug products, there are safety concerns related to the biocompatibility of these products with ocular tissues. These products have special design and evaluation concerns, since a product instilled into the anterior chamber may contact for up to 2 hours such essential and delicate tissues as the endothelium and trabecular meshwork [78]. For such drug products, it is mandatory to design specific testing that mimics this length of exposure. Methods may include ex vivo models that continuously infuse the specific product composition, both freshly made and aged, into the anterior chamber of excised rabbit eyes for prolonged periods. Judgments for product-tissue compatibility can then be made by observing corneal endothelium with specular microscopy [79] and histopathology. These materials can also be evaluated against specific cell lines in tissue culture, particularly corneal endothelial tissue. As tissue culture technology progresses, cell lines for the other tissues in the anterior segment of the eye are being established and will become useful in tissue compatibility testing as well.

The sensitivity of the intraocular tissues places certain restrictions on intraocular dosage forms. In general, preparations that incorporate fewer ingredients in a properly balanced solution will have less likelihood of tissue incompatibility. This is not to say that a simple solution of drug in water is optimal. Indeed, a simple isotonic solution of sodium chloride is toxic to human corneal epithelial, endothelial, iris, and conjunctival cells, whereas a solution properly balanced with various organic and inorganic ions and nutrients is nontoxic to these cells in vitro and in vivo. In the electron photomicrographs of human corneal endothelium presented in Figs. 4–6, the effect of solution composition on tissue integrity is illustrated. Figure 4 shows human corneal endothelial tissue after corneal perfusion for 3 hours with lactated Ringer's solution, while Fig. 5 illustrates the same tissue perfused for 3 hours with Ringer's solution containing glutathione, adenosine, and bicarbonate. In the former, cell darkening and swelling are in evidence, whereas in the latter, normal cell confluence is retained. Fig. 6 shows the same tissue after a 3-hour perfusion with a solution devoid of ingredients essential for normal cell confluence. The discontinuity of cell structure is quite evident.

Other agents commonly used in topical ocular drugs can be used only sparingly or not at all for intraocular use. The preservative agents commonly used in topical ophthalmic preparations are not compatible with the tissues of the anterior segments of the eye and in several cell lines in tissue culture [80]. The USP recognizes this problem and specifically warns against their use in intraocular solutions [81,82]. Drug stabilizers, such as antioxidants and chelating agents, must be used with care and should be used in absolutely minimal quantities only when necessary. Occasionally, it may seem desirable to solubilize an otherwise sparingly soluble ingredient. Whereas this may be a practical consideration in some injectables, only aqueous solutions should be employed intraocularly. Furthermore, only fairly low concentrations of typical cosolvents such as glycerin and propylene glycol can be employed because of their osmotic effect on the surrounding tissues. Hyperosmotic solutions may elicit some transient desiccation of the anterior chamber tissues, whereas hy-

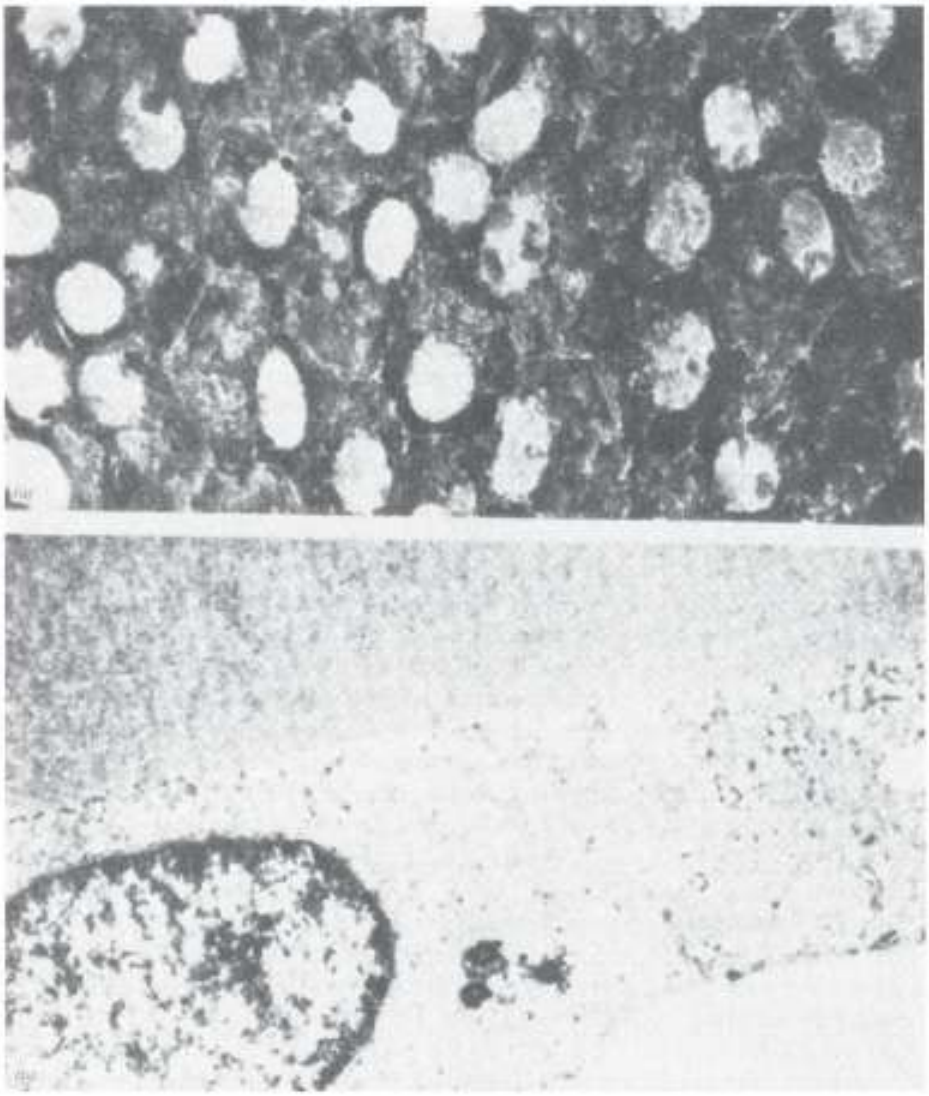

Fig. 4 Human corneal endothelium following 3-hour perfusion with lactated Ringer's solution: (a) scanning electron micrograph (2100 ×); (b) transmission electron micrograph (9100 ×). (Courtesy of H. Edelhauser.)

potonic solutions may cause edema that could lead to corneal clouding. There appears to be little or no experience with these or other common cosolvents in products of this type, and their use should be avoided.

Another formulation variable that must be considered is that of the solution pH and buffer capacity. Since the anterior chamber fluid (aqueous humor) contains essentially the same buffering systems as the blood, products with a pH outside the physiological range of 7.0–7.4 are converted to this range by the buffering capacity of the aqueous humor if a relatively small volume of the solution is introduced. Often, however, aqueous humor is lost in the procedure or the volume of solution is relatively large, therefore, drug products should be formulated as closely as possible to this physiological range although the use of buffering agents should be avoided if possible.

The question of particulate matter is also of great importance. Although the total effect of particulate inclusion in the anterior chamber is not completely known, some possible results have been postulated [82]. Certain amounts of iritis and uveitis might be expected, as well as the production of granulomas similar to the type reported for pulmonary tissue that

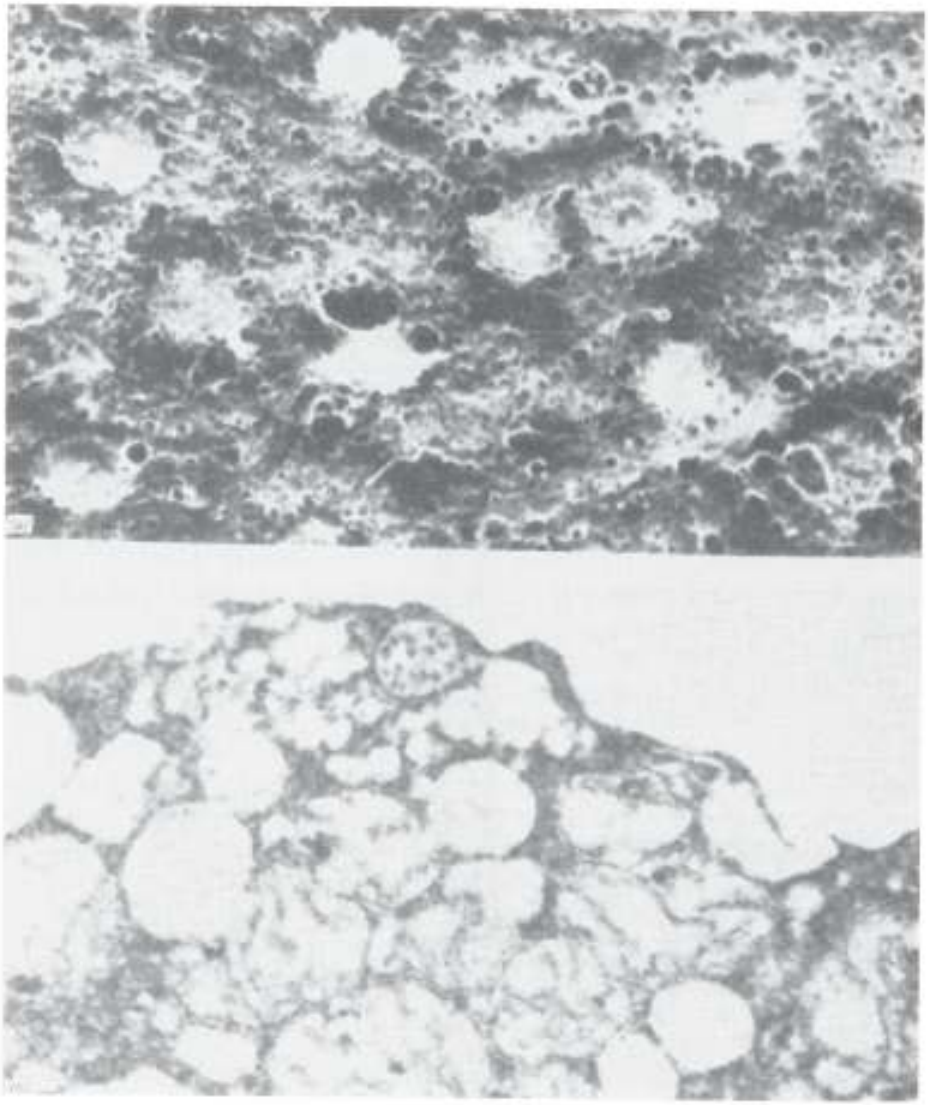

Fig. 5 Human corneal endothelium following 3-hour perfusion with glutathione bicarbonated Ringer's solution: (a) scanning electron micrograph (1950 ×); (b) transmission electron micrograph (8450 ×). (Courtesy of H. Edelhauser.)

results from particulates in large-volume parenterals. At least as important is the possibility that particulate matter can block the canals of Schlemm, which provide the outflow mechanism for the aqueous humor. If this should occur to any great extent, the normal continual production of aqueous humor could lead to a rapid increase in intraocular pressure and the onset of an acute attack of glaucoma. The formulator should be aware that particulates may originate from raw materials as well as glass fragments produced in glass ampoule fracture or elastomeric particles generated during stopper penetration. Very specialized stopper design, cleaning procedures, and lubrication should be considered when the latter type of packaging is used.

To provide a complete assessment of all these variables, the final evaluation of safety must be made in the in vivo model using the preparation under the proposed conditions for use, following tissue compatibility with many of the techniques already discussed. Confocal microscopy is a relatively new noninvasive technique that allows a detailed examination of the endothelium in the live animal, and thus may prove useful in following changes in this delicate tissue over time. As in ex vivo models, the

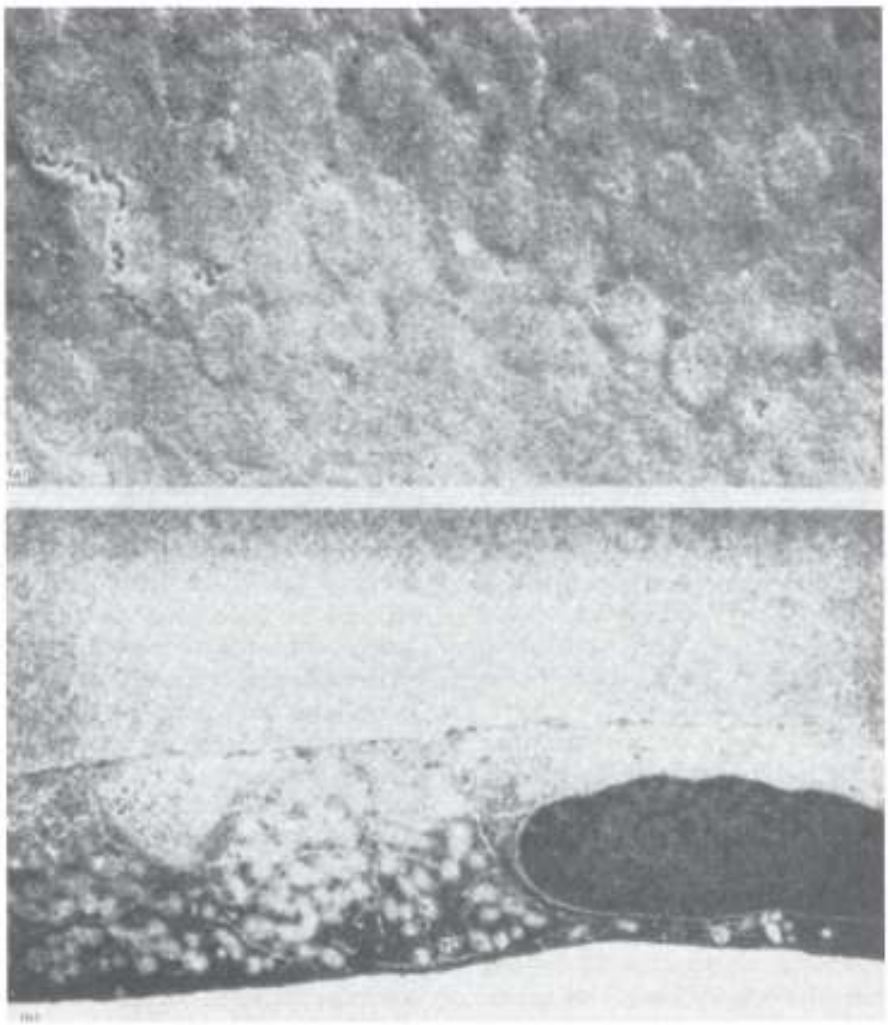

Fig. 6 Human corneal endothelium following 3-hour perfusion with solution devoid of essential nutrients: (a) scanning electron micrograph (2100 ×); (b) transmission electron micrograph (9100 ×). (Courtesy of H. Edelhauser.)

experimental design must address the nature of the intraocular preparation and the type of contact. Irrigating solutions of low viscosity may have limited contact while the gel-like viscoelastic materials that maintain the corneal dome, or the solutions and gases used as vitreous replacements to prevent retinal detachment, may have prolonged contact with delicate ocular tissues or the retina. In vivo studies can thus become quite lengthy even during early phases of development, underscoring the utility of preliminary in vitro or ex vivo evaluations, in which experiments utilize harvested tissues maintained viable for the duration of the evaluation.

A new therapy involves treatment for neovascularization of the retina, a disease in which proliferation of blood vessels can lead to blindness. The treatment combines a systemic chemical that localizes in the new blood vessels followed by laser treatment to destroy the vessels. Such new therapies and new routes of administration require special care in their design and evaluation.

During the application of the various guidelines for ophthalmic, contact lens, and intraocular products, ocular examination and biomicroscopic examination of rabbit eyes are completed with objective reproducible grading for conjunctival congestion, conjunctival swelling, conjunctival discharge, aqueous (humor) flare, iris involvement, severity and area of corneal opacity or cloudiness, pannus, and intensity of fluorescein staining [39,103]. Other available methods

measure intraocular pressure, corneal thickness, cells in the aqueous humor, and posterior segment changes.

In addition to in vivo testing of ophthalmic preparations, primarily in rabbit eyes and secondarily in a primate eye, numerous in vitro methods have been developed over the past few years as alternatives to in vivo ocular testing [83–92]. In vivo methods that incorporate new technology and reduced numbers of animals have also been developed. Particular attention has been given recently to evaluation of preservative effects on corneal penetration [93,94], cytotoxicity [95–99], and affects on wound healing [100–102]. These methods have been able so far to mimic only acute dosing regimens, and validation efforts have not substantiated the correlation of any method with rabbit or human responses. However, these methods are useful for comparing relative toxicity under controlled conditions, and several manufacturers currently are using in vitro toxicity tests in the development of ophthalmic solutions.

C. Preservation and Preservatives

In 1953 the FDA imposed the federal requirement that all manufactured ophthalmic solutions be sterile [104]. Preservatives are included as a major component of all multiple-dose eye solutions for the primary purpose of maintaining that sterility in the opened product over its lifetime of use. Packaging ophthalmic solutions in the popular plastic eyedrop container has reduced, but not completely eliminated, the chances of inadvertent contamination. There can be a "suckback" of an unreleased drop when pressure on the bottle is released. If the tip is allowed to touch a nonsterile surface, contamination may be introduced. Therefore, it is important that the pharmacist instruct the patient on the proper method of dispensing from a plastic eyedrop container in order to minimize the hazards of contamination. The hazard is magnified in the busy clinical practice of the eye care professional where a diagnostic solution – there are many, including cycloplegics, mydriatics, and dyes – may be used for many patients from the same container. The cross-contamination hazard can be eliminated by the use of packages containing small volumes designed for single application only (i.e., unit-dose). Since preservatives are not included in solutions packaged in unit-dose containers, and because these single-use packages still contain (as a large-scale manufacturing necessity) an amount in excess of the several drops (0.05–0.20 mL) required, patient and physician alike should be cautioned to avoid exhausting their entire contents in a multi-use application which will increase the hazard of contamination and defeat the purpose of this special packaging.

The USP outlines a test procedure for antimicrobial effectiveness and how to interpret the results. This test is not a mandatory requirement of the USP or FDA [105], but is applied by manufacturers as a guide in developing adequately preserved products. This testing of the antimicrobial characteristics of alternate formulas is carried out as a part of the development sequence. Cultures of *Candida albicans*, *Aspergillus niger*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* are used. Standardized inocula with organism counts of 10^5–10^6 per mL for each microorganism are prepared and tested against the preserved formula. The inoculated tubes or containers are incubated at 20 or 25°C for 28 days, with examination at days 7, 14, 21, and 28. The product's preservative is effective if (a) the concentrations of viable bacteria are reduced to no more than 0.1% of the initial concentrations by day 14, (b) the concentrations of viable yeasts and molds remain at or below the initial concentrations during the first 14 days, and (c) the concentration of each test microorganism remains at or below these designated levels during the remainder of the 28-day test period. Importantly, most manufacturers of ophthalmic products apply this as a minimum standard for a preservative and attempt to formulate their products with an even greater margin of safety.

In the ophthalmic literature because of reports of loss of eyes from corneal ulcerations caused by eye solutions contaminated with *P. aeruginosa*, considerable emphasis is placed on the effectiveness of preservatives against *Pseudomonas* species. This organism is not the most prevalent cause of bacterial eye infections, even though it is a common inhabitant of human skin, but it is the most opportunistic and virulent. *Staphylococcus aureus* is responsible for most bacterial infections of the eye. The eye seems to be remarkably resistant to infection when the corneal epithelium is intact due to the barrier properties discussed previously as well as the antimicrobial activity of lysozyme and other enzymes present in tears. When there is a corneal epithelial abrasion, organisms can enter freely and *P. aeruginosa* can grow readily in the cornea, rapidly producing an ulceration and loss of vision. This microorganism has been found as a contaminant in a number of studies on sterility of ophthalmic solutions, particularly in sodium fluorescein solutions used to detect corneal epithelial damage. The chances for serious infections and cross-contamination are greatly

enhanced by multiple use of this dye solution—a danger that has led to the practice by the ophthalmologist of using sterile disposable applicator strips of fluorescein. Although infrequent, *P. aeruginosa* has been found on contact lenses.

An additional test procedure employed by one manufacturer is the preservative evaluation "cidal" test. A formulation is tested against 5–14 species of microorganism, including gram-negative and gram-positive bacteria, fungi, and yeasts in a standardized inoculum. Cidal times (no growth) are measured for each organism within 24, 48, and 72 hours of contact.

One area of ophthalmic products for which stricter microbiological guidelines have been imposed recently is in the area of soft (hydrophilic) contact lens accessory products. Specific guidelines have been devised by FDA and international organizations for this area of ophthalmic products and differ primarily in the required kill rate, which depends on the intended use, for a single disinfecting product or in combination with other lens care solutions. The microbiological guidelines, which have evolved during the last decade, are discussed in Sec. IX of this chapter.

In some applications the use of preservatives is not recommended. For example, preservatives should not be used in a corneal storage media for donor corneas; instead, antibiotics such as gentamicin are used. Alternative packaging for multidose nonpreserved preparations [106] and drugs administered in dry form [107] may offer nonpreserved choices for the formulator, but efficacy and compatibility of each drug with these systems must be investigated. Because experimental results reported in the literature have shown a somewhat higher incidence of adverse effects with preserved solutions compared with unpreserved, there is some question of the necessity for preservatives in some applications [108,109]. However, preservatives can enhance drug efficacy, chemically balance a preparation, and enable a dosing form that promotes patient compliance. While some ophthalmic drugs may be formulated in an unpreserved form, many drugs cannot, and it is the challenge of the formulator to provide an acceptable balance of safety and effectiveness.

Although this chapter is directed toward ophthalmic products, it is largely applicable to parenteral and even nonsterile products (solutions, emulsions, and suspensions). The choice of preservative is limited to only a few chemicals that have been found, over the years, to be safe and effective for this purpose. These are benzalkonium chloride, thimerosal, methyl- and propylparaben, phenylethanol, chlorhexidine, polyquaternium-1, and polyaminopropyl biguanide. The chelating agent disodium edetate (EDTA) is sometimes used to increase activity against certain *Pseudomonas* strains, particularly solutions preserved with benzalkonium chloride. Chlorhexidine—as the hydrochloride, acetate, or gluconate salt—is used widely in the United Kingdom and Australia but was not introduced into the United States until 1976, and only then for solutions intended for disinfection of soft contact lenses. This limited choice of preservative agents is further narrowed by the requirements of chemical and physical stability and compatibility with drugs, packaging, and contact lens materials. Many times it is necessary to design the formula to fit the requirements of the chosen preservative system since the buffer system and excipients can alter preservative action significantly. While it is recognized that excipients themselves may produce toxicity and their use needs be controlled, the large variety and number of available excipients prohibits discussion here, and the reader is referred to a recent pharmaceutical text that provides an excellent review [110].

Several guidelines are available in the literature for the pharmacist who must extemporaneously prepare an ophthalmic solution. The USP contains a section on ophthalmic solutions, as do other compendia and several standard textbooks. Since the pharmacist does not have the facilities to test the product, he or she should dispense only small quantities, with an expiration date of no more than 30 days. Refrigeration of the product should also be required as a precautionary measure. To reduce the largest potential source of microbial contamination, only sterile purified water should be used in compounding ophthalmic solutions. Sterile water for injection, USP, from unopened IV bottles or vials is the highest-quality water available to the pharmacist. Prepackaged sterile water with bacteriostatic agents should *not* be used.

Benzalkonium Chloride

The most widely used preservative remains benzalkonium chloride, which often is supplemented with disodium edetate. The benzalkonium chloride defined in the USP monograph is the quaternary ammonium compound alkylbenzyldimethylammonium chloride, in which the alkyl portion is composed of a mixture of chain lengths ranging from C_8 to C_{16}. This compound's popularity is based, despite its compatibility limitations, on its being the most effective and rapid-acting preservative with excellent chemical stability. It is stable over a wide pH range and does not

degrade, even under excessively hot storage conditions. It has pronounced surface-active properties, and its activity can be reduced by adsorption. It is cationic, which unfortunately can lead to a number of incompatibilities with large negatively charged molecules with the potential for producing salts of lower solubility and possibly precipitation. For example, it cannot be used with nitrates, salicylate, anionic soaps, and large anionic drugs, such as sodium sulfacetamide and sodium fluorescein. When feasible, it is usually advisable to design the formula to avoid these incompatible anions, rather than to substitute a less effective preservative. There are a number of helpful lists of incompatibilities of benzalkonium chloride in the literature, but they should not be relied upon entirely. Compatibility is determined by the total environment in which the drug molecules exists (i.e., the total product formula). The pharmaceutical manufacturer can sometimes design around what appears to be an incompatibility, whereas the extemporaneous compounder may not have this option or, more importantly, the ability to test the final product for its stability, safety, and efficacy.

The conventional concentration of benzalkonium chloride in eyedrops is 0.01%, with a range of 0.004–0.02% [111]. While uptake of benzalkonium chloride itself into ocular tissues is limited [113], even lower concentrations of benzalkonium chloride have been reported to enhance corneal penetration of other compounds including therapeutic agents [93,112,114]. The differential effect of this preservative on the cornea compared to the conjunctiva can be exploited to target a drug for corneal absorption and delivery to the posterior segment of the eye [115]. Its use has been proposed as a means of delivering systemic doses by an ocular route of administration [116].

Richards [117], Mullen et al. [118], and the American College of Toxicology [119] have summarized the literature of benzalkonium chloride. The conclusion drawn was that benzalkonium chloride, up to 0.02%, has been well substantiated as being suitable for use in topical ophthalmic solutions when the conditions of its use are properly controlled. McDonald [121] found up to 0.02% to be permissible in ophthalmic solutions following extensive testing in rabbits.

Numerous studies comparing benzalkonium chloride with other preservatives have been described in the literature. Many of the articles give conflicting results, not surprising considering the many different test methods, formulas, and criteria used to arrive at these diverse conclusions. However, adequate information is available in the literature to permit the manufacturer to select appropriate tests for nearly any product. Generally, the USP (or similarly validated) test can be employed to decide which preservative system is most compatible with a specific composition. While recent reports show benzalkonium chloride to have a somewhat higher incidence of ocular effects [122–124], this preservative is one of the most effective available and generally assures an adequate level of preservative efficacy.

Some strains of *P. aeruginosa* are resistant to benzalkonium chloride and, in fact, can be grown in solutions concentrated in this agent. This has caused great concern because of the virulent nature of this organism in ocular infections, as discussed previously. Thus, it was an important finding in 1958 that the acquired resistance could be eliminated by the presence of ethylenediaminetetracetic acid (sodium edetate) in the formulation. This action of EDTA has been correlated with its ability to chelate divalent cations, and it is commonly used as a preservative aid [125]. The use of disodium EDTA, where compatible, is recommended in concentrations up to 0.1%.

Other quaternary ammonium germicides, benzethonium chloride and benzalkonium bromide, have been used in several ophthalmic solutions. While these have the advantage of not being a chemical mixture, they do not possess the bactericidal effectiveness of benzalkonium chloride and are subject to the same incompatibility limitations. In addition, the maximum concentration for benzethonium chloride is 0.01%. Several new products that form gels in the eye, like Timolol Gel Forming Solution and Timoptic-XE, employ another quaternary preservative, BDAB, in the formulation.

Organic Mercurials

When benzalkonium chloride could not be used in a particular formulation of a therapeutic agent (e.g., pilocarpine nitrate, serine salicylate, or fluorescein sodium) because of potential anion-cation association, one of three organic mercurials, phenylmercuric nitrate, phenylmercuric acetate, and thimerosal, had until recent years been used. Because of environmental concerns, however, the use of organic mercurials has fallen into disfavor. Although organic mercurials have not been implicated in classical mercurial toxicity, several countries have banned their use entirely, and other countries require its rigorous defense based on the absence of any suitable alternative. In those situations for which the use of an organic mercurial is the only avenue available, the usual range in concentration for the phenylmercuric compounds is 0.002–

0.004% and for thimerosal, 0.02–0.01%. Although they can be used effectively in some products, the mercurials are relatively weak and slow in their antimicrobial activity. The organic mercurials are generally restricted to use in neutral to alkaline solutions; however, they have been used successfully in slightly acid formulations. The phenyl mercuric ion can react with halide ions to form salts of lower solubility, reducing their effectiveness. Thimerosal has a greater solubility and is relatively more stable than the phenylmercuric compounds and has not been shown to deposit in the lens of the eye. The latter phenomenon has been observed with phenylmercury compounds.

Ocular sensitization to thimerosal has been well documented over the years [126–132]. Although thimerosal had at one time been referred to as the preservative of choice for soft contact lens care products [133–135], its use has been supplanted almost completely by the polyquaternium-l and polybiguanide preservatives.

Since the organic mercurials offer an alternative to quaternary ammonium preservatives, and since preservative efficacy of ophthalmic solutions is essential, the choice among these alternatives should be based on a benefit-to-risk analysis as long as a ban is not imposed on the use of these organometallic preservatives.

Chlorobutanol

This aromatic alcohol has been an effective preservative and still is used in several ophthalmic products. Over the years it has proved to be a relatively safe preservative for ophthalmic products [138] and has produced minimal effects in various tests [99,136,139]. In addition to its relatively slower rate of activity, it imposes a number of limitations on the formulation and packaging. It possesses adequate stability when stored at room temperature in an acidic solution, usually about pH 5 or below. If autoclaved for 20–30 minutes at a pH of 5, it will decompose about 30%. The hydrolytic decomposition of chlorobutanol produces hydrochloric acid (HCl), resulting in a decreasing pH as a function of time. As a result, the hydrolysis rate also decreases. Chlorobutanol is generally used at a concentration of 0.5%. Its maximum water solubility is only about 0.7% at room temperature, which may be lowered by active or excipients, and is slow to dissolve. Heat can be used to increase dissolution rate but will also cause some decomposition and loss from sublimation. Concentrations as low as 0.125% have shown antimicrobial activity under the proper conditions.

Methyl- and Propylparaben

These esters of *p*-hydroxybenzoic acid have been used primarily to prevent growth of molds but in higher concentrations possess some weak antibacterial activity. Their effective use is limited by low aqueous solubility and by reports of stinging and burning sensations related to their use in the eye. They bind to a number of nonionic surfactants and polymers, thereby reducing their bioactivity. They are used in combination, with the methyl ester at 0.03–0.1% and the propyl ester at 0.01–0.02%. Parabens have also been shown to promote corneal absorption [140].

Phenylethyl Alcohol

This substituted alcohol has been used at 0.5% concentration, but in addition to its weak activity it has several limitations. It is volatile and will lose activity by permeation through a plastic package. It has limited water solubility, can be "salted out" of solution, and can produce burning and stinging sensations in the eye. It has been recommended primarily for use in combination preservative systems.

Polyquaternium-1 (POLYQUAD®)

This preservative is comparatively new to ophthalmic preparations and is a polymeric quaternary ammonium germicide. Its advantage over other quaternary ammonium seems to be its inability to penetrate ocular tissues, especially the cornea. It has been used at concentrations of 0.001–0.01% in contact lens solutions as well as dry eye products. At clinically effective levels of preservative, POLYQUAD is approximately 10 times less toxic than benzalkonium chloride [87,137]. Various in vitro tests and in vivo evaluations substantiate the safety of this compound [137,141,142]. This preservative has been extremely useful for soft contact lens solutions because it has the least propensity to adsorb onto or absorb into these lenses, and it has a practically nonexistent potential for sensitization. Its adsorption/absorption with high water and high ionic lenses can be resolved by carefully balancing formulation components [143].

Chlorhexidine

Chlorhexidine, a bisbiguanide, has been demonstrated to be somewhat less toxic than benzalkonium chloride and thimerosal at clinically relevant concentrations [87,89,95,144,145]. This work was confirmed in a series of in vitro and in vivo experiments [137,146–148].

Polyaminopropyl Biguanide

This preservative is also comparatively new to ophthalmic formulations and has been used as a disinfectant in contact lens solutions. Polyaminopropyl biguanide (polyhexamethyl biguanide) also is a polymeric compound that has a low toxicity potential at the concentrations generally used in these solutions [141, 149, 150].

Cetrimonium Chloride

This preservative has been used in a dry eye treatment and was shown in a clinical study to have the same biocompatibility as another marketed preparation [152]. Cetrimonium chloride (0.01%) produced the same corneal and conjunctival changes after one-month ocular administration in rats as the effective levels of other major preservatives [153].

VI. OCULAR DRUG TRANSPORT AND DELIVERY

A. Modes of Transport

Passive transport or simple diffusion of molecules is a transport process dependent on water and lipid solubility, size of the molecule, and concentration gradient across the cellular membrane. No energy is expended in the process, and transport will cease when the concentrations of the molecules on both sides of the membrane are equal. Passive transport is not inhibited by metabolic inhibitors (inhibiting ATP production or utilization) or by competitive substrates. In general, hydrophilic molecules pass through proteinaceous pores in the cellular membrane and lipophilic molecules diffuse through the lipid portion of the membrane. Transport through the pores is limited by the pore size that is specific to each tissue. The low lipid solubility of ionized molecules may be increased by altering the degree of ionization with changes in solution pH. Passive transport is important in diffusion of drugs across the cornea and in nutrient uptake across the corneal endothelium.

Active transport is an energy-dependent process requiring ATP, is carrier-mediated, and is capable of transporting substrates against a concentration gradient. Macromolecular carriers are membrane-bound and have varying degrees of substrate specificity. The carrier reversibly binds to the substrate, transports and releases the molecule on the other side of the membrane, and returns to the original state. These characteristics also make active transport subject to metabolic inhibitors, competitive inhibition from other similar substrates, and saturation at high substrate concentrations. Active transport in the corneal endothelium is essential to maintenance of proper stromal hydration.

Facilitated transport combines some properties of both mechanisms discussed above. This type of transport is carrier mediated so that there is substrate specificity, a transport maximum, and competitive inhibition. However, facilitated transport is not energy-dependent and is unable to transport a substrate against a concentration gradient.

B. Biological Barriers and Fundamentals of Passive Transport

Membranes as Barriers

In a very general sense, biological membranes serve an extremely useful function, effectively walling off the body from invasive and destructive pathological microorganisms as well as noxious influences of the environment. They allow tissues to customize their environments. Dosage forms are therefore devised so that either the therapeutic agent is introduced by a physical or chemical means, which penetrates the barrier and introduces the drug behind the impediment, or the drug design or dosage form itself enables the therapeutic agent to penetrate the barrier. If the latter is the preferred means, both the drug and the vehicle need to avoid producing a significant toxic insult to the barrier, lest that barrier be compromised in its ability to prevent intrusion of foreign chemical or biological agents or be rendered sufficiently uncomfortable that the delivery is not effective nor the patient compliant.

The significance of the barrier function of membranes has been the topic of considerable research. The blood-brain barrier and the blood-retinal barrier are well understood, and the microscopic structures imparting and controlling barrier properties have been quite thoroughly investigated and the science reviewed [15, 154–155]. The structures and functions of ocular membranes specific to transport associated with ophthalmic drug administration also have been topics of extensive research [15, 157–158].

The most common means of administering drugs to the eye is by topical administration of agents capable of penetrating the cornea and targeting the appropriate tissue for either physiological or medicinal effect [159,160]. The trilaminar structure of the transparent avascular cornea has been described previously. The

corneal epithelium exposes a hydrophobic barrier to hydrophilic therapeutic agents and a hydrophilic corneal stromal barrier to hydrophobic agents. Nonetheless, as the models considered below rationalize, low molecular weight therapeutic agents of modest hydrophobicity and high water solubility are often capable of penetrating the eye, and may be effective ocular therapeutic agents if their potency—or receptor affinity if that is appropriate—can be maintained in the accommodation to these requirements.

More recently alternative routes of drug administration have been sought and utilized. Scientists are developing technologies to circumvent the constraints imposed on molecular weight, water solubility, and modest hydrophobicity by the conventional transcorneal route. Patents exist for ophthalmically acceptable penetration enhancers. More water-soluble therapeutic agents now in use for glaucoma appear to achieve approximately equal access by both scleral-limbal and transcorneal routes of administration [161,162]. Research is ongoing to understand and utilize scleral administration of therapeutic agents; the role of hydrostatic pressure on the transport of both water and drug has been investigated in order to determine the classes of therapeutic agent for which this mode of delivery may be utilized [163–166]. One consequence will be the determination of the diminished transport constraints imposed by a barrier from which the hydrophobic layer is absent. Both academic and industrial investigations have led to technologies for scleral implants and sustained release.

Role of Hydrodynamics

Basic hydrodynamic phenomena govern the duration of exposure of corneal and conjunctival membranes to the therapeutic agents. Rapid clearance provides a temporal barrier to drug delivery.

Drainage of the drop through the nasolacrimal system into the gastrointestinal tract begins immediately on instillation. This takes place when either reflex tearing or the dosage form causes the volume of fluid in the cul-de-sac and precorneal tears to exceed the normal lacrimal volume of 7–10 μL. Reference to Fig. 7 indicates the pathway for this drainage. The excess fluid volume enters the superior and inferior lacrimal puncta, moves down the canaliculi into the lacrimal sac, and continues into the gastrointestinal tract. It is due to this mechanism that significant systemic effects for certain potent ophthalmic medications have been reported [170–172]. This also is the mechanism by which a patient may occasionally sense a bitter or salty taste, typical of therapeutic ammonium salts, following the use of eye drops. The influence of drop size on bioavailability has been investigated thoroughly for conventional formulations and is significant [173,174]. Even for nonconventional viscoelastic formulations, drop volume can be expected to influence efficacy and needs to be optimized [175]. The clinical significance of drainage is so well recognized that manual nasolacrimal occlusion has been recommended as a means of improving the therapeutic index of antiglaucoma medications [176]. Once the dynamics of tear-flow excess have taken their course, steady-state hydrodynamics can be expected.

Loss of drug from a precorneal volume has been investigated both in vivo and in vitro. These studies relate to both design of dosage forms as well as investigations of transport, bioavailability and pharmacokinetics. Simultaneous release profiles of drugs and adjuvant from an artificial in vitro reservoir, designed with its volume to be characteristic of the eye, can be correlated simply with exposure for transmembrane transport [181]. An example of release profiles and the influence of dosage form from one of these models, the CRAS model, is shown in Fig. 8.

Simple hydrodynamic analysis of the in vitro mechanism indicates that the elution concentration, in the absence of absorption, is a linear kinetic process, with a release profile that scales as the ratio of the tear production to the volume of the tear reservoir, $\dot{V}_T/V_T$. Specifically:

$$N_E(t) = N_I\left(1 - \exp\left(\frac{-\dot{V}_T \cdot t}{V_T}\right)\right) \tag{1}$$

where

$N_E(t)$ = time-dependent total amount eluted from volume in time t
V_T = volume of the reservoir
$\dot{V}_T$ = flow rate through reservoir (alternatively, Q_T)
N_I = amount of drug in reservoir at time zero

and where the complementary amount, the amount of drug in the reservoir at time t, is defined as

$$N_T(t) = N_I - N_E(t) \tag{2}$$

characteristic of the stirred-tank chemical reactor models [182–184]. Combining these containment profiles, $N_T(t)$, with diffusional transmembrane transport, yields expected tissue profiles. The time-dependent concentrations are dictated by both containment profile and tissue affinities, and the magnitude is often

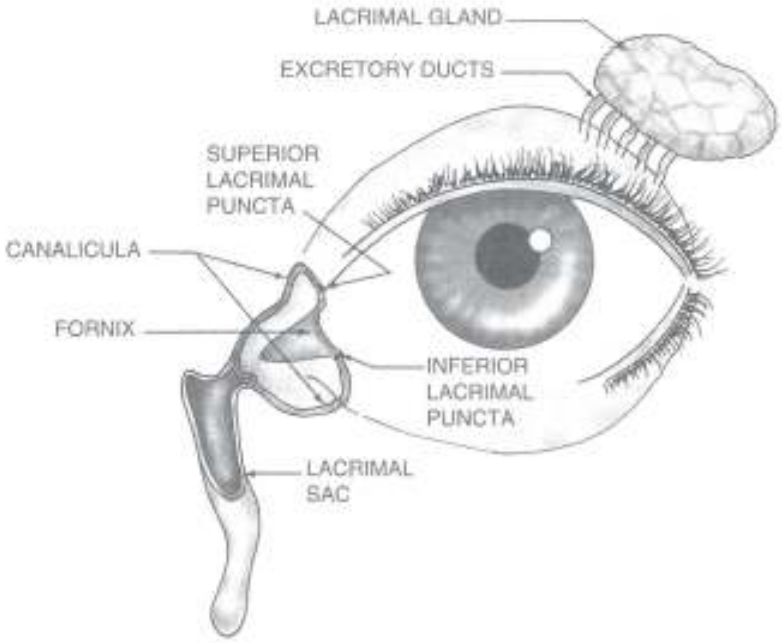

Fig. 7 Anatomical view of the lids and lacrimal systems.

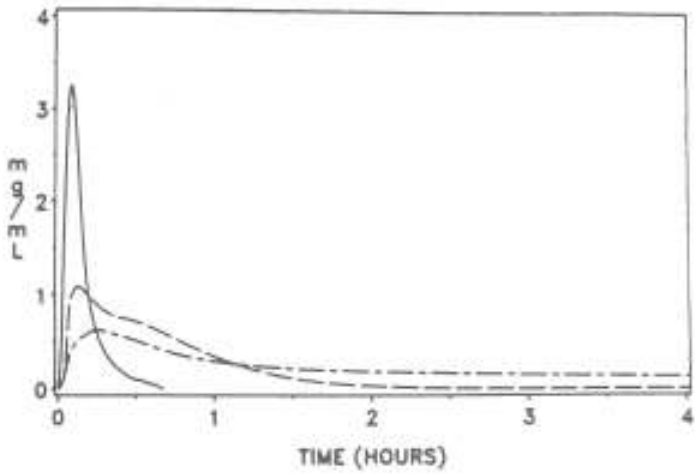

Fig. 8 Comparison of time-release profiles from three different preparations of betaxolol: (—) drug solution representing marketed product; (— —) supension formulation; (- — - —) gel formulation.

dominated by transmembrane flux (below). A pictorial representation of the processes is shown in Fig. 9. Pharmacokinetic modeling with this scheme has been successful in fitting the aqueous humor levels of pilocarpine following topical administration (Fig. 10) [173]. Although this type of data fitting has been quite successful, there has not been a sufficient number of systematic studies to determine the role of every molecular and physiological property influencing each of the various pharmacokinetic parameters. The pharmacokinetic consequences of these competing transport processes have been reviewed [180]. Elaborate analyses of such data using Green's function solutions, for responses to unit impulse, can be integrated as a means of generating responses to more complicated dosage regimens [185,186]. Alternatively,

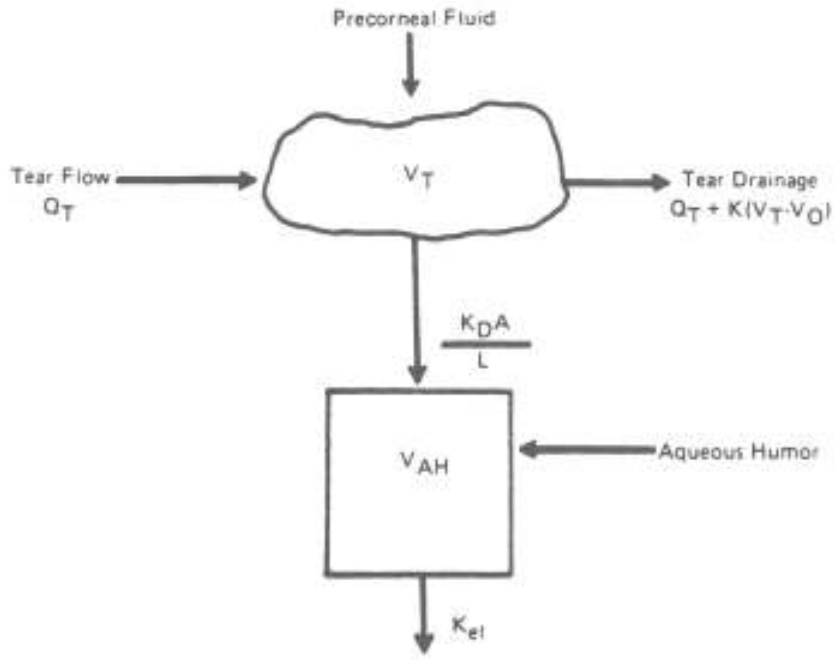

Fig. 9 Pharmacokinetic scheme for ocular absorption, distribution, and elimination.

and more simply, the differential equations representing the coupled effects of instillation, hydrodynamics and drainage, and membrane transport can be readily integrated numerically to provide predictions of the impact of drug and dosage form on bio availability [15].

Mechanisms and Models of Transmembrane Transport

At a physical level the description of the cornea is as a transparent, avascular tissue that, with the adherent precorneal tear film, is the first refracting surface operant in the process of sight. At a morphological and chemical level the description is of a three-layered structure: a multilayered, lipid-rich epithelium, a well-hydrated and lipid-poor stroma, and a lipid-rich endothelium of one-cell-layer thickness. Differential studies of the relative lipid densities for these three corneal layers have shown that the densities of lipid in epithelium and endothelium are approximately 40 times as large as that in the stroma [194], although more recent studies suggest the disparity may be less [195,196]. This can be a primary physiological factor influencing drug penetration through the cornea and into the aqueous humor. For a topically administered drug to traverse an intact cornea and to appear in the aqueous humor, it must possess dual or differential solubility. But as ever more explicit descriptions have been developed by histologists, microscopic anatomists, and electron microscopists, increasingly detailed mechanisms of transport through these tissues have been envisioned and tested.

The multilayered corneal epithelium consists of cells attached by microstructural junctions of well-established morphology and function and separated by water-filled intercellular spaces. Drug transport through such an environment can be imagined to consist of two competing pathways. Predominantly water-soluble compounds presumably pass through the tortuously connected aqueous channels, establishing a path through the maze from epithelial surface to stroma, a paracellular pathway. Predominantly lipid-soluble compounds presumably pass by surface diffusion along the lipid surfaces, passing in a tortuous path from adjacent cell to cell—the transcellular pathway. In either case boundaries of lipid junctions for water-soluble compounds or aqueous channels for lipid-soluble compounds would be more readily surmounted by compounds with shared funtionality. The characteristics of diffusion through and along such well-defined structures is well known, and the statistical mechanics of percolation phenomena governing such random paths has been well investigated.

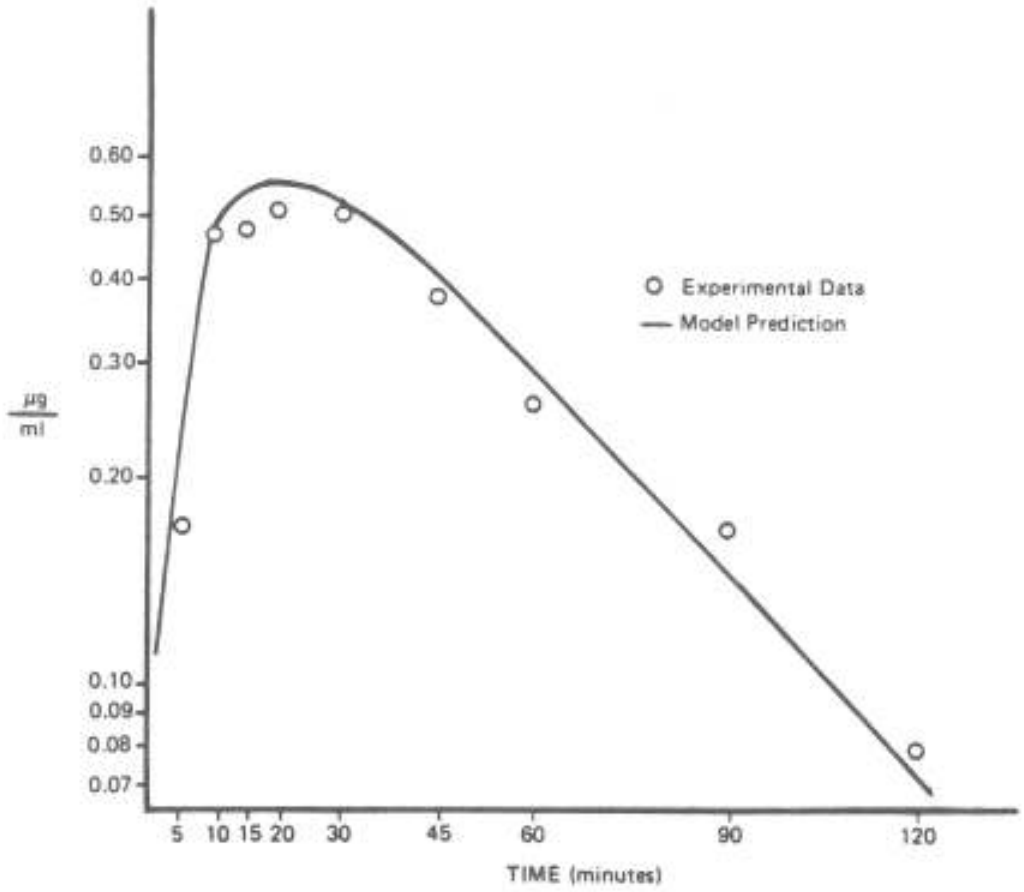

Fig. 10 Comparison of predicted and experimental aqueous humor concentrations following topical administration of pilocarpine.

For example, several recent studies have attempted to provide a molecular basis for the earlier largely empirical observations and essentially macroscopic continuum analyses [197,198]. For the stroma and sclera much is known about their structure and composition. These tissues consist primarily of water, collagen, and glycosaminoglycans wherein the lamellar order is derived primarily from collagen, which has a fivefold organizational hierarchy. The collagen molecule consists of three α-chains of peptides. These α-chains are organized into ordered, relatively stiff collagen fibrils, typically 50 nm in diameter. Many fibrils, along with proteoglycan-rich ground substance, compose collagen fibers, which are about a half micrometer in diameter and in stroma and sclera are organized into nearly lamellar sheets [199–201]. These membranes, over which there will be hydrodynamic pressure gradients, will be barriers to fluid flow, and with the administration of drugs these membranes, over which there will be concentration gradients, will be barriers to molecular diffusional flow. The effects of fibrous obstructions on both fluid flow and solute diffusion have been the topic of intense research in chemical engineering and physics. The flow and diffusional characteristics have been related to the relative dimensions and volume fractions of the fibers and the permeabilities (influenced by the state of hydration) of the different materials to the solvent and solutes, respectively. The diffusional characteristics of solute molecules will be influenced by the relative solubilities of these molecules in the different environments; more water-soluble solutes will diffuse more rapidly through the highly hydrated stroma.

These effects, specialized for the geometries and materials properties of the collagen-rich stroma and sclera, have been calculated in a paper by Edwards and Prausnitz [197]. They also modeled diffusion across the corneal endothelium assuming that the major path was

between cells and that this was governed by the most restrictive portion, the diffusion through the tight junctions. The diffusional flow was predicted based on the density and width of these parallel channels. These authors generalized this description for both corneal endothelium and epithelium by allowing there to be a balance between this paracellular pathway and a transcellular pathway. The only difference between the epithelial and endothelial paracellular pathways was the geometry of the junctions and their number, larger for the multilayered epithelium. The transcellular pathway was modeled from the known geometry of the cells, which determined the length of the diffusional pathway, and the partitioning characteristics of the molecules.

The cumulative effects of these barriers and the resistance to flow they produce were computed, and it was demonstrated these macroscopically derived laws applied at molecular dimensions were able to provide semiquantitative agreement with the available data. While further tests of these models will undoubtedly provide refinements to our understanding, the agreement supports our understanding of the basic phenomena regulating transport of therapeutically active substances through these barriers and the role of disease states that impact hydrodynamic pressure on the efficacy of drug delivery.

C. Passive Absorption and Intraocular Delivery

Considerations Influencing Drug Design for Topical Administration

From the perspective of drug design for conventional topical delivery, several requirements need to be satisfied by ophthalmic therapeutic agents. The drug must be (a) both biochemically and pharmacologically potent, (b) nontoxic to both ocular and systemic tissues, (c) sufficiently stable that neither significant loss in potency from diminished availability nor increase in toxicity from by-products of degradation arises, (d) targetable either to tissues and location of primary disease-state etiology or to sites responsible for symptomatic response, and (e) sufficiently compatible with the dosage form, and with the tissues exposed to it, to achieve an effective pharmacokinetic tissue profile.

Often the demand for such a complement of properties requires a hierarchical strategy in which only the broadest possible limits are satisfied by the less demanding design requirements. For example, topical administration assists in limiting toxicity while improving targeting and pharmacokinetic response. On the other hand, the requirements for effective absorption of such topical ophthalmic medications often places significant demands on the physical, chemical, and transport characteristics of the drug, which in most cases was designed primarily to satisfy more stringent biological, physiological and pharmacological criteria. Simple guidelines can be appreciated readily by examining the factors influencing absorption of an antiglaucoma agent administered in the conventional manner as drops into the cul-de-sac, discussed in the next section [167].

Efficacy is also influenced by minimizing those factors that diminish availability. The first factor reducing drug availability is loss of drug from the palpebral fissure. This takes place by spillage of drug from the eye and its removal by the nasolacrimal drainage. The normal volume of tears in the human eye is estimated to be approximately 7 μL, and if blinking occurs the human eye can accommodate a volume of up to 30 μL without spillage from the palpebral fissure. With an estimated drop volume of 50 μL, 70% of the administered volume of two drops can be seen to be expelled from the eye by overflow. If blinking occurs, the residual volume of 10 μL indicates that 90% of the administered volume of two drops will be expelled within the first several minutes [168,169].

Many technologies have been devised, some discussed below, for modifying the dosage form as a means of slowing the escape of drug from the precorneal location from which it can be transported to tissues influencing ocular physiology. In addition, other approaches have been recommended. For example, temporary manual punctal occlusion immediately after instillation of drug transiently prevents drainage of the enriched tears from the puncta. For patients with dry eye, often permanent occlusion, which is implemented either by cautery or by one of several designs of punctal plug, results in a diminished rate of tear clearance. Transient occlusion can be expected to influence drug delivery only modestly and be effective only in rather specific circumstances, when either the molecular weight or the aqueous solubility of the therapeutic agent is high. For those circumstances in which the therapeutic agent is reasonably lipophilic, the kinetics of absorption by transepithelial transport can be quite rapid (see below).

A second factor reducing drug availability is the drainage associated with hydrodynamic flow of tears through the precorneal space and cul-de-sac, discussed above. A third and more difficult problem for delivery by nondirectional technologies and devices is the undesirable adsorption and absorption by nearby noncorneal tissues competing for therapeutic agents.

These include absorption by adjacent palpebral and bulbar conjunctiva, with concomitant rapid removal from ocular-tissues by peripheral blood flow. For example, the extensive vascularity of the uvea underlies the bulbar conjunctiva, a mucous membrane, and the sclera, a white tissue providing a tough outer covering [177]. Binding of drug to either external sites, like the tear polymers such as mucins or lysozyme, or internal tissues like the sclera can be detrimental to efficacy.

To the extent that these competing and detrimental effects can be controlled, delivery can be enhanced. But their control is inconsequential if the molecular properties regulating transmembrane transport are not selected in a manner to facilitate corneal permeation, the topic of the next section. Finally, in competition with the three foregoing forms of therapeutically ineffective drug removal from the palpebral fissure is the transcorneal absorption of drug, often the route most effective in bringing drug to the anterior portion of the eye. Although transport of hydrophilic and macromolecular drugs has been reported to occur by limbal or scleral routes, often this is at rates significantly reduced from those expected for transcorneal transport of conventional, modestly lipophilic agents of low molecular weight [178–180,191–193]. Even here, transmembrane transport is a significant requirement for availability.

A Generalized Phenomenological Transport Model and Simple Consequences

One of the key parameters for correlating molecular structure and chemical properties with bioavailability has been transcorneal flux or, alternatively, the corneal permeability coefficient. The epithelium has been modeled as a lipid barrier (possibly with a limited number of aqueous "pores" that, for this physical model, serve as the equivalent of the extracellular space in a more physiological description) and the stroma as an aqueous barrier (Fig. 11). The endothelium is very thin and porous compared with the epithelium [189] and often has been ignored in the analysis, although mathematically it can be included as part of the lipid barrier. Diffusion through bilayer membranes of various structures has been modeled for some time [202] and adapted to ophthalmic applications more recently [203,204]. For a series of molecules of similar size, it was shown that the permeability increases with octanol/water distribution (or partition) coefficient until a plateau is reached. Modeling of this type of data has led to the earlier statement that drugs need to be both oil and water soluble. If pores are not included in the analysis, the steady-state corneal fux, J_s can be approximated by:

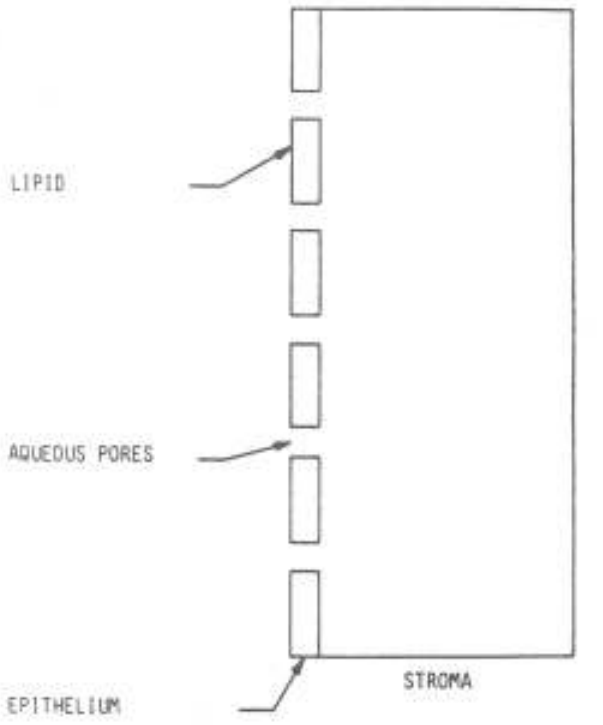

Fig. 11 Schematic diagram of the physical model for transcorneal permeation; features are not to scale.

$$J_s = \frac{PC_w}{\frac{Pl_s}{D_s} + \frac{l_e}{D_e}} \tag{3}$$

where

C_w = concentration of drug in donor phase
l_s, l_e = stromal and epithelial thickness, respectively
D_s, D_e = corresponding difffusion coefficients
P = distribution coefficient

The permeability coefficient K_{per} is just the flux divided by C_w. It is apparent that the permeability coefficient is linear with P for small distribution coefficients and constant for large P. Thus, for small P the epithelium is the barrier, and for large P the stroma is the barrier. A fit for steroid permeability is shown in Fig. 12, where the regression analysis gave $D_e = 1.4 \times 10^{-9}\,cm^2/s$ and $D_s = 2.0 \times 10^{-6}\,cm^2/s$ for $l_e = 4 \times 10^{-3}$ cm and $l_s = 3.6 \times 10^{-2}$ cm [205]. These values for the diffusion coefficients are reasonable compared with those of aqueous gels and lipid membranes.

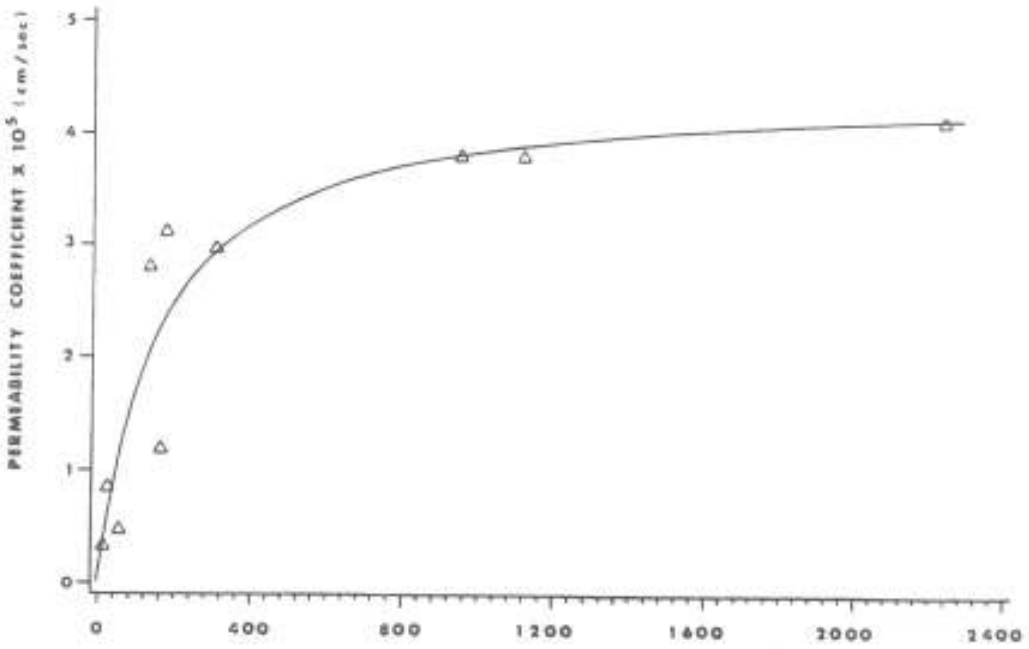

Fig. 12 Predicted versus experimental values for corneal steroid permeability as a function of partition coefficient.

A simple estimate of the diffusion coefficients can be approximated from examining the effects of molecular size on transport through a continuum for which there is an energy cost of displacing solvent. Since the molecular weight dependence of the diffusion coefficients for polymers obeys a power law equation [206], a similar form was chosen for the corneal barriers. That is, the molecular weight (M) dependence of the diffusion coefficients was written as:

$$D_c = D_c^{(0)} M^{\alpha}$$
$$D_s = D_s^{(0)} M^{\delta} \qquad (4)$$

Using regression analysis on a data set of about 50 different molecules, it was found that $\alpha = -4.4$, $\delta = -0.5$, $D_c^{(0)} = 12\ \text{cm}^2/\text{s}$, and $D_s^{(0)} = 2.5 \times 10^{-5}\ \text{cm}^2/\text{s}$ [192]. A graphic representation of the effect of relative molecular mass (M_r) and distribution coefficient on corneal permeability is shown in Fig. 13. One observes a rapid reduction in permeability coefficient with decreasing P and increasing M_r. The addition of pores to the model, a mathematical construct, is necessary to account for permeability of polar molecules, such as mannitol and cromolyn. These would also be required for correlating effects of compounds, such as benzalkonium chloride, which may compromise the epithelial barrier by increasing the volume of the extracellular space.

Another perspective provided by this model is the effect of three physiochemical parameters—solubility, distribution coefficient, and molecular mass—on transcoreal flux. All of these properties can be influenced by molecular design. The effects of these properties are illustrated in Fig. 13, in which the logarithm of the flux is plotted as a function of solubility and distribution coefficient for two different M_r. Several features of the model are depicted, and these qualitative, or semi-quantitative, aspects presumably encompass the principles of corneal permeation.

Inferred from this model is the relative independence of the effects of solubility and partitioning. For each property there is a characteristic threshold above which the log of the flux increases more slowly than below it, and the value of the threshold for one variable is not very dependent on the value of the other variable. This tabletop perspective has led to the name *mesa model*. The relative independence signifies that neither property can totally compensate for a deficiency in the other. This is not to say that these properties are independent of one another in a chemical sense—quite the contrary. However, in the hypothetical sense that if one property were varied independently of the other, then the consequences on flux are relatively independent. Clearly dependence

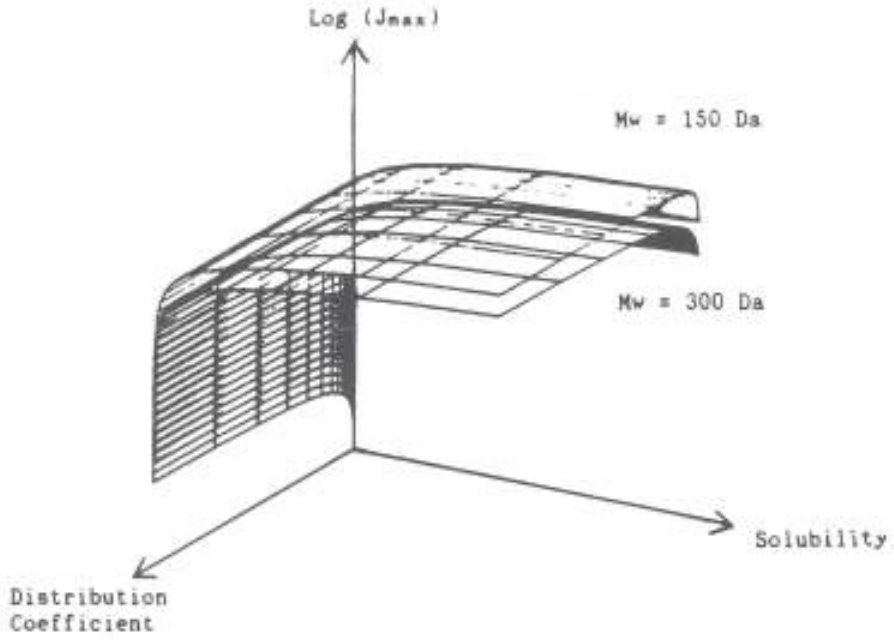

Fig. 13 This figure illustrates the "mesa" response for the diffusion model. Two plateau functions corresponding to different M_r are shown.

on molecular mass, even for relatively low molecular mass agents, can be significant.

Ex vivo studies of transcorneal transport in animal models have been used to establish the characteristics of passive diffusional motion, the conventional means by which drugs reach internal ocular tissues. Although such analysis neglects the complications of tear flow, tear drainage, nonproductive membrane absorption, elimination from the aqueous humor, and so forth, measurements of corneal transport measurements have been important in establishing correlations of model calculations with experimental measurements of transmembrane transport. Modifications [187] of the classical ex vivo experiments of transport across excised, but metabolizing, rabbit corneas [188–191] have provided information both about targeting of similar molecules from the same pharmacological class [192] and confirmation of the balance of different anatomical pathways for accession [193].

The rough brush stroke agreement between model and experiment is illustrated by the results shown in Fig. 14, for which the correspondences of theoretical with experimental permeability coefficients for the compounds listed in Table 2, β-adrenegic blockers studied by Lee et al. [207,208] and Schoenwald and Huang [191], are plotted. The calculated values utilized the physical model with pores [205]. Characteristic of correlations of this type is the slope's value—less than 1. The origin of the smaller calculated values of permeability coefficients is unknown. A reasonable conjecture, however, is that the estimated diffusion coefficients [i.e., the laws presented in Eq. (4) on which the permeability is based] are not quite correct for the drugs in different ocular environments. The predictability of the model is useful both for providing approximate values and for distinguishing departure from simple diffusional transport. Also apparent from a comparison of the last two figures (Figs. 13 and 14) is the significance of solubility, since it is the value of C_w that controls flux by orders of magnitude.

A significant inference from the model is that if, as is the conventional behavior of a family of molecules, the solubility decreases with an increase of distribution coefficient, eventually this effect will profoundly reduce the transcorneal flux. Alternatively and conceptually, for any class of molecules with a desirable physiological response and without significant differences in potency or therapeutic index, the member of that family with the greatest promise for ophthalmic application is the one with the lowest molecular weight, the highest distribution coefficient, and the highest aqueous solubility. However, since the last two requirements are in general inconsistent (the most soluble molecule is generally the one with lowest partition

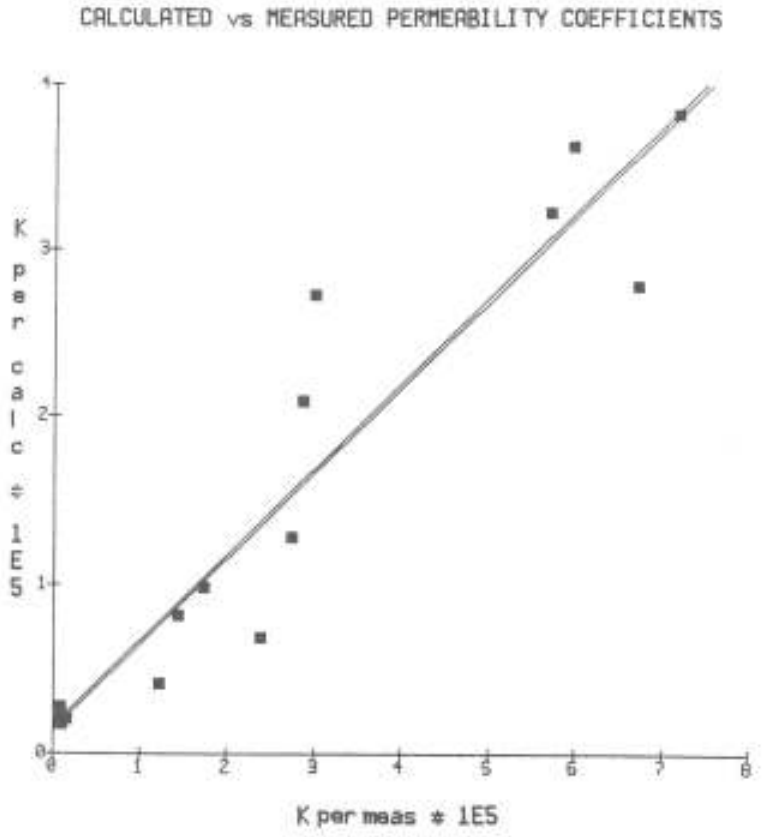

Fig. 14 Plot of data in Table 2: the theoretically computed permeability coefficient versus that measured. The larger influence on flux is often the range of solubility, which can increase the range in flux by several orders of magnitude.

Table 2 Permeability of β-Adrenergic Blockers

Compound	Chemical formula	Molecular weight	Distribution coefficient	K_{per}^{calc} *1E5 cm/s	K_{per}^{meas} *1E5 cm/s
Acebutolol	$C_{18}H_{28}N_2O_4$	336.43	1.58	0.28	0.085
Alprenolol	$C_{15}H_{23}NO_2$	249.34	8.92	2.09	2.86
Atenolol	$C_{14}H_{22}N_2O_3$	266.34	0.03	0.20	0.068
Betaxolol	$C_{18}H_{29}NO_3$	307.44	60.3	2.72	3.02
Bevantolol	$C_{20}H_{27}NO_3$	345.44	154.8	2.78	6.76
Bufuralol	$C_{16}H_{21}NO_2$	261.36	204.2	3.82	7.24
Labetolol	$C_{19}H_{24}N_2O_3$	328.41	7.77	0.82	1.43
Levobunolol	$C_{17}H_{25}NO_3$	291.39	5.25	0.99	1.74
Metoprolol	$C_{15}H_{25}NO_3$	267.38	1.91	0.69	2.40
Nadolol	$C_{17}H_{27}NO_4$	309.42	0.15	0.17	0.10
Oxprenolol	$C_{15}H_{23}NO_3$	265.34	4.90	1.28	2.75
Penbutolol	$C_{18}H_{29}NO_2$	291.44	338.84	3.62	6.03
Propranolol	$C_{16}H_{21}NO_2$	259.34	41.69	3.22	5.75
Sotalol	$C_{12}H_{20}N_2O_3S$	272.36	0.06	0.20	0.16
Timolol	$C_{13}H_{24}N_4O_3S$	316.42	2.19	0.42	1.23

coefficient), the model helps select the molecular structure for which the flux is greatest.

Perhaps as more is learned about the molecular requirements for binding therapeutic agents to active sites of macromolecules as part of the intention to control physiological function, these simple transport requirements can be incorporated into the molecular design.

Role of Specialized Formulations

Many materials and specialized formulations have been devised with the intention of improving delivery of drugs to intraocular tissues by means of the transcorneal route. Carriers have been used both alone and in conjunction with viscosifying or responsive formulations to control concentration of the active therapeutic compound or sustain delivery. As calculations clearly demonstrate and experiments confirm, the impact on total drug availability for such systems is crucially dependent on the degree to which the vehicle is capable of sustaining residence time of the drug or drug carrier in the eye [15]. The historical and current challenge remains to devise spontaneously responsive systems that are capable of being retained in the eye, sustaining the presence of the carrier without degrading its reservoir and delivery characteristics and without producing such conventional side effects as blurring or undesirable residues.

In recent years a barrage of technologies have been developed for sustaining delivery of drug to the cornea. Corneal collagen shields and contact lenses loaded with drug have been placed directly on the cornea. But undesirable side effects, including blurring, dumping of drug, packaging and storage problems, have prevented these technologies from being successful in the marketplace. Responsive polymeric systems have been more successful to date. Polymers whose solubilities and interactions are dominated by hydrogen bonding can be controlled with temperature, whose solubilities are dominated by coacervation-type interactions can be controlled by the concentration of the complementary polymer, whose solubilities are dominated by weak acid ionization can be controlled by pH, and whose solubilities are dominated by ion pairing condensation can be controlled by ionic strength or even specific ion concentrations. Those systems utilizing mechanisms less influenced by the environment have proven more widely applicable. Polymers like xanthan gum or gelrite, which interact with one or more tear components to form a gel in situ, have been employed in timolol maleate formulations that require dosing only once a day.

D. Active Transport, a Potential Mechanism for Specific Structures

As more is learned about accession of drugs into the eye, it is becoming more obvious that passive diffusion through the cornea is not the only pathway likely to be exploited for future delivery of drugs. Many drugs are known either to bind to, or to be taken up by and accumulated in, epithelial cells. Interesting work is emerging in the areas of facilitated transport in which enhancers are used to diminish diffusional barriers temporarily [209,210] and areas of active transport in which drug carriers can be employed for transport of larger molecules [187].

As ever more potent therapeutic agents are developed, concentrations required diminish and the importance of drug targeting as a means of reducing systemic toxicity increases. For biochemical and therapeutic agents included in specific classes of amino acids, dipeptides, polypeptides with resemblance to specific peptide sequences (e.g., the undecapeptide cyclosporin A), small cationic molecules, or monocarboxylates, and nucleosides, there are known transporters, antiports, co-transporters, etc., in conjunctiva and sometimes in cornea that at low concentrations of a drug may actively contribute to controlling flux into or out of specific tissues [211–216]. Carrier-mediated transport is not restricted to ocular conjunctiva and cornea, of course, but has been identified in other ocular tissues, specifically the retinal pigment epithelium (RPE), as well as in numerous systemic tissues such as gastric, intestinal, hepatic, renal, and cardiac tissues and in some ex vivo cell-culture lines. As a consequence, information concerning structural and geometric specificity, co- or counterion requirements, proton and energy dependence, pump capacity (saturability), total ion flux and current, and directionality of mediated transport have been provided by biochemists, physiologists, and pharmacologists studying a variety of human and mammalian tissues.

For conventional therapeutic agents the presence of active drug transport is either nonexistent or obscured, since while both active and passive transport may occur concurrently at high concentrations, the passive component is the dominating and overwhelming fraction. However, as the concentration decreases, as it will for potent agents for which concentrations in the micromolar range may be adequate, some of these agents will experience facilitated, active, carrier-mediated transport. For example, the flux can be expected to have a complicated concentration dependence:

$$J = \frac{J_{max}}{\frac{K_m}{[C]} + 1} + K_d[C] \quad (5)$$

where J_{max} is the maximum saturable flux from the active transport process, K_m is the Michaelis-Menten constant and K_d is the passive diffusive permeation rate [214]. Note both K_m and K_d are temperature-dependent; however, the temperature dependence of K_m is much greater, so that the diagnostic for the presence of active transport is the essentially complete loss of the active component by the time the temperature is reduced to 4°C.

Some measure of the importance of active transport is the diversity of systems where it has been observed. For example, carrier-mediated transport of L-argenine, a substrate for nitric oxide synthase, can impact the concentrations of NO, a neurotransmitter. The same carrier present in the conjunctiva can be inhibited by competitive inhibitors such as nitro-L-argenine. This transporter appears to be coupled to the transport of Na^+ ions and directionally transports the inhibitor preferentially into the tissues from the mucosal exterior surface. The utility of such a path might be to regulate production of NO in vivo and thereby control inflammation, a complication, for example, in Sjögren's syndrome. The potential for delivering a therapeutic agent to the uveal tract is also promising. Nucleoside transport for uridine has also been demonstrated to have similar directionality, preferential flow from mucosal to serosal, or apical to basolateral, sides of the conjunctival cells. Its role is presumably to salvage nucleosides from the tears, and it might be able to be exploited for compounds with antiviral activity.

Not all transporters, however, show the same preferential directions. Lee and coworkers also have discovered a pump glycoprotein in the conjunctiva with preferential flux directed toward the mucosal side of the tissue. This transporter has been shown to restrict conjunctival absorption of therapeutic agents such as cyclosporin A, verapamil, and dexamethasone. In some circumstances, transient inhibition of such xenobiotic transporters might be an effective means of increasing the efficacy of particular classes of therapeutic agents.

E. Delivery to the Vitreous and Posterior Segment

There are a number of drugs that would be of benefit for the treatment of diseases in the interior of the eye, but for which therapeutic levels cannot be achieved by topical administration [217]. Until recently the only method of achieving an effective dose was by direct intravitreal injection, employed first for antibiotics, with animal experiments beginning about the 1940s [218]. A more modern approach has been the use of a sustained-release device for implantation into the vitreous, such as the Vitrasert® (developed by Controlled Delivery Systems), the only such device approved for intraocular implantation [219]. The device contains 4.5 mg of the drug gancyclovir and is used to treat the condition of cytomegaloviral (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS). The therapy appears to be effective and well tolerated according to clinical reports and provides sustained therapy over many months [220–222].

Several practical factors must be considered when designing a device intended for intraocular use [223]. For example, the placement of the device should interfere as little as possible with vision. In the case of the Vitrasert, the device is sutured to the sclera in the region of the pars plana (Fig. 15). This region is devoid of retina; the device is also out of the central visual field and is close enough to allow visual inspection to determine when the supply of drug has been exhausted [225]. Drug release is controlled by a rate-controlling membrane.

Fig. 15 Drawing showing the optimum placement of an intravitreal sustained-release device in the eye. (From Ref. 224.)

In order to design such an efficient and effective device, one must understand the mechanisms by which drug is transported in the ocular interior. One issue debated in the literature for some time has been the relative importance of transport by passive diffusion versus that facilitated by the flow of fluid in the vitreous (see, e.g., Ref. 226). To predict the geometric distribution even at steady state of drug released from an implant or an intravitreal injection, one must appreciate which of these mechanisms is at work or, as appropriate, their relative balance.

The conclusion that convective flow may provide an important contribution was based upon observations of the distribution of colloidal particles and its evolution following intravitreal injection [227]. Such experiments could have been complicated by the large volumes that were generally injected, which might have created artificial flow channels in the vitreous gel [223], and/or by backflow out through the needle hole [228]. When intravitreal injection is performed through the superior rectus muscle, the latter complication appears to be minimized. When fluorescently labeled polymers are injected intravitreally, the ratio of polymer in the aqueous versus the vitreous cavities is inversely proportional to polymer molecular weight [229]. This suggests that the vitreous cavity is essentially stagnant and that passive diffusion is the major factor determining the flow of any xenobiotic agent.

Elimination from the vitreous occurs by one of two pathways. This can be visualized by injecting fluorescent compounds and examining the concentration distribution in frozen sections obtained after a steady state has been established [230]. If the major route of elimination is by means of the retina/choroid, at steady state the lowest concentration would be in the vicinity of the retina. The contours observed in frozen sections of the rabbit eye obtained after intravitreal injection of fluorescein exhibit this pattern, with the highest concentration immediately behind the lens (Fig. 16A). Compounds not chiefly eliminated through the retina exit the vitreous by passive diffusion and enter the posterior aqueous, where they are eliminated by the natural production and outflow of aqueous humor. In such a situation, the contours would be perpendicular to the retina, with the highest concentration towards the rear of the vitreous cavity. This appears to be the case for fluorescently labeled dextran polymer, whose contours decrease in concentration toward the hyaloid membrane (Fig. 16B).

Various articles have examined the pharmacokinetics of fluorescent compounds in the eye, developing mathematical models for the blood-retinal permeability, mainly in closed form [231–234]. More recently, sophisticated numerical methods have been developed which model the geometrical anatomical and physiological features of the eye more closely. Tojo et al. have applied the method of lines to a cylindrical model of the eye to simulate the biodistribution of several different compounds using extemporaneous Fortran code [235–239]. Begun more recently has been the application of finite element methods, at times harnessing the power of very sophisticated codes traditionally employed in modeling of fluid dynamics and mass transfer [240–245].

The power of these methods for accurately predicting the disposition of drug in the eye is illustrated in Fig. 17, where finite element analysis was used to simulate the experiments of Ref. 230 (FlexPDE was used, www.pdesolutions.com). When the retinal permeability is high, the contours resemble the experimental result for fluorescein, with the highest concentration immediately behind the lens. When the only pathway allowed is through the hyloid membrane, the contours resemble those obtained for the polymer, with the highest concentration at the rear of the vitreous cavity. Other physiological details included in simulations have been the hydrodynamics of the aqueous humor [241], the influence of the directionality of release from an intravitreal device [244], and dynamic partitioning of drug between various ocular tissues [245].

Numerical simulation methods can provide a useful predictive tool for simulating drug release from complex devices [246,247] and can aid in optimizing device design to provide sustained release of drug under idealized conditions. Their proper use will require careful characterization of the important physiological constants that govern the disposition of a particular drug and may indicate the dependency of efficacy on individual-to-individual variation [248,249]. An example of this is demonstrated in Fig. 18. The steady-state drug release profile is predicted for a hypothetical circular intravitreal device, which releases drug from only one side at a fixed rate. In the example, the retinal permeability was taken to be 4.5×10^{-6} cm/s, and the diffusion coefficient was 6×10^{-6} cm^2/s, values appropriate for the drug gancyclovir [244]. The influence of hydrodynamics of the aqueous humor were approximated by applying a permeability boundary condition at the hyloid annulus in which the clearance of drug there was 100 times higher than that for the drug at the retina.

Two issues are suggested by the Fig. 18. First, the drug concentration at the retinal surface varies by

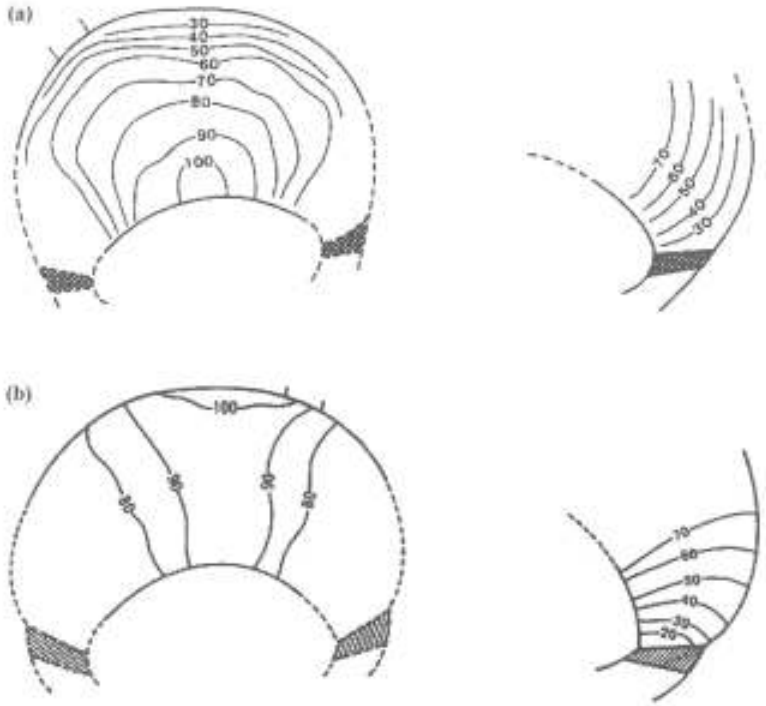

Fig. 16 Contours of fluorescent intensity in frozen sections of the rabbit eye following 15 μL injection of marker solution in the central vitreous cavity; injection was conducted through the superior rectus muscle: 15 hours following injection of 0.2% sodium fluorescein; 14 days following injection of 0.1% FITC-dextran, molecular weight 66,000. (From Ref. 230.)

orders of magnitude depending upon proximity to the implanted device. Depending upon the therapeutic index of the drug, tissues far away from the device may be undertreated, whereas tissues near the device may be overtreated and in danger of toxic exposure. Second, there is a twofold difference in average vitreous drug concentration between the front versus back-facing device, with the higher average concentration resulting from backwards placement. This illustrates the importance of geometric factors when engineering such devices, in that they impact the average and local concentrations and duration of action of therapy.

F. Conclusions

In conclusion, it should be apparent from this discussion of the absorption mechanisms that, although the major features influencing drug absorption are well known, implementation of a coherent delivery strategy is highly specific for any compound, and many variables need to be adjusted for their significant influence on absorption and more importantly, on bioavailability. In addition, from the suggestion of the role of ocular hydrodynamics, delivery strategies will also include consideration of the dosage form and its effect on local systemic and target pharmacokinetics.

Finally, from the available research into the variety of mechanisms for targetting ophthalmic drugs to specific tissues, means for integrating—both figuratively and literally—combinations of effects are now available [15]. Certainly, the combination of hydrodynamics, retention or sustained release, and diffusional or even active transport can be computed, their influence anticipated, and some specific deficiencies addressed. Nonetheless, many unanticipated interactions may often intrude and still leave the field heavily dependent on empirical assessment.

VII. MANUFACTURING CONSIDERATIONS

Because the official compendia require all topically administered ophthalmic medications to be sterile, manufacturers of such medications must weigh numerous alternative approaches as they design manufacturing procedures. Ideally, as preferred by some regulators, especially in Europe, all ophthalmic pro-

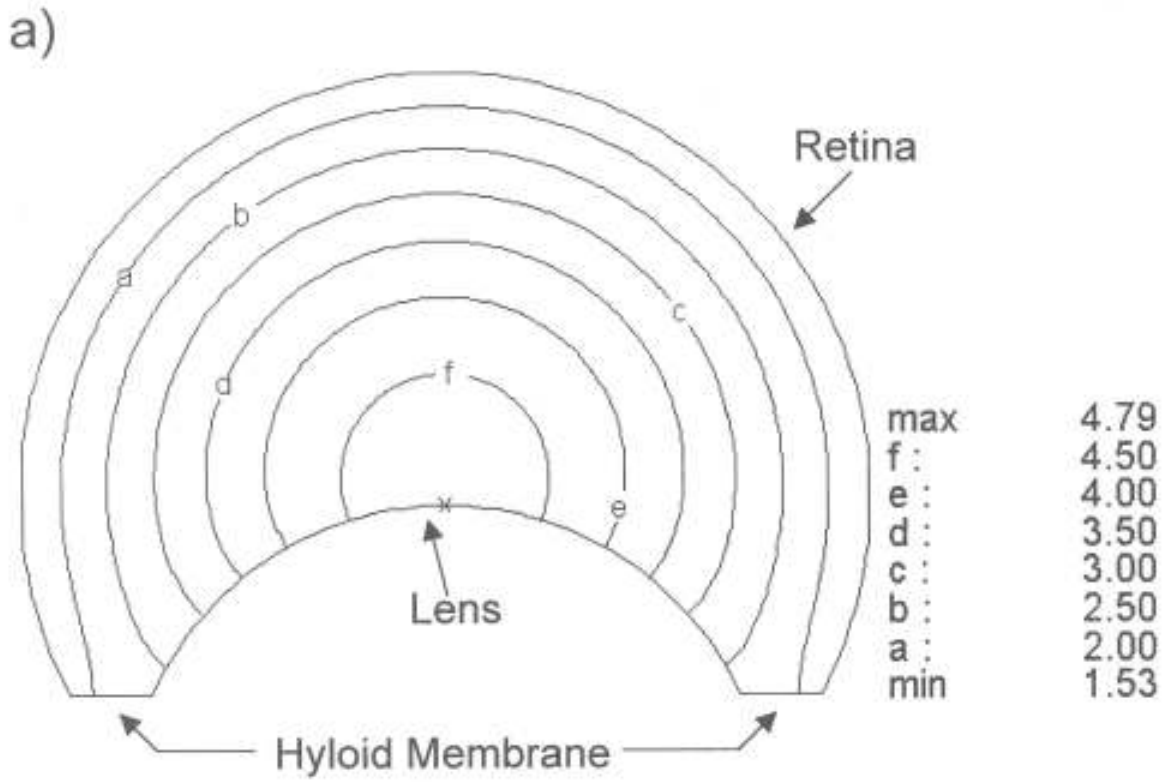

Fig. 17 Finite element modeling of concentration profiles established after central intravitreal bolus injection using FlexPDE v2.17 and a 3-D geometric model for the rabbit eye similar to Ref. 241. Arbitrary concentration units; highest concentration is marked ×. (a) Contours of drug concentration simulated 15 hours after injection, assuming reasonable values[230] for the diffusion coefficient (6×10^{-6} cm^2 s^{-1}) and retinal permeability (2.3×10^{-5} cm s^{-1}) for fluorescein. Permeability across of lens and hyloid membrane is assumed to be negligible. (b) Simulated concentration profile 14 days after injection for FITC-dextran (diffusion coefficient 6×10^{-7} cm^2 s^{-1}), assuming zero retinal permeability, and hyloid permeability 2.3×10^{-5} cm s^{-1}. Finite element mesh used is shown in the inset.

ducts would be terminally sterilized in the final packaging because it offers the best chance of assuring patients of their sterility. In effect, this would rule put any aseptic processing for the manufacture of ophthalmic products; however, the use of sterile filtration and/or aseptic assembly of ophthalmic products has been shown not to constitute a risk to public health.

It is quite rare that the composition or the packaging of an ophthalmic pharmaceutical will lend itself to terminal sterilization, the simplest form of manufacture of sterile products. Only a few ophthalmic drugs formulated in simple aqueous vehicles are stable to normal autoclaving temperatures and times (121°C for 20–30 min). Such heat-resistant drugs may be packaged in glass or other heat-deformation-resistant packaging and thus can be sterilized in this manner. The convenience of plastic dispensing bottles is possible today using modern polyolefins that resist heat deformation with proper sterilization cycles.

Most ophthalmic products, however, cannot be heat sterilized. In general, the active principle is not particularly stable to heat, either physically or chemically. Moreover, to impart viscosity, aqueous products are generally formulated with the inclusion of high molecular weight polymers, which may, similarly, be affected adversely by heat.

Because of these product sensitivities, most ophthalmic pharmaceutical products are aseptically manufactured and filled into previously sterilized containers in aseptic environments using aseptic filling-and-capping techniques. This is the case for ophthalmic solutions, suspensions, and ointments, and specialized technology is involved in their manufacture.

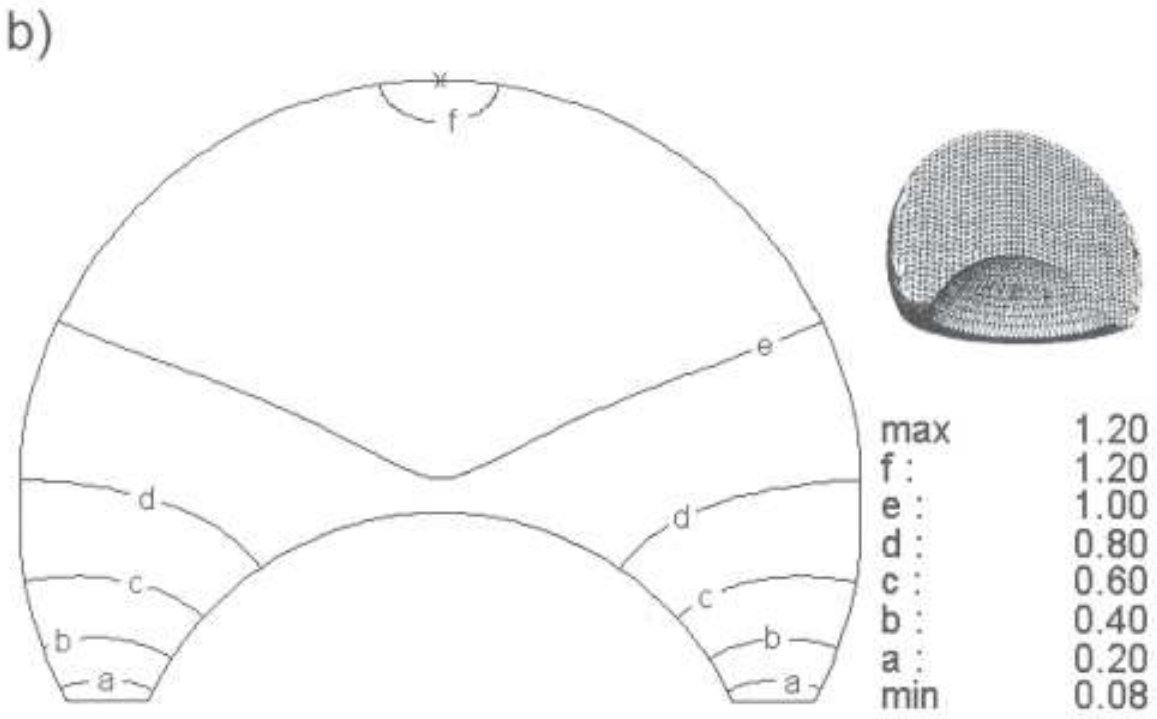

Fig. 17b

All pharmaceutical manufacturers are required to follow Current Good Manufacturing Practice (CGMPs) Part 210—Current Good Manufacturing Practice in Manufacturing, Processing, Packaging, or Holding of Drugs; General Part 211—Current Good Manufacturing Practice for Finished Pharmaceuticals. Readers can access more information from FDA's website at www.fda.gov. These guidelines cover all aspects of manufacture of pharmaceutical products.

A. Manufacturing Environment

Aside from drug safety, stability, efficacy, and shelf-life considerations associated with tonicity, pH, and buffer capacity, the major design criteria of an ophthalmic pharmaceutical product are the additional safety criteria of sterility, preservative efficacy, and freedom from extraneous foreign particulate matter. Current U.S. standards for Good Manufacturing Practices (GMPs) [250] provide for the use of specially designed environmentally controlled areas for the manufacture of sterile large- and small-volume injections for terminal sterilization. These environmentally controlled areas must meet the requirements of class 100,000 space in all areas where open containers and closures are *not* exposed, or where product filling-and-capping operations are *not* taking place. The latter areas must meet the requirements of class 100 space [251]. As defined in Federal Standard 209E, class 100,000 and 100 spaces contain not more than 100,000 or 100 particles, respectively, per cubic foot of air of a diameter of 0.5 μm or larger. The readers are also referred to the British Standard 5295, 1989, for classification of cleanroom environments. Often these design criteria are coupled with laminar airflow concepts [252,253]. This specification deals with total particle counts and does not differentiate between viable and nonviable particles. Federal Standard 209 was promulgated as a "hardware" or mechanical specification for the aerospace industry and has found applications in the pharmaceutical industry as a tool for the design of aseptic and particle-free environments. Class 100,000 conditions can be achieved in the conventionally designed cleanroom, where proper filtration of air supply and adequate turnover rates are provided. Class 100 conditions over open containers can be achieved with properly sized HEPA (high-efficiency particulate air) filtered laminar airflow sources. Depending on the

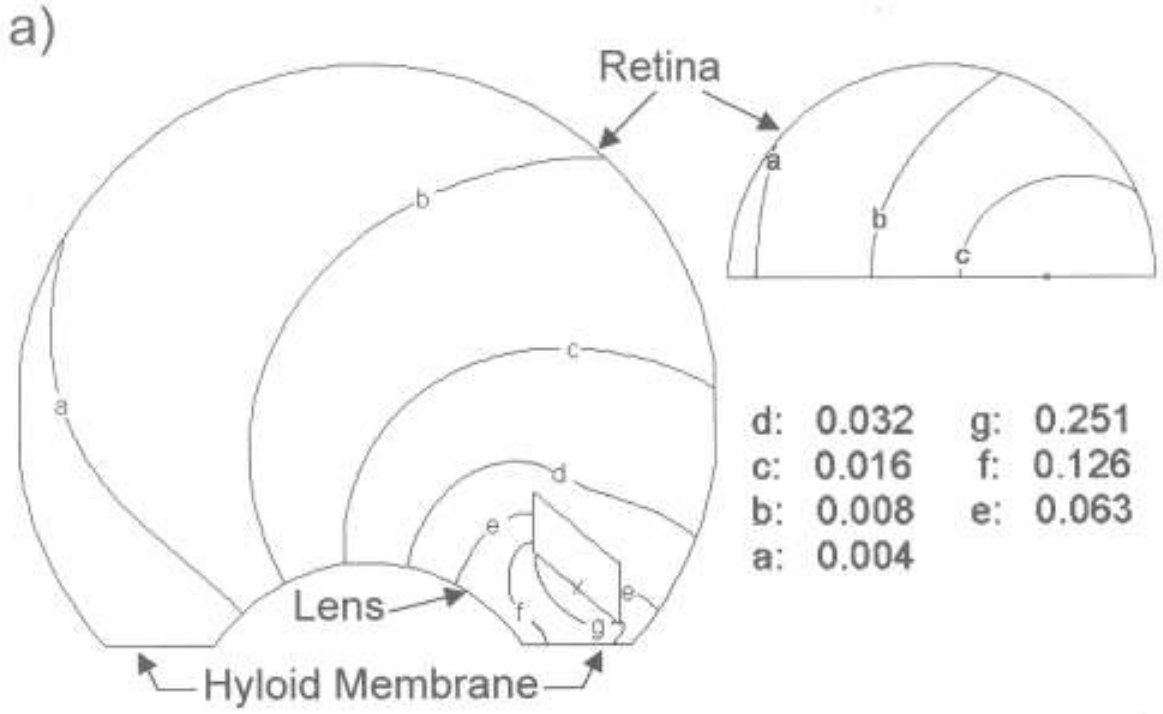

Fig. 18 Finite element modeling of steady-state concentration profiles in the human eye[241] from a hypothetical device that releases from one side only. (a) Device releases towards the front; (b) device releases towards the back. Arbitrary concentration units (scale, inset a); highest concentration marked ×. Contours are shown for x-z plane and for x-y plane through the center. x-z portion of finite element mesh displayed (inset b); device (opaque to diffusion) represented by voided region. (Adapted from Ref. 244.)

product need and funds available, some aseptic pharmaceutical environments have been designed to class 100 laminar-flow specifications throughout the manufacturing area. However, during actual product manufacture the generation of particulate matter by equipment, product, and (most importantly) people may cause these environments to demonstrate particulate matter levels two or more orders of magnitude greater than design. It is for this reason that specialists in the design of pharmaceutical manufacturing and hospital operating room environments are beginning to view these environments not only from the standpoint of total particles per cubic foot of space alone, but also from the standpoint of the types of particles, for example, the ratio of disease-transmitting biocontaminants to inert particulates [254].

Such environmental concepts as mass air transfer may lead to meaningful specifications for the space in which a nonterminally sterilized product can be manufactured with a high level of confidence [255].

When dealing with the environment in which a sterile product is manufactured, the materials used for construction of the facility, as well as personnel attire, training, conduct in the space, the entrance and egress of personnel, equipment, and packaging, and the product, all bear heavily on the assurance of product sterility and minimization of extraneous particulate matter.

The importance of personnel training and behavior cannot be overemphasized in the maintenance of an acceptable environment for the manufacture of sterile ophthalmic products or sterile pharmaceutical agents in general. Personnel must be trained in the proper mode of gowning with sterile, nonshedding garments and in the proper techniques and conduct for aseptic manufacturing. The Parenteral Drug Association can be contacted at their offices in Bethesda, Maryland, for a listing of available training films on this subject. To maximize personnel comfort and to minimize sloughing of epidermal cells and hair, a cool working environment should be maintained, with relative humidities controlled to between 40 and 60%.

Additional guidelines on pharmaceutical cleanroom classifications (which became effective on January 1, 1997, for Europe) are contained in Ref. 263.

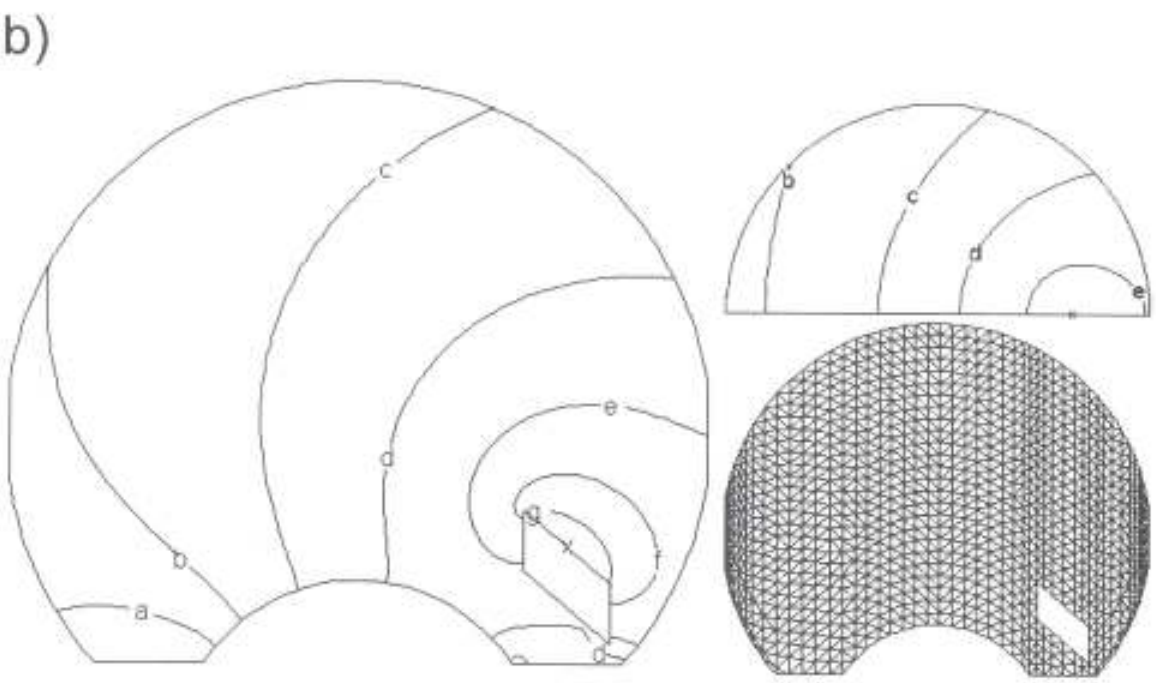

Fig. 18b

B. Manufacturing Techniques

In general, aqueous ophthalmic solutions are manufactured by methods that call for the dissolution of the active ingredient and all or a portion of the excipients into all or a portion of the water and the sterilization of this solution by heat or by sterilizing filtration through sterile depth or membrane filter media into a sterile receptacle. If incomplete at this point, this sterile solution is then mixed with the additional required sterile components, such as previously sterilized solutions of viscosity-imparting agents, preservatives, and so on, and the batch is brought to final volume with additional sterile water.

Aqueous suspensions are prepared in much the same manner, except that before bringing the batch to final volume with additional sterile water, the solid that is to be suspended is previously rendered sterile by heat, by exposure to ethylene oxide or ionizing radiation (gamma or electrons), or by dissolution in an appropriate solvent, sterile filtration, and aseptic crystallization. The sterile solid is then added to the batch, either directly or by first dispersing the solid in a small portion of the batch. After adequate dispersion, the batch is brought to final volume with sterile water. Because the eye is sensitive to particles larger than 25 μm in diameter, proper raw material specifications for particle size of any dispersed solids must be established and verified on each lot of raw material and final product. The control of particle size of the final suspended material is very important, not only for comfort of the product but also for improving physical stability and resuspendability of the suspension throughout the shelf life and the in-use life by patients. Manufacturing of some suspension products [256] may require modified processes in order to control particle size and obtain a sterile product.

When an ophthalmic ointment is manufactured, all raw material components must be rendered sterile before compounding unless the ointment contains an aqueous fraction that can be sterilized by heat, filtration, or ionizing radiation. The ointment base is sterilized by heat and appropriately filtered while molten to remove extraneous foreign particulate matter. It is then placed into a sterile steam-jacketed kettle to maintain the ointment in a molten state under aseptic conditions, and the previously sterilized active ingredient(s) and excipients are added aseptically. While still molten, the entire ointment may be passed through a previously sterilized colloid mill for adequate dispersion of the insoluble components.

After the product is compounded in an aseptic manner, it is filled into previously sterilized containers. Commonly employed methods of sterilization of packaging components include exposure to heat, ethylene oxide gas, and ^{60}Co (gamma) irradiation. When a product is to be used in conjunction with ophthalmic surgical procedures and must enter the aseptic operating area, the exterior of the primary container must be rendered sterile by the manufacturer and maintained sterile with appropriate packaging. This may be accomplished by aseptic packaging or by exposure of the completely packaged product to ethylene oxide gas, ionizing radiation, or heat. Whenever ethylene oxide is used as a sterilant for either the raw material or packaging components, strict processing controls and validated aeration cycles are required to assure lower residual limits permitted by the regulatory agencies.

With the need of, and the preference for, unpreserved formulations of active drug(s) by ophthalmologists and patients, the blow/fill/seal concept, also termed the form/fill/seal method, has gained acceptance for manufacture of unpreserved ophthalmic products, especially for artificial tear products. In this process, the first step is to extrude polyethelene resin at high temperature and pressure and to form the container by blowing the resin into a mold with compressed air. The product is filled as air is vented out, and finally the container is sealed on the top. There are several published articles describing and validating this technology [257–262]. Automatic Liquid Packaging, Incorporated (Woodstock, IL) designs and fabricates Blow/Fill/Seal machines and provides contract manufacture in the United States. Hollopack (BottlePack-6) provides similar equipment in Europe.

C. Raw Materials

All raw materials used in the compounding of ophthalmic pharmaceutical products must be of the highest quality available. Complete raw material specifications for each component must be established and verified for each lot purchased. As many pharmaceutical companies improve efficiency and increase product distribution by qualifying a single plant to provide product globally, it becomes necessary to qualify excipients for global distribution. Excipients used in the product need to be tested for multiple pharmacopeial specifications to meet global requirements (USP, Pharma Europe, Japanese Pharmacopoeia). When raw materials are rendered sterile before compounding, the reactivity of the raw material with the sterilizing medium must be completely evaluated, and the sterilization must be validated to demonstrate its capability to sterilize raw materials contaminated with large numbers (10^5–10^7) of microorganisms that have been demonstrated to be most resistant to the mode of sterilization appropriate for that raw material. As mentioned previously, for raw material components that will enter the eye as a suspension in an appropriate vehicle, particle size must be carefully controlled both before use in the product and as a finished product specification.

As for most sterile (and nonsterile) aqueous pharmaceuticals, the largest portion of the composition is water. At present, USP 24 allows the use of "purified water" as a pharmaceutical aid for all official aqueous products, with the exception of preparations intended for parenteral administration [264]. For preparations intended for parenteral administration, USP 24 requires the use of water for injection (WFI), sterile water injection, or bacteriostatic water for injection as a pharmaceutical aid. Because some pharmaceutical manufacturers produce a line of parenteral ophthalmic drugs and devices (large-volume and small-volume irrigating and "tissue-sparing" solutions) as well as topical ophthalmic drugs, the provision of WFI manufacturing capability is being designed into new and existing facilities to meet this requirement. Some manufacturers have made the decision to compound *all* ophthalmic drugs from WFI, thus employing the highest grade of this raw material economically available to the pharmaceutical industry. In doing so, systems must be designed to meet all the requirements for WFI currently listed in the USP [264] and the guidelines listed for such systems by FDA in its Good Manufacturing Practices guidelines for large- and small-volume parenterals [265]. Briefly, these proposals call for the generation of water by distillation or by reverse osmosis and its storage and circulation at relatively high temperatures of up to 80°C (or, alternatively, its disposal every 24 hours), in all stainless steel equipment of the highest attainable corrosion-resistant quality.

D. Equipment

The design of equipment for use in controlled environment areas follows similar principles, whether for general injectable manufacturing or for the manufacturer of sterile ophthalmic pharmaceuticals. All tanks, valves, pumps, and piping must be of the best available grade of corrosion-resistant stainless steel. In general, stainless steel type 304 or 316 is preferable.

All product-contact surfaces should be finished either mechanically or by electropolishing to provide a surface as free as possible from scratches or defects that could serve as a nidus for the commencement of corrosion [266]. Care should be taken in the design of such equipment to provide adequate means of cleaning and sanitization. For equipment that will reside in aseptic-filling areas, such as filling and capping machines, care should be taken in their design to yield equipment as free as possible from particle-generating mechanisms. Wherever possible, belt- or chain-drive concepts should be avoided in favor of sealed gear or hydraulic mechanisms. Additionally, equipment bulk located directly over open containers should be held to an absolute minimum during filling-and-capping operations in order to minimize introduction of equipment-generated particulate matter or creation of air turbulence. This precaution is particularly important when laminar flow is used to control the immediate environment around the filling-capping operation.

In the design of equipment for the manufacture of sterile ophthalmic (and nonophthalmic) pharmaceuticals, manufacturers and equipment suppliers are turning to the advanced technology in use in the dairy and aerospace industries, where such concepts as CIP (clean-in-place), COP (clean-out-of-place), automatic heliarc welding, and electropolishing have been in use for several years. As a guide here, the reader is referred to the so-called 3A Standards of the dairy industry issued by the U.S. Public Health Service [267].

Some of the newer and more potent drugs, like the prostaglandins, which are produced at very low concentrations in the finished formulation, may require special precautions during compounding and processing in order to prevent loss of actives due to adsorption/absorption to the walls of fill lines and/or storage tanks.

VIII. CLASSES OF OPHTHALMIC PRODUCTS

A. Topical Eyedrops

Administration and Dosage

Although many alternate experimental methods have been tried, the use of eyedrops remains the major method of administration for the topical ocular route. The usual method of self-administration is to place the eyedrop from a dropper or dropper bottle into the lower cul-de-sac by pulling down the eyelid, tilting the head backward, and looking at the ceiling after the tip is pointed close to the sac, and applying a slight pressure to the rubber bulb or plastic bottle to allow a single drop to form and fall into the eye. Most people become quite adept at this method with some practice and may develop their own modifications. However, elderly, arthritic, low-vision, and glaucoma patients often have difficulty in self-administration and may require another person to instill the drops.

The pharmacist should instruct patients to keep in mind the following considerations in administering drops to help improve the accuracy and consistency of dosage and to prevent contamination: be sure that the hands are clean; do not touch the dropper tip to the eye, surrounding tissue, or any surface; prevent squeezing or fluttering of lids which causes blinking; place the drop in the conjunctival sac, not on the globe; close the lids for several moments after instillation. The administration of eyedrops to young children can be a difficult task. A way to simplify the task involves the parent's sitting on the floor or a flat surface and placing the child's head firmly between the parent's thighs and crossing legs over the child's lower truck and legs. The parent's hands are then free to lower the eyelid and administer the drops.

In addition to the proper technique to administer eyedrops, the pharmacist may need to explain to the patient the correct technique for temporary punctal occlusion. Punctal occlusion is usually reserved for use with potent drugs which can have adverse systemic effects from topical ocular administration such as with ocular β-blockers. Tear fluid drains into the nasolacrimal duct via the puncta located on the medial portion of the eyelid and fluid is directed into the puncta by the blinking action of the lids. The nasal meatus is a highly vascular area within the nasal cavity which receives the fluid of the nasolacrimal duct, and drugs contained in tears can be absorbed into the systemic circulation from this area as well as from gastrointestinal absorption. Punctal occlusion can be performed immediately after instillation of an eyedrop by closing the eye and placing a finger between the eyeball and the nose and applying pressure for several minutes.

Eyedrops are one of the few dosage forms not administered by exact volume or weight dosage, yet this seemingly imprecise method of dosing is quite well established and accepted by ophthalmologists. The volume of a drop is dependent on the physiochemical properties of the formulation, particularly surface tension; the design and geometry of the dispensing office; and the angle at which the dispenser is held in relation to the receiving surface. The manufacturer of ophthalmic products controls the tolerances necessary

for the dosage form and dispensing container to provide a uniform drop size. How precise does the actual dose have to be? As noted earlier, the normal tear volume is about 7 μL, and with blinking about 10 μL can be retained in the eye. Approximately 1.2 μL of tears is produced per minute, for about a 16% volume replacement per minute. Commercial ophthalmic droppers deliver drops of about 30–50 μL. Therefore, the volumes delivered normally are more than threefold larger than the eye can hold, and the fluid that does remain in the eye is continuously being removed until the normal tear volume is attained. It can be seen, then, that the use of more than 1 drop/dose must take into account the fluid volume and dynamics of the lacrimal system of the eye. If the effect of multiple drops is desired, they should be administered 1 drop at a time with a 3- to 5-minute interval in between dosings. Some doctors may prescribe more than 1 drop/dose to ensure that the patients retains at least 1 drop in the eye.

Dosage Forms

Solutions. The two major physical forms of eyedrops are aqueous solutions and suspensions. Nearly all the major ophthalmic therapeutic agents are water soluble or can be formulated as water-soluble salts. A homogeneous solution offers the assurance of greater uniformity of dosage and bioavailability and simplifies large-scale manufacture. The selection of the appropriate salt form depends on its solubility, therapeutic concentrations required, ocular toxicity, the effect of pH, tonicity, and buffer capacity, its compatibility with the total formulation, and the intensity of any possible stinging or burning sensations (i.e., discomfort reactions). The most common salt forms used are the hydrochloride, sulfate, nitrate, and phosphate. Salicylate, hydrobromide, and bitartrate salts are also used. For drugs that are acidic, such as the sulfonamides, sodium and diethanolamine salts are used. The effect that choice of salt form can have on resulting product properties is exemplified by the epinephrine solutions available, as shown in Table 3. The bitartrate form is a 1:1 salt, and the free carboxyl group acts as a strong buffer, resisting neutralization by the tears, and may cause considerable stinging. The borate form results in a solution with lower buffer capacity, a more nearly physiological pH, and better patient tolerance; however, it is less stable than the other two salts. The hydrochloride salt combines better stability than the borate with acceptable patient tolerance.

Gel-Forming Solutions. One disadvantage of solutions is their relatively short residence time in the eye. This has been overcome to some degree by the development of solutions that are liquid in the container and thus can be instilled as eyedrops but gel on contact with the tear fluid and provide increased contact time with the possibility of improved drug absorption and increased duration of therapeutic effect.

A number of liquid-gel phase transition-dependent delivery systems have been researched and patented. They vary according to the particular polymer(s) employed and their mechanism(s) for triggering the transition to a gel phase in the eye. The mechanisms that make them useful for the eye take advantage of changes in temperature, pH, ion sensitivity, or ionic strength upon contact with tear fluid or due to the presence of proteins such as lysozyme in the tear fluid. Thermally sensitive systems, which are transformed to a gel phase by the change in temperature associated with reaching body temperature, have the disadvantage of possibly gelling in the container when subjected to warmer climatic conditions. The pH-sensitive systems may have limited use for drugs that require a neutral to slightly alkaline environment for stability, solubility, etc.

Gel-forming ophthalmic solutions have been developed and approved by FDA for timolol maleate, which is used to reduce elevated intraocular pressure (IOP) in the management of glaucoma. Timolol maleate ophthalmic solutions, as initially developed, require twice-a-day dosage for most patients. With the gel-forming solutions, IOP-lowering efficacy was extended from 12 to 24 hours and thus required only once-a-day dosing. This extended duration of efficacy was demonstrated for both gel-forming products in controlled clinical

Table 3 Effects of Salt Form on Product Properties

Salt form	Discomfort reaction	pH range	Buffer capacity
Epinephrine hydrochloride	Mild to moderate stinging	2.5–4.5	Medium
Epinephrine bitartrate	Moderate to severe stinging	3–4	High
Epinephrine borate	Only occasional mild stinging	5.5–7.5	Low

trials. The first gel-forming product, Timolol® XE, uses the polysaccharide gellan gum and is reported to gel in situ in response to the higher ionic strength of tear fluid (U.S. Patent 4,861,760). Alternative ion-sensitive gelling systems have been patented [3–5]. The second product, (timolol maleate), uses the polysaccharide xanthan gum as the gelling agent and is reported to gel upon contact with the tear fluid, at least in part due to the presence of tear protein lysozyme (U.S. Patent 6,174,524).

Suspension. If the drug is not sufficiently soluble, it can be formulated as a suspension. A suspension may also be desired to improve stability, bioavailability, or efficacy. The major topical ophthalmic suspensions are the steroid anti-inflammatory agents prednisolone acetate, dexamethasone, fluorometholone, and rimexolone. Water-soluble salts of prednisolone phosphate and dexamethasone phosphate are available; however, they have a lower steroid potency and are poorly absorbed.

An ophthalmic suspension should use the drug in a microfine form; usually 95% or more of the particles have a diameter of 10 μm or less. This is to ensure that the particles do not cause irritation of the sensitive ocular tissues and that a uniform dosage is delivered to the eye. Since a suspension is made up of solid particles, it is at least theoretically possible that they may provide a reservoir in the cul-de-sac for slightly prolonged activity. However, it appears that this is not so, since the drug particles are extremely small, and with the rapid tear turnover rate they are washed out of the eye relatively quickly.

Pharmaceutical scientists have developed improved suspension dosage forms to overcome problems of poor physical stability and patient-perceived discomfort attributed to some active ingredients. An important development aspect of any suspension is the ability to resuspend easily any settled particles prior to instillation in the eye and ensure that a uniform dose is delivered. It would be ideal to formulate a suspension that does not settle since the patient may not always follow the labeled instructions to shake well before using. However, this is usually not feasible or desirable since the viscosity required to retard settling of the insoluble particles completely would likely be excessive for a liquid eyedrop. The opposite extreme, of allowing complete settling between doses, usually leads to a dense layer of agglomerated particles that are difficult to resuspend.

An improved suspension has been developed, which controls the flocculation of the insoluble active ingredient particles, such that they will remain substantially resuspended (95%) for many months and any settled particles can be easily resuspended with only a few seconds of gentle hand shaking. This improved vehicle utilizes a charged water-soluble polymer and oppositely charged electrolyte such as negatively charged carbomer polymer of very high molecular weight and large dimension and a cation such as sodium or potassium. The negatively charged carboxy vinyl polymer is involved in controlling the flocculation of the insoluble particles, such as the steroid rimexolone, and the cation assists in controlling the viscosity of the vehicle such that the settling is substantially retarded, yet can be easily and uniformly resuspended and can be dispensed from a conventional plastic eyedrop container (U.S. Patent 5,461,081).

In some cases it may be advantageous to convert a water-soluble active ingredient to an insoluble form for development as an ophthalmic suspension dosage form. This could be the case when it is beneficial to extend the practical shelf life of the water-soluble form, to improve the compatibility with other necessary compositional ingredients, or to improve its ocular tolerability. Such an example is the β-blocker betaxolol HCL, which is an effective IOP-lowering agent with clinically significant safety advantages for many asthmatic patients. With the ophthalmic solution dosage form some patients experienced discomfort characterized as a transient stinging or burning upon instillation. Although this did not interfere with the safety or efficacy of the product, it was desirable to improve the patient tolerability. Many solution-based formulations were tried but with limited success. It was discovered that an insoluble form of betaxolol (Betoptic®S) could be produced in situ with the use of a combination of a high molecular weight polyanionic polymer such as carbomer and a sulfonic acid cation exchange resin. The resultant optimized suspension increased the ocular bioavailability of betaxolol such that the drug concentration required to achieve equivalent efficacy to the solution dosage form was reduced by one half and the ocular tolerance was improved significantly. It would appear that the sustained release of the active betaxolol occurs through exchange with cations such as sodium and potassium in tear fluid resulting in prolonged tear levels of the drug and substantial increase in ocular bioavailability (U.S. Patent 4,911,920).

Powders for Reconstitution. Drugs that have only limited stability in liquid form are prepared as sterile powders for reconstitution by the pharmacist prior to dispensing to the patient. In ophthalmology, these drugs include α-chymotrypsin, echothiophate iodide

(Phospholine Iodide®), dapiprazole HCl (Rev-Eyes®), and acetylcholine (Miochol®). The sterile powder is usually manufactured by lyophilization in individual glass vials. In powder form these drugs have a much longer shelf life than in solution. Mannitol is usually used as a bulking agent and lyophilization aid and is dissolved in the solution with the drug prior to drying. In the case of echothiophate iodide, it was found that potassium acetate used in place of mannitol as a drying aid produced a more stable product. Apparently the presence of potassium acetate with the drug allows freeze-drying to a lower residual moisture content (U.S. Patent 3,681,495). A stable echothiophate product has also been produced by freeze-drying from an alcoholic solution without a co-drying or bulking agent, but the product is no longer marketed.

A separately packaged sterile diluent and sterile dropper assembly is provided with the sterile powder and requires aseptic technique to reconstitute. The pharmacist should only use the diluent supplied by the manufacturer since it has been developed to maintain the optimum potency and preservation of the reconstituted solution. The storage conditions and expiration dating for the final solution should be emphasized to the patient.

Inactive Ingredients in Topical Drops

The therapeutically inactive ingredients in ophthalmic solution and suspension dosage forms are necessary to perform one or more of the following functions: adjust concentration and tonicity, buffer and adjust pH, stabilize the active ingredients against decomposition, increase solubility, impart viscosity, and act as solvent. The use of unnecessary ingredients is to be avoided, and the use of ingredients solely to impart a color, odor, or flavor is prohibited.

The choice of a particular inactive ingredient and its concentration is based not only on physical and chemical compatibility, but also on biocompatibility with the sensitive and delicate ocular tissues. Because of the latter requirement, the use of inactive ingredients is greatly restricted in ophthalmic dosage forms.

The possibility of systemic effects due to nasolacrimal drainage as previously discussed should also be kept in mind. FDA has catalogued all inactive ingredients in approved drug products and provides this information at www.fda.gov/cder/drug/iig. The listings are alphabetical by inactive ingredient and provide the routes of administration, dosage forms, and quantitative usage ranges.

Tonicity and Tonicity-Adjusting Agents. In the past a great deal of emphasis was placed on teaching the pharmacist to adjust the tonicity of an ophthalmic solution correctly (i.e., exert an osmotic pressure equal to that of tear fluids, generally agreed to be equal to 0.9% NaCl). In compounding an eye solution, it is more important to consider the sterility, stability, and preservative aspects and not jeopardize these aspects to obtain a precisely isotonic solution. A range of 0.5–2.0% NaCl equivalency does not cause a marked pain response, and a range of about 0.7–1.5% should be acceptable to most persons. Manufacturers are in a much better position to make a precise adjustment, and thus their products will be close to isotonic, since they are in a competitive situation and are interested in a high percentage of patient acceptance for their products. In certain instances, the therapeutic concentration of the drug will necessitate using what might otherwise be considered an unacceptable tonicity. This is the case for sodium sulfacetamide, for which the isotonic concentration is about 3.5%, but the drug is used in 10–30% concentrations. Fortunately, the eye seems to tolerate hypertonic solutions better than hypotonic ones. Various textbooks deal with the subject of precise tonicity calculations and determination. Several articles [268] have recommended practical methods of obtaining an acceptable tonicity in extemporaneous compounding. Common tonicity-adjusting ingredients include NaCl, KCl, buffer salts, dextrose, glycerin, propylene glycol, and mannitol.

pH Adjustment and Buffers. The pH and buffering of an ophthalmic solution is probably of equal importance to proper preservation, since the stability of most commonly used ophthalmic drugs is largely controlled by the pH of their environment. Manufacturers place particular emphasis on this aspect, since economics indicate that they produce products with long shelf lives that will retain their labeled potency and product characteristics under the many and varied storage conditions outside the makers' control. The pharmacist and wholesaler must become familiar with labeled storage directions for each product and assure that it is properly stored. Particular attention should be paid to products requiring refrigeration. The stability of nearly all products can be enhanced by refrigeration except for those few in which a decrease in solubility and precipitation might occur. Freezing of ophthalmic products, particularly suspensions, should be avoided. A freeze-thaw cycle can induce particle growth or crystallization of a suspension and increase the chance of ocular irritation and loss of dosage uniformity.

Glass-packaged liquid products may break owing to the volume expansion of the solution when it freezes. It is especially important that the pharmacist fully advise the patient on proper storage and use of ophthalmic products to ensure their integrity and their safe and efficacious use.

In addition to stability effects, pH adjustment can influence comfort, safety, and activity of the product. Comfort can be described as the subjective response of the patient after instillation of the product in the cul-de-sac (i.e., whether it may cause a pain response such as stinging or burning). Eye irritation is normally accompanied by an increase in tear fluid secretion (a defense mechanism) to aid in the restoration of normal physiological conditions. Accordingly in addition to the discomfort encountered, products that produce irritation will tend to be flushed from the eye, and hence a more rapid loss of medication may occur with a probable reduction in the therapeutic response [15].

Ideally, every product would be buffered to a pH of 7.4, considered the normal physiological pH of tear fluid. The argument for this concept is that the product would be comfortable and have optimum therapeutic activity. Various experiments, primarily in rabbits, have shown an enhanced effect when the pH was increased, owing to the solution containing a higher concentration of the nonionized lipid-soluble drug base, the species that can penetrate the corneal epithelial barrier more rapidly. This would not be true if the drug were an acidic moiety. The tears have some buffer capacity of their own, and it is believed that they can neutralize the pH of an instilled solution if the quantity of solutions is not excessive and if the solution does not have a strong resistance to neutralization. Pilocarpine activity is apparently the same whether applied from vehicles with nearly physiological pH values or from more acidic vehicles, provided the latter are not strongly buffered [269]. A pH difference of 6.6 versus 4.2 produced a statistically insignificant difference in pilocarpine miosis [270]. The pH values of ophthalmic solutions are adjusted within a range to provide an acceptable shelf life. When necessary, they are buffered adequately to maintain stability within this range for at least 2 years. If buffers are required, their capacity is controlled to be as low as possible, thus enabling the tears to bring the pH of the eye back to the physiological range. Since the buffer capacity is determined by buffer concentration, the effect of buffers on tonicity must also be taken into account—another reason that ophthalmic products are usually only lightly buffered.

The pH value is not the sole contributing factor to discomfort with use of some ophthalmic solutions. It is possible to have a product with a low pH and little buffer capacity that is more comfortable than a similar product with a higher pH and a stronger buffer capacity. Epinephrine hydrochloride and dipivefrin hydrochloride solutions, used for treatment of glaucoma, have a pH of about 3, yet they have sufficiently acceptable comfort to be used daily for many years. The same pH solution of epinephrine bitartrate has an intrinsically higher buffer capacity and will produce much more discomfort.

The acidic nonsteroidal anti-inflammatory agents produce significant stinging and burning upon topical ocular instillation, and this limits the concentration of drug that can be developed. Caffeine, a xanthine derivative, has been found to improve significantly the comfort of drugs such as suprofen (Profenal®) by forming in situ weak complexes with the NSAID (U.S. Patent 4,559,343).

Stablizers. Stabilizers are ingredients added to a formula to decrease the rate of decomposition of the active ingredients. Antioxidants are the principal stabilizers added to some ophthalmic solutions, primarily those containing epinephrine and other oxidizable drugs. Sodium bisulfite or metabisulfite are used in concentration up to 0.3% in epinephrine hydrochloride and bitartrate solutions. Epinephrine borate solutions have a pH range of 5.5–7.5 and offer a more difficult challenge to formulators who seek to prevent oxidation. Several patented antioxidant systems have been developed specifically for this compound. These consist of ascorbic acid and acetylcysteine, and sodium bisulfite and 8-hydroxyquinoline. Isoascorbic acid is also an effective antioxidant for this drug. Sodium thiosulfate is used with sodium sulfacetamide solutions.

Surfactants. The use of surfactants is greatly restricted in formulating ophthalmic solutions. The order of surfactant toxicity is anionic > cationic >> nonionic. Several nonionic surfactants are used in relatively low concentrations to aid in dispersing steroids in suspensions and to achieve or to improve solution clarity. Those principally used are the sorbitan ether esters of oleic acid (Polysorbate or Tween 20 and 80), polymers of oxyethylated octyl phenol (Tyloxapol), and polyoxyl 40 stearate. The lowest concentration possible is used to perform the desired function. Their effect on preservative efficacy and their possible binding by macromolecules must be taken into account, as well as their effect on ocular irritation. The use of surfactants as cosolvents for an ophthalmic solution of chloramphenicol has been described [271]. This com-

position includes polyoxyl 40 stearate and polyethylene glycol to solubilize 0.5% chloramphenicol. These surfactants-cosolvents provide a clear aqueous solution of chloramphenicol and a stabilization of the antibiotic in aqueous solution. Polyethoxylated ethers of castor oil are used reportedly for solubilization in Voltaren® (diclofenac sodium) ophthalmic solution (U.S. Patent 4,960,799).

Viscosity-Imparting Agents. Polyvinyl alcohol, methylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, and one of the several high molecular weight cross-linked polymers of acrylic acid, known as Carbomers [270], are commonly used to increase the viscosity of ophthalmic solutions and suspensions. Although they reduce surface tension significantly, their primary benefit is to increase the ocular contact time, thereby decreasing the drainage rate and increasing drug bioavailability. A secondary benefit of the polymer solutions is a lubricating effect that is largely subjective, but noticeable to many patients. One disadvantage to the use of the polymers is their tendency to dry to a film on the eyelids and eyelashes; however, this can be easily removed by wiping with a damp tissue.

Numerous studies have shown that increasing the viscosity of ophthalmic products increases contact time and pharmacological effect, but a plateau is reached after which further increases in viscosity produce only slight or no increase in effect. The location of the plateau is drug- and formulation-dependent. Blaugh and Canada [271] using methylcellulose solutions found increased contact time in rabbits up to 25 cP (centipoise) and a leveling off at 55 cP. Linn and Jones [272] studied the rate of lacrimal excretion in humans using a dye solution in methylcellulose concentration from 0.25 to 2.5%, corresponding to viscosities of 6–30,000 cP, the latter being a thick gel. The results are shown in Table 4.

Chrai and Robinson [273] conducted studies in rabbits and found that, over a range of 1.0–12.5 cP viscosity, there is a threefold decrease in the drainage rate constant and a further threefold decrease over the viscosity range of 12.5–100 cP. This decrease in drainage rate increased the concentration of drug in the precorneal tear film at zero time and subsequent time periods, which resulted in a higher aqueous humor drug concentration. The magnitude of the increase in drug concentration in the aqueous humor was smaller than the increase in viscosity, about 1.7 times, for the range 1.0–12.5 cP, and only a further 1.2-fold increase at 100 cP. Since direct determination of ophthalmic bioavailability in humans is not possible without endangering the eye, investigators have used fluorescein to study factors affecting bioavailability in the eye, because its penetration can be quantified in humans through the use of slit-lamp fluorophotometer. Adler et al. [274], using this technology, found only small increases in dye penetration over a wide range of viscosities. The use of fluorescein data to extrapolate vehicle effects to ophthalmic drugs in general would be questionable owing to the large differences in chemical structure, properties, and permeability existing between fluorescein and most ophthalmic drugs.

Table 4 Effect of Viscosity on Product Contact Time

Methylcellulose concentration (%)	Time to dye appearance through nasolacrymal duct (s)
0.0	60
0.25	90
0.50	140
1.00	210
2.50	255

The major commercial viscous vehicles are hydroxypropyl methylcellulose (Isopto®) and polyvinyl alcohol (Liquifilm®). Isopto products most often use 0.5% of the cellulosic and range from 10 to 30 cP in viscosity. Liquifilm products have viscosities of about 4–6 cP and use 1.4% polymer.

Although usually considered to be inactive ingredients in ophthalmic formulations added because they impart viscosity, many of these polymers function as ocular lubricants. They are marketed as the active ingredients in OTC ocular lubricants used to provide relief from dry eye conditions. The regulatory requirements for these OTC products are found in the FDA Code of Federal Regulations (21CFR349.12), and their formulations are presented in the Twelfth Edition of the *APhA Handbook of Nonprescription Drugs*.

In summary, there are numerous variables to be adjusted and many choices of excipients required when tailoring a formulation of a particular therapeutic agent for ophthalmic application. But ultimately the choice rests on finding an economically viable formulation that clinically enhances the therapeutic index for that drug.

Vehicles. Ophthalmic drops are, with few exceptions, aqueous fluids using purified water USP as the solvent. Water for injection is not required as it is in parenterals. Purified water meeting USP standards may

be obtained by distillation, deionization, or reverse osmosis. All ophthalmic drops must be rendered sterile.

Oils have been used as vehicles for several topical eyedrop products that are extremely sensitive to moisture. Tetracycline HCl is an antibiotic that is stable for only a few days in aqueous solution. It is supplied as a 1% sterile suspension with Plastibase 50W and light liquid petrolatum. White petrolatum and its combination with liquid petrolatum to obtain a proper consistency is routinely used as the vehicle for ophthalmic ointments.

When oils are used as vehicles in ophthalmic fluids, they must be of the highest purity. Vegetable oils such as olive oil, castor oil, and sesame oil have been used for extemporaneous compounding. These oils are subject to rancidity and, therefore, must be used carefully. Some commercial oils, such as peanut oil, contain stabilizers that could be irritating. The purest grade of oil, such as that used for parenteral products, would be advisable for ophthalmics.

Packaging

Eyedrops have been packaged almost entirely in plastic dropper bottles since the introduction of the Drop-Tainer® plastic dispenser in the 1950s. A few products still remain in glass dropper bottles because of special stability considerations. The main advantage of the Drop-Trainer and similarly designed plastic dropper bottles are convenience of use by the patient, decreased contamination potential, lower weight, and lower cost. The plastic bottle has the dispensing tip as an integral part of the package. The patient simply removes the cap and turns the bottle upside down and squeezes gently to form a single drop that falls into the eye. The dispensing tip will deliver only one drop or a stream of fluid for irrigation, depending on the tip design and pressure applied. When used properly, the solution remaining in the bottle is only minimally exposed to airborne contaminants during administration; thus, it will maintain very low to nonexistent microbial content as compared with the old-style glass bottle with its separate dropper assembly.

The plastic bottle and dispensing tip is made of low-density polyethylene (LDPE) resin, which provides the necessary flexibility and inertness. Because these components are in contact with the product during its shelf life, they must be carefully chosen and tested for their suitability for ophthalmic use. In addition to stability studies on the product in the container over a range of normal and accelerated temperatures, the plastic resins must pass the USP biological and chemical tests for suitability. The LDPE resins used are compatible with a very wide range of drugs and formulation components. Their one disadvantage is their sorption and permeability characteristics. Volatile ingredients such as the preservatives chlorobutanol and phenylethyl alcohol can migrate into the plastic and eventually permeate through the walls of the container. The sorption and permeation can be detected by stability studies if they are significant. If the permeating component is a preservative, a repeat test of the preservative effectiveness with time will determine if the loss is significant. If necessary, a safe and reasonable excess of the permeable component may be added to balance the loss during the product's shelf life. Another means of overcoming permeation effects is to employ a secondary package, such as a peel-apart blister or pouch composed of nonpermeable materials (e.g., aluminum foil or vinyl). The plastic dropper bottles are also permeable to water, but weight loss by water vapor transmission has a decreasing significance as the size of the bottle increases. The consequences of water vapor transmission must be taken into consideration when assessing the stability of a product.

The LDPE resins are translucent, and if the drug is light-sensitive, additional package protection may be required. This can be achieved by using a resin containing an opacifying agent such as titanium dioxide, by placing an opaque sleeve over the exterior of the container, or by placing the bottle in a cardboard carton. Extremely light-sensitive drugs, such as epinephrine and proparacaine, may require a combination of these protective measures. Colorants, other than titanium dioxide, are rarely used in plastic containers; however, the use of colorants is common for the cap. Red has historically been used for mydriatics such as atropine and green for miotics such as pilocarpine. FDA and the ophthalmic industry have extended the cap color scheme to differentiate different classes of newer prescription drugs for the benefit of the patient who may be using more than one product. The intent is to help prevent errors in medication and improve patient compliance. It is important for the pharmacist to explain this color coding to the patient and/or caregiver since it can be defeated if the cap is not returned to the proper container after each use. Colors used for certain medications are as follows:

β-Blockers: Yellow or blue
Nonsteroids: Grey
Anti-infectives: Brown, Tan
Carbonic anhydrous inhibitors: Orange

The pharmacist should dispense the sterile, ophthalmic product only in the original unopened container. A tamper-evident feature such as a cellulosic or metal band around the cap and bottleneck is provided by the manufacturer, and the container should not be dispensed if these are missing or there is evidence of prior removal and reapplication. The LDPE resin used for the bottle and the dispensing tip cannot be autoclaved, and they are sterilized either by ^{60}Co gamma irradiation or ethylene oxide. The cap is designed such that when it is screwed tightly onto the bottle, it mates with the dispensing tip and forms a seal. The cap is usually made of a harder resin than the bottle, such as polystyrene or polypropylene, and is also sterilized by gamma radiation or ethylene oxide gas exposure. A plastic ophthalmic package has been introduced that uses a special grade of polypropylene that is resistant to deformation at autoclave temperatures. With this specialized packaging, the bottle can be filled, the dispensing tip and cap applied, and the entire product sterilized by steam under pressure at 121°C.

The glass dropper bottle is still used for products that are extremely sensitive to oxygen or contain permeable components that are not sufficiently stable in plastic. Powders for reconstitution also use glass containers, owing to their heat-transfer characteristics, which are necessary during the freeze-drying process. The glass used should be USP type I for maximum compatiblity with the sterilization process and the product. The glass container is made sterile by dry heat or steam autoclave sterilization. Amber glass is used for light resistance and is superior to green glass. A sterile dropper assembly is usually supplied separately. It is usually gas-sterilized in a blister composed of vinyl and Tyvek, a fused, porous polypropylene material. The dropper assembly is made of a glass or LDPE plastic pipette and a rubber dropper bulb. The manufacturer carefully tests the appropriate plastic and rubber materials suitable for use with the product; therefore, they should be dispensed with the product. The pharmacist should place the dropper assembly aseptically into the product before dispensing and instruct the patient on precautions to be used to prevent contamination.

Multidose Packaging of Unpreserved Topical Drops. In some cases it may be desirable to provide a product without an antimicrobial preservative for patients who exhibit sensitivity to various preservatives. This can be accomplished with the use of unit dose containers, but these usually contain more than that needed for a single use, so if the patient ignores the labeling and makes multiple use of the contents there is increased risk for contamination.

FDA regulations for ophthalmic liquids allow the use of unpreserved multidose packaging if the product is packaged and labeled in such a manner as to afford adequate protection and minimize the hazards resulting from contamination during use (21CFR 200.50). Thus, the same unit dose containers can be modified to use a resealable cap, the labeling modified to limit the usage to a minimum number of doses such as to discard after 12 hours from initial use and limit the content volume to the expected number of doses with only a small overfill if necessary. It may be necessary to use a secondary package to retard moisture vapor transmission significantly, depending on the surface-to-volume ratio of the primary package.

B. Semisolid Dosage Forms: Ophthalmic Ointments and Gels

Formulation

The principle semisolid dosage form used in ophthalmology is an anhydrous ointment with a petrolatum base. The ointment vehicle is usually a mixture of mineral oil and white petrolatum. The mineral oil is added to reduce the melting point and modify the consistency. The principal advantages of the petrolatum-based ointments are their blandness and their anhydrous and inert nature, which make them suitable vehicles for moisture-sensitive drugs. Ophthalmic ointments containing antibiotics are used quite frequently following operative procedures, and their safety is supported by the experience of a noted eye surgeon [275], who, in over 20,000 postsurgical patients, saw no side effects secondary to ointment use. No impediment to epithelial or stromal wound healing was exhibited by currently used ophthalmic ointments tested by Hanna et al. [276]. The same investigators reported that, even if these ointments were entrapped in the anterior chamber and did not exceed 5% of the volume, little or no reaction was caused [277]. Granulomatous reactions requiring surgical excision have been reported secondary to therapeutic injection of ointment into the lacrimal sac [278].

The chief disadvantages of the use of ophthalmic ointments are their greasy nature and the blurring of vision produced. They are most often used as adjunctive nighttime therapy, with eyedrops administered during the day. The nighttime use obviates the difficulties produced by blurring of vision and is stated

to prolong ocular retention when compared with drops. Ointments are used almost exclusively as vehicles for antibiotics, sulfonamides, antifungals, and anti-inflammatories. The petrolatum vehicle is also used as an ocular lubricant following surgery or to treat various dry eye syndromes. Anesthesiologists may prescribe the ointment vehicle for the non-ophthalmic surgical patients to prevent severe and painful dry eye conditions that could develop during prolonged surgeries. A petrolatum ointment is recognized as a safe and effective OTC emollient (21CFR 349.14), and marketed OTC emollient products are discussed in the twelfth edition of the *APhA Handbook of Nonprescription Drugs*.

The anhydrous petrolatum base may be made more miscible with water through the use of an anhydrous liquid lanolin derivative. Drugs can be incorporated into such a base in aqueous solution if desired. Polyoxyl 40 stearate and polyethylene glycol 300 are used in an anti-infective ointment to solubilize the active principle in the base so that the ointment can be sterilized by aseptic filtration. The cosmetic-type bases, such as the oil-in-water (o/w) emulsion bases popular in dermatology, should not be used in the eye, nor should liquid emulsions, owing to the ocular irritation produced by the soaps and surfactants used to form the emulsion.

In an attempt to formulate an anhydrous, but water-soluble, semisolid base for potential ophthalmic use, five bases were studied [279]. The nonaqueous portion of the base was either glycerin or polyethylene glycols in high concentrations. The matrix used to form the phases included silica, Gantrez® AN-139, and Carbopol® 940. Eye irritation results were not reported, but the authors studied representative bases from that research report and found them to be quite irritating in rabbit eyes. The irritation is believed to be primarily due to the high concentration of the polyols used as vehicles.

An aqueous semisolid gel base has been developed that provides significantly longer residence time in the cul-de-sac and increases drug bioavailability and, thereby, may prolong the therapeutic level in the eye. The gel contains a high molecular weight cross-linked polymer to provide the high viscosity and optimum rheological properties for prolonged ocular retention. Only a relatively low concentration of polymer is required, so that the gel base is more than 95% water.

Schoenwald et al. [280] demonstrated the unique ocular retention of this polymeric gel base in rabbits, in which the miotic effect of pilocarpine was significantly prolonged. The use of other polymers, such as cellulosic gums, polyvinyl alcohol, and polyacrylamides at comparable apparent viscosities, did not provide a significantly prolonged effect. The prolonged effect of pilocarpine has also been demonstrated in human clinical trials, in which a single application of 4% pilocarpine HCl–containing carbomer gel at bedtime, provided a 24-hour duration of reduced intraocular pressure (IOP), compared with the usually required q.i.d. dosing for pilocarpine solution [281]. As a result, some glaucoma patients can now use pilocarpine in this aqueous gel base (Pilopine® HS Gel), dosing only once a day at bedtime to control their IOP without the significant vision disturbance experienced during the day for the use of conventional pilocarpine eyedrops. The gel is applied in a small strip in the lower conjunctival sac from an ophthalmic ointment tube.

The carbomer polymeric gel base itself has been used successfully to treat moderate to severe cases of dry eye (*keratoconjunctivitis sicca*) [282]. The dry eye syndrome is usually characterized by deficiency of tear production and, therefore, requires frequent instillation of aqueous artificial tear eyedrops to keep the corneal epithelium moist. The gel base applied in a small amount provides a prolonged lubrication to the external ocular tissues, and some patients have reduced the frequency of dosing to control their symptoms to three times a day or fewer.

Sterility and Preservation

Since October 1973, FDA regulations require that all U.S. ophthalmic ointments be sterile. This legal requirement was a result of several surveys on microbial contamination of ophthalmic ointments, and followed reports in Sweden and the United Kingdom of severe eye infections resulting from use of nonsterile ointments. In its survey published in 1973, FDA found that of 82 batches of ophthalmic ointments tested from 27 manufacturers, 16 batches were contaminated, including 8 antibiotic-containing ointments. The contamination levels were low and were principally molds and yeasts [283]. The time lag in imposition of a legal requirement for sterility of ointments compared with solutions and suspensions was due to the absence of a reliable sterility test for the petrolatum-based ointments until isopropyl myristate was employed to dissolve these ointments and allow improved recovery of viable microorganisms by membrane filtration. Manufacturers found that, in fact, many of their ointments were sterile, but they revised their manufacturing procedures to increase the assurance of sterility.

A suitable substance or mixture of substances to prevent growth of, or destroy, microorganisms accidentally introduced during use must be added to ophthalmic ointments that are packaged in multiuse containers, regardless of the method of sterilization employed, unless otherwise directed in the individual monograph, or unless the formula itself is bacteriostatic (USP 24). Schwartz [284] commented that a sterile ointment cannot become excessively contaminated by ordinary use because of its consistency and the fact that in a nonaqueous medium microogranisms merely survive but do not multiply. Antimicrobial preservative effectiveness is evaluated by use of the USP 24 testing methodology and criteria for ointments with aqueous bases (Category 1) or nonaqueous bases (Category 2). The test criteria for an anhydrous petrolatum ointment are met if there is no increase in the initial concentration of viable bacteria, yeast, or molds at 14 and 28 days of the test.

Packaging

Ophthalmic ointments are packaged in small collapsible tin tubes, usually holding 3.5 g of product. The pure tin tube is compatible with a wide range of drugs in petrolatum-based ointments. Aluminum tubes have been considered and may eventually be used because of their lower cost and as an alternative should the supply of tin become a problem. Until internal coating technology for these tubes advances, the aluminum tube will be a secondary packaging choice. Plastic tubes made from flexible LDPE resins have also been considered as an alternative material, but they do not collapse and tend to suck back the ointment. Plastic tubes recently introduced as containers for toothpaste have been investigated and may offer the best alternative to tin. These tubes are laminates of plastic and various materials, such as paper or foil. A tube can be designed by selection of the laminate materials and their arrangement and thickness to provide the necessary compatibility, stability, and barrier properties. The various types of metal tubes are sealed using an adhesive coating covering only the inner edges of the bottom of the open tube to form the crimp, which does not contact the product. Laminated tubes are usually heat-sealed. The crimp usually contains the lot code and expiration date. Filled tubes may be tested for leakers by storing them in a horizontal position in an oven at 60°C for at least 8 hours. No leakage should be evidenced except for a minute quantity that could only come from within the crimp of the tube or the end of the cap. The screw cap is made of polyethylene or polypropylene. Polypropylene must be used for autoclave sterilization, but either material may be used when the tubes are gas sterilized. A tamper-evident feature is required for sterile ophthalmic ointments and may be accomplished by sealing the tube or the carton holding the tube such that the contents cannot be used without providing visible evidence of destruction of the seal. The Teledyne Wirz tube used by most manufacturers has a flange on the cap that is visible only after the tube has been opened the first time.

The tube can be a source of metal particles and must be cleaned carefully before sterilization. The USP contains a test procedure and limits the level of metal particles in ophthalmic ointments. The total number of metal particles detected under 30 × magnification that are 50 μm or larger in any dimension is counted. The requirements are met if the total number of such particles counted in 10 tubes is not more than 50 and if not more than one tube is found to contain more than 8 such particles.

C. Solid Dosage Forms: Ocular Inserts

In earlier times lamellae or disks of glycerinated gelatin were used to supply drugs to the eye by insertion beneath the eyelid. The aqueous tear fluids dissolved the lamella and released the drug for absorption. The medical literature also describes a sterile paper strip impregnated with drug for insertion in the eye. These appear to have been the first attempts at designing a sustained-release ocular dosage form.

Nonerodible Ocular Inserts

In 1975, the first controlled-release *topical* dosage form was marketed in the United States by the Alza Corporation. Zaffaroni [285] describes the Alza therapeutic system as a drug-containing device or dosage form that administers a drug or drugs at programmed rates, at a specific body Site, for a prescribed time period to provide continuous control of drug therapy and to maintain this control over extended periods. Therapeutic systems for uterine delivery of progesterone, transdermal delivery of scopolamine, and oral delivery of systemic drugs have also been developed.

The Ocusert® Pilo-20 and Pilo-40 Ocular Therapeutic System is an elliptical membrane that is soft and flexible and designed to be placed in the inferior cul-de-sac between the sclera and the eyelid and to release pilocarpine continuously at a steady rate for 7 days. The design of the dosage form is described by Alza in terms of an open-looped therapeutic system, having three major components: (a) the drug, (b) a

drug-delivery module, and (c) a platform. In the Ocusert Pilo-20 and Pilo-40 systems, the drug-delivery module consists of (a) a drug reservoir, pilocarpine (free base), and a carrier material, alginic acid; (b) a rate controller, ethylene vinyl acetate (EVA) copolymer membrane; (c) an energy source, the concentration of pilocarpine in the reservoir; and (d) a delivery portal, the copolymer membrane. The platform component for the pilocarpine Ocusert consists of the EVA copolymer membranes, which serve as the housing, and an annular ring of the membrane impregnated with titanium dioxide that forms a white border for visibility. The laminate structure of the Ocusert is seen in Fig. 19. The free-base form of pilocarpine is used, since it exhibits both hydrophilic and lipophilic characteristics. Use of the extremely water-soluble salts of pilocarpine would have necessitated the use of a hydrophilic membrane, which, if it osmotically imbibed an excessive amount of water, would cause a significant decline in the release rate with time. Use of the free base allowed a choice of more hydrophobic membranes that are relatively impermeable to water; accordingly the release rate is independent of the environment in which it is placed. EVA, the hydrophobic copolymer chosen, was found to be very compatible with the sensitive ocular tissues [286], an important feature.

The pilocarpine Ocusert is seen by Alza to offer a number of theoretical advantages over drop therapy for the glaucoma patient. The Ocusert exposes a patient to only one-fourth to one-eighth the amount of pilocarpine, compared with drop therapy. This could lead to reduced local side effects and toxicity. It provides continuous around-the-clock control of IOP, whereas drops used four times a day can permit periods where the IOP might rise. Additionally, the Ocusert provides for more patient convenience and improved compliance, as the dose needs to be administered only once per week. However, clinical experience seems to indicate that the Ocusert has a compliance problem of its own (i.e., retention in the eye for the full 7 days). The patient must check periodically to see that the unit is still in place, particularly in the morning on arising. Replacement of a contaminated unit with a fresh one can increase the price differential of the already expensive Ocusert therapy compared with the inexpensive drop or once-a-day gel therapy. In addition, some patients find positioning the Ocusert in the eye to be challenging.

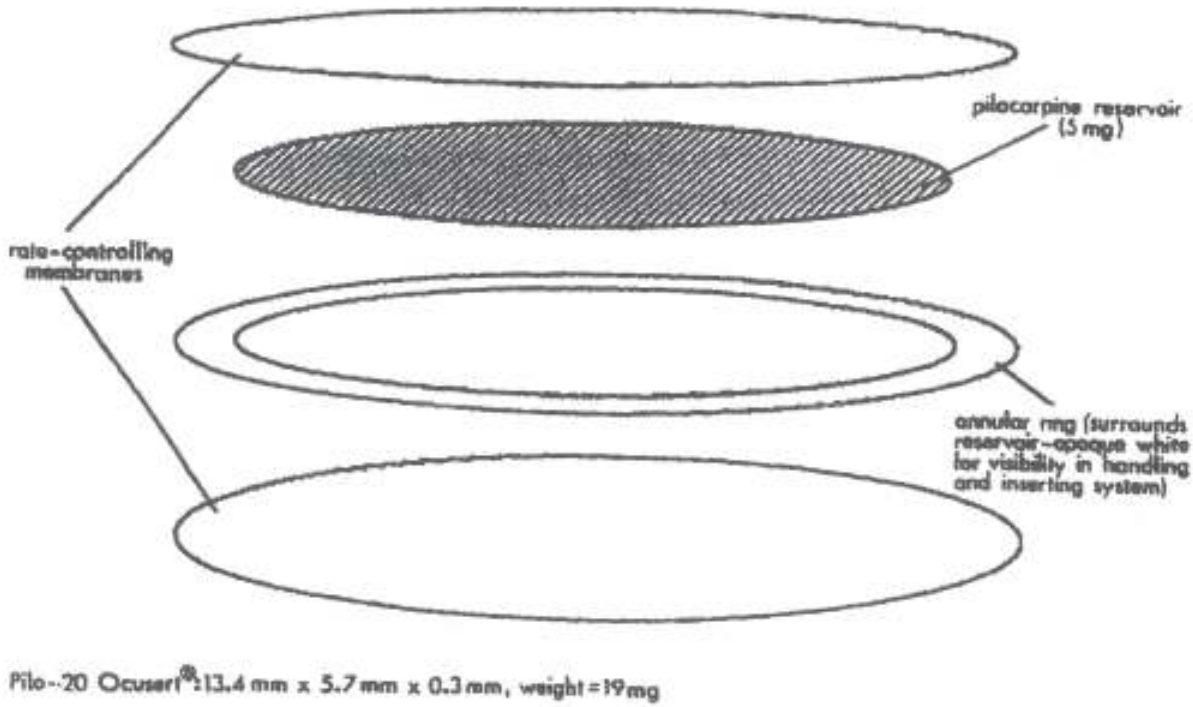

Fig. 19 Elements and dimensions of pilocarpine Ocusert system.

Soft contact lenses, made of the same hydrophilic plastic materials used for vision correction, are also used as corneal bandages to protect the cornea during the healing process following surgery. They can be fitted to the eye and inserted and removed by the ophthalmologist. They are usually used without correction (plano lens) and removed by the ophthalmologist. Since they are used in a compromised cornea, great care must be taken to prevent microbial contamination.

Erodible Ocular Inserts

Since polymers have been added to solutions to increase viscosity and ocular retention, it is not surprising that similar solutions have been dried to form films of the polymer-drug system. These films inserted into the lower cul-de-sac of the eye have been reported to increase retention time, increase drug bioavailability, and prolong therapeutic effect. Ocular inserts made with water-soluble polymers imbibe the tear fluid and slowly dissolve and erode, releasing their drug content. The erodible inserts have the potential advantages of not having to be removed at the end of their useful dosing interval, providing a more precise dosage to the eye from a unit dosage form, and requiring no preservative, thus reducing the risk of inducing sensitivity. Also, it may be possible to reduce the applied dose compared to conventional eyedrops and reduce the risk of local or systemic adverse effects. Potential disadvantages include the difficulty of achieving constant zero-order drug delivery as the matrix is eroding, and in some cases they may be squeezed out of the eye due to movement of the eyelids before their delivery cycle is complete. They may require terminal sterilization, and this may adversely affect stability and could produce unwanted degradation products. Considerable drug-delivery research has been conducted and reported for various erodible ocular inserts [287–291].

An erodible insert developed as a potential ocular drug-delivery system is marketed as a prescription drug for the lubricant properties of the polymer base. Lacrisert® is a sterile ophthalmic insert used in the treatment of moderate to severe dry eye syndrome and is usually recommended for patients unable to obtain symptomatic relief with artificial tear solutions. The insert is composed of 5 mg of hydroxypropylcellulose in a rod-shaped form about 1.27 mm diameter by about 3.5 mm long. No preservative is used, since it is essentially anhydrous. The quite rigid cellulose rod is placed in the lower conjunctival sac and first imbibes water from the tears and after several hours forms a gel-like mass, which gradually erodes as the polymer dissolves. This action thickens the tear film and provides increased lubrication, which can provide symptomatic relief for dry eye states. It is usually used once or twice daily.

Corneal shields are medical devices used as bandages for protection of the cornea and to allow healing following surgery. Initially, hydrophilic soft contact lenses used for vision correction were employed as corneal shields. Collagen was then introduced as a substitute for the plastic noneroding bandage lens. They are widely used today as temporary protective devices for healing corneas. In addition to their approved use of corneal bandages, they have been investigated as drug-delivery vehicles to provide sustained delivery of drugs to the cornea by the ophthalmologist [292].

Collagen is widely used for biomedical applications. It accounts for about 25% of the total body protein in mammals and is the major protein of connective tissue, cartilage, and bone. Importantly, the secondary and tertiary structures of human, porcine, and bovine collagen are very similar, making it possible to use animal-sourced collagen in the human body. Collagen shields are designed to be sterile, disposable, temporary bandage lenses that conform to the shape of the eye and protect the cornea. They are not optically clear and reduce visual acuity to the 20/80–20/200 range. They differ mainly in the source of collagen, usually bovine or porcine, and their dissolution time on the cornea, ranging from 12 to 72 hours. The dissolution time is controlled during manufacture by varying the degree of cross-linking usually by exposure to ultraviolet light.

D. Intraocular Dosage Forms

Opthalmic products, which are introduced into the interior structures of the eye primarily during ocular surgery, are a special class that require the application of technology from parenteral dosage forms in their design, packaging, and manufacture. The development of cytomegalovirus (CMV) retinitis as a common opportunistic infection in patients with AIDS has resulted in expansion of this class of ocular product to include solid inserts and injections of antiviral agents administered directly to the vitreous cavity. As discussed previously, topical and systemic administration often fails to achieve therapeutic concentrations in the vitreous cavity.

Ophthalmic surgery has rapidly advanced in the last three decades, particularly with the ability of

the surgeon to operate in the posterior segment. The ophthalmologist can perform vitreoretinal surgery and restore significant visual function in patients with diabetic complications, endophthalmitis, and retinal tears and detachments. Also, significant advances have been made in anterior segment surgery, especially for cataract surgery, where replacement of a cloudy or opaque natural crystalline lens with a plastic or silicone intraocular lens can restore visual acuity and allow the patient to achieve a significant improvement in his or her quality of life. These technological advances have placed greater emphasis on the development of products specifically formulated and packaged for intraocular use. This has led to the development of improved irrigating solutions, intraocular injections, viscoelastics, vitreous inserts, and intravitreal injections.

Intraocular Irrigating Solutions

An essential component of ocular surgery is the use of a simulated physiological solution to moisten and irrigate ocular tissue on the external surface as well as intraocular anterior and posterior segments of the eye. Externally, the solution maintains a moist surface preventing cellular desiccation, which can inhibit the surgeon's ability to see inside the eye. The solution also acts as a substitute for the natural aqueous intraocular fluid and aids in the removal of blood and cellular debris. Normal saline and lactated Ringer's solution were used initially since they were available in parenteral dosage form, but they lacked key components of ocular fluids. In the 1960s a balanced salt solution was developed specifically for ocular surgical use and became widely used. It contains the five essential ions: sodium, potassium, calcium, magnesium, and chloride. It also contains citrate and acetate ions, which provide some buffer capacity and a potential source of bicarbonate. It is formulated to be isoosmotic with aqueous humor (about 305 mOsm) and has a neutral to slightly alkaline physiological pH [293–295].

Balanced salt solution (BSS®) provided an improved ocular irrigating solution; however, as the surgical techniques for cataract surgery evolved and new vitreoretinal surgical procedures were introduced, larger volumes of irrigating solutions were used, and surgical operating times for the very delicate vitreoretinal procedures can now exceed several hours. This has placed additional physiological demands on the irrigating solution, and an enriched balanced salt solution (BSS® Plus) was developed. The enriched product contains the essential electrolyte components of BSS with the addition of glutathione (oxidized) and dextrose as energy sources, bicarbonate as a physiological buffer, and a phosphate buffer system to maintain the products storage pH in the physiological range [296,297].

The enriched BSS formulation presented chemical and physical stability issues not present in the original BSS product. It was necessary to use a two-part formulation in order to develop a commercially viable product with several years of storage stability; the two parts are aseptically combined just prior to surgery. The two-part formulation consists of a large volume part containing sodium, potassium, chloride, phosphate, and bicarbonate components at physiological pH and osmolality. The second part contains the calcium and magnesium divalent ions and the oxidized glutathione and dextrose in an acidic environment for long-term storage stability. The smaller-volume second part has a minimal buffer capacity and, when added to the larger-volume first part, does not significantly change the final product's physiological pH. Once aseptically combined, it is stable for at least 24 hours, although it is labeled to be used within 6 hours as a sterility precaution.

Providing the product as a two-part system was necessary to overcome the physical and chemical incompatibilities inherent in the final composition. Bicarbonate is stable only in an alkaline environment, while glutathione and dextrose are stable in a pH range of about 3–5. Consideration was also given to which of the two parts should be the larger volume in the irrigation bottle, since inadvertent failure to mix the two parts prior to use could occur. The large-volume component contains a bicarbonate saline solution at physiological pH and osmolality and thus would be more tissue compatible than irrigating with a hypoosmotic acidic pH solution.

The large-volume part is packaged in Type 1 glass IV bottle and as such can be autoclaved sterilized. The quality of the glass is important to prevent leaching of silicates, which can increase pH during autoclaving and storage. IV parenteral grade rubber stoppers must be used to minimize coring and extraction. Type 1 glass is also used for the additive part vial with a parenteral grade rubber stopper. The smaller-volume part is added aseptically to the larger-volume container via a sterile transfer needle.

Intraocular irrigating solutions are required to be preservative-free to prevent toxicity to the internal tissues of the eye, particularly the corneal endothelium, lens, and retina [298,299]. These products are intended for single use only to prevent intraocular infections,

which can be difficult to treat and seriously threaten sight. In addition to being sterile, they must be non-pyrogenic, therefore requiring sterile water for injection (WFI) as the vehicle.

These irrigating solutions have been developed and are labeled to be used without the addition of any drugs, i.e., not as a delivery vehicle. However, some drugs such as epinephrine are added to the irrigating solution prior to surgery and used extensively by cataract surgeons to achieve and maintain pupillary dilation, facilitating removal of the natural lens and insertion of the prosthetic intraocular lens. Use of some commercial epinephrine injections that contain sodium bisulfite in addition to their acidic pH as the source for the epinephrine additive have been reported to be the cause of intraocular toxicity, even though it is diluted as much as 500-fold before irrigation [300].

FDA has approved a generic version of the enriched BSS product. The generic product is equivalent only in the final composition after mixing the two parts. To avoid the originator's patents, the generic uses different compositions in the two-part formulations. The larger volume part is an acidic solution, and the second part is a lyophilized product for stability of the dextrose and glutathione components. If the larger volume part is used without the addition of the second part, the eye will be irrigated with an acidic nonphysiological solution.

Intraocular Injections

Very few injectable dosage forms have been specifically developed and approved by FDA for intraocular use. However, the ophthalmologist uses available parenteral dosage forms to deliver antiinfectives, corticosterioids, and anesthetic products to achieve higher therapeutic concentrations intraocularly than can ordinarily be achieved by topical or systemic administration. These unapproved or off-label uses have developed over time as part of the physician's practice of medicine. However, these drugs are usually administered by subconjunctival or retrobulbar injection and rarely are they injected directly in the eye [301].

FDA approved intraocular injections include miotics, viscoelastics, and viscoadherents and an antiviral agent for intravitreal injection. The approved intraocular miotics, carbachol (Miostat®) and acetylcholine (Miochol®), are injected into the anterior chamber at the end of cataract surgery to constrict the pupil and allow the iris to cover the implanted intraocular lens. Carbachol is formulated in a BSS vehicle in sterile water for injection at a physiological pH and packaged in a rubber-stoppered glass vial. Acetylcholine has very limited stability and so is lyophilized with mannitol in a two-chambered vial with a modified BSS vehicle in sterile water for injection in the upper chamber. The product is reconstituted just prior to use. Both products are introduced into the sterile surgical field, and therefore the primary package vial must have a sterile exterior. This is accomplished by ethylene oxide sterilization of the vial in a special secondary package that is permeable to the sterilant gas but protective to contamination of the vial prior to use.

Viscoelastics

Highly purified fractions of sodium hyaluronate have become an important ocular surgical adjunct because of their lubricant and viscoelastic properties. They are injected into the anterior segment of the eye during surgery for removal of cataracts and implantation of an IOL, trabeculectomy, and corneal transplantation. They are also used as a surgical aid in the vitreous cavity during retinal surgery. Their viscoelasticity provides a mechanical barrier between tissues and allows the surgeon more space for manipulation with less trauma to surrounding tissues, particularly the corneal endothelium. It is also used to coat the IOL prior to insertion and lessen the potential for tissue damage upon implantation. In posterior segment surgery, it is used to separate tissue away from the retina and as a tamponade to maneuver tissue, such as a detached retina, back into place for reattachment. The viscoelastic material is usually removed at the end of the surgery since it may take several days to be cleared from the eye and has the potential to elevate IOP.

Sodium hyaluronate is a high molecular weight polysaccharide which is widely distributed throughout the tissues of the body of animals and humans. The viscoelastic materials used as ocular surgical aids are specific fractions from animal tissue, which are highly purified to remove foreign proteins and are tested to be nonantigenic and noninflammatory in the eye. The purified fraction is formulated to yield a high viscoelasticity determined by the interplay of molecular weight and concentration. The solution is packaged in disposable glass syringes, which are terminally sterilized and aseptically packaged so that they can be used in the sterile surgical field (Healon®, ProVisc®, Amvisc®).

Chondroitin sulfate (Viscoat®, DuoVisc®) is also used in combination with sodium hyaluronate as a viscoelastic surgical aid to provide higher viscosities, which may provide additional tissue protection

during the irrigation and aspiration accompanying phacoemulsification, a common means of removing the cloudy crystalline lens prior to IOL implantation.

Nonpyrogenic solutions of sterile hydroxypropyl methylcellulose are also used as ocular surgical aids similar to the viscoelastics in cataract surgery (OcuCoat®). These lubricants are sometimes classified as viscoadherents because they are used to coat the IOL prior to implantation and the tips of surgical instruments prior to deployment inside the eye. This is the same cellulosic material but in a highly purified form, serving as a viscosifying agent in topical eyedrops and as an OTC ocular lubricant. Since it is not a natural product, it does not have the antigenic potential of the other viscoelastics. It can be stored at room temperature, whereas the sodium hyaluronate solutions must be stored in the refrigerator.

Intravitreal Injection and Implant

Antivirals are used to treat the ocular sequelae of AIDS such as CMV retinitis. They are treated with systemic administration, but with the need for higher localized ocular therapeutic concentrations, products have been developed and approved for direct administration into the vitreous cavity.

An intravitreal implant containing ganciclovir was the first such ophthalmic product developed and approved for CMV retinitis (Vitrasert®, cf. Section 6 and Fig. 15). The sterile implant is a tablet of ganciclovir with magnesium stearate and is coated to retard drug release with polyvinyl alcohol and ethylene vinyl acetate polymers such that the device when surgically implanted in the vitreous cavity releases drug over a 5- to 8-month period. When the implant is visually observed to be depleted, and based on clinical observation of the progression of the disease, it is surgically removed and replaced with a new implant. The implant is provided in a sterile Tyvek package and contains a suture tab for handling prior to and during implantation so that the polymer release rate controlling coating is not damaged. Also, precautions for handling and disposal of antineoplastic agents should be observed.

A new antiviral agent, developed for treatment of CMV retinitis, can be administered by intravitreal injection. Formivirsen sodium is a phosphorothioate oligonucleotide that inhibits CMV replication through an antisense mechanism. It is formulated as a sterile and preservative-free solution and supplied in single-use vials (Vitravene®). The product is administered directly into the vitreous cavity posterior to the limbus through a 30-gauge needle. This procedure can be performed on an outpatient basis—an advantage over an intravitreal device, which must be surgically implanted and removed. The frequency of injection, based on the clinical progression of the disease, is every 2–4 weeks.

IX. CONTACT LENS CARE PRODUCTS

Contact lenses are optical devices that are either fabricated from preformed polymers or polymerized during lens manufacture. The main purpose of contact lenses is to correct defective vision. For this application, they are called *cosmetic lenses*. Contact lenses used medically for the treatment of certain corneal diseases are called *bandage lenses*.

A. Evolution of Contact Lenses

In 1508 Leonardo da Vinci conceived the concept of the contact lens. It was not until 1887 that scleral contact lenses were fabricated by Dr. A. E. Fick, a physician in Zurich; F. A. Mueller, a maker of prosthetic eyes in Germany; and Dr. E. Kalt, a physician in France. Muller, Obrig, and Gyorry fabricated contact lenses made from polymethyl methacrylate (PMMA) in the late 1930s. K. Tuohy filed the patent for contact lens design in 1948; the lenses were made of PMMA material [302]. Although they were safe and effective, these lenses were uniformly uncomfortable, thus suppressing their potential use for contact lens wear. Lenses made from polyhydroxyethyl methacrylate (HEMA), so-called soft lenses or hydrophilic lenses, were introduced in 1970. Since then, significant technological advances have been made in lens materials, lens fabrication, and lens designs [303]. Consequently, a phenomenal growth in lens wearers necessitated the need for, and development of, lens care products. Today, rigid lenses made from materials polymerized with PMMA and in combination with various siloxanes and fluorocarbons are available to meet the broadest needs of lens wearers.

B. Composition of Contact Lenses

Contact lenses are broadly classified as PMMA, rigid gas-permeable (RGP), and soft hydrogel (HEMA) lenses. Dyes may be added during polymerization or after fabrication to improve lens handling or to change the color of the lens wearer's eyes. Lenses made from numerous polymers are available today [304]. In soft hydrogel lenses, HEMA is a commonly used monomer. However, to avoid infringement of existing patents, many comonomers, e.g., methyl methacrylic acid

or a blend of comonomers, are used. Comonomers produce changes in the water content or ionic nature of lenses that is significantly different from HEMA lenses. For example, addition of acrylic acid in HEMA increases the water content and ionic nature of lenses. Some lenses are made from *n*-vinylpyrrolidone and have high water contents. Such lenses have pore sizes that are much larger than low water content lenses. Cross-linkers, such as ethyleneglycol dimethacrylate, and initiators such as benzyl peroxide in appropriate amounts are added for polymerization and to achieve desirable physical and chemical properties. Recently, contact lenses made from HEMA and silicone were made available. These lenses combine the properties of hydrogel and gas-permeable polymers [305]. Table 5 gives a list of monomers, comonomers, and cross-linkers along with their effects on polymer properties. In 1985, FDA published a classification for soft hydrophilic lenses based on their water content and ionic nature. Groupings for soft lenses and their generic names are listed in Table 6. Adequate levels of oxygen are necessary to maintain normal corneal metabolism [306]. Lenses that are poorly designed and worn overnight deprive the cornea of oxygen, causing edema [307].

Generally, oxygen permeability for soft lenses is acceptable when worn on a daily basis. Hypoxia related side effects such as corneal swelling, epithelial microcysts, limbal redness, neovascularization, epithelial polymegathism and blebs are well known and mainly observed with extended contact lens wear. Recent development of hydrophilic silicone hydrogel materials combines the high oxygen permeability of silicone with the good water and ion permeability of hydrogels resulting in acceptable extended wear lenses. The oxygen (gas) transmissibilty of these lenses is greater than all other available lenses.

Contact lenses made from PMMA materials are virtually impermeable to gases [308]. The PMMA lenses are also inflexible, causing discomfort in a large percentage of individuals while the lens is worn. During the 1980s, lenses were made from either cellulose acetate butyrate (CAB) or silicone elastomer. Although comfortable and flexible, such lenses accumulated lipids, were nonwettable, and adhered to the cornea. Several reports detailing difficulty in removing CAB and silicone lenses appeared in the published literature [309]. Lenses made from fluorocarbons and in various combinations of fluorocarbon, silicone, methyl methacylate, and acrylic acid are currently available. Desirable properties of these lenses include flexibility, wettability, and gas transmissibility. Grouping for rigid gas-permeable lenses was published by FDA in 1989. The generic names and oxygen permeabilities of rigid gas-permeable (RGP) lens materials are provided in Table 7 [310].

C. Complications of Contact Lens Wear and the Need for Care Products

Lens design, user compliance with manufacturer's instructions, hygiene, environmental conditions, poor fit, lens materials, and tear chemistry are the major causes of lens wear complications. Complications owing to lens design, compliance, hygiene, environmental conditions, and poor fit are beyond the scope of this chapter and are not critical to an understanding of the concepts required for the development of care products. However, knowledge of tear chemistry is important in understanding the complex chemical interactions between tear components and contact lenses. The tear film can be broadly divided into three distinct layers: lipids, aqueous, and mucin [311]. Each layer of the tear film performs a specific function. The mucin layer spreads and coats the hydrophobic corneal cells and extends into the aqueous layer. The aqueous layer contains 98% water and 2% solids. Dissolved solids in this layer are predominately the electrolytes (Na^+, K^+, C^{2+}, Mg^{2+}, Cl^-, and HCO_3^-), nonelectrolytes (urea and glucose), and proteins. Major proteins in the tear film are presented in Table 8.

The lipid layer, which consists of cholesterol esters, phospholipids, and triglycerides, prevents and regulates aqueous evaporation from the tear film.

Components of the tear attach to contact lenses by electrostatic and van der Waals forces and build up to form deposits. Deposits on the surface and in the lens matrix may result in reduced visual acuity, irritation, and in some instances serious ocular complications. The composition of deposits vary because of the complexity of an individual's ocular physiology-pathology. Lysozyme is a major component of soft lens deposits, especially found on high-water-content ionic lenses [312]. Calcium [313] and lipids [314] are infrequent components of deposits, occurring as inorganic salts, organic salts, or as an element of mixed deposits, or as a combination thereof [315,316].

Lenses are exposed to a broad spectrum of microbes during normal wear and handling and become contaminated relatively quickly. Failure to remove microorganisms effectively from lenses can cause ocular infections. Ocular infections, particularly those caused by pathogenic microbes, such as *P. aeruginosa*, can lead to the loss of the infected eye if left untreated.

Table 5 Commonly Used Monomers, Comonomers, and Cross-Linkers in Contact Lens Polymers

Name	Abbreviation	Lens properties
Acrylic acid	AA	Flexibility Hydrophilicity pH sensitivity —acidic Reactivity—ionically interacts with positively charged tear components Wettability
Butyl methacrylate	BMA	Softness Flexibility Hydrophobicity—attracts lipids Wettability Gas transmissibility
Cellulose acetate butyrate	CAB	Clarity Wettability Gas transmissibility Physical stability
Dimethyl siloxane	DMS	Hydrophobicity Wettability Gas transmissibility Physical stability
Diphenyl siloxane	DPS	Hydrophobicity Wettability Gas transmissibility Physical stability
Ethonylethyl methacrylate	EOEMA	Flexibility Softness Hydrophobicity Wettability Gas transmissibility
Ethylene glycol dimethacrylate	EGDMA	Hydrophobicity Wettability
Glyceryl methacrylate	GMA	Wettability Gas transmissibility Hydrophilicity Machineability
Hydroxyethyl methacrylate	HEMA	Flexibility Wettability Gas transmissibility Softness Machineability
Methacrylic acid	MA	Hardness Machineability Wettability Gas transmissibility Hydrophobicity
Methyl methacrylate	MMA	Hardness Machineability Wettability Gas transmissibility Hydrophobicity
Methylphenyl siloxane	MPS	Hydrophobicity Gas transmissibility
Methyl vinyl siloxane	MVS	Hydrophobicity

Table 5 (Continued)

Name	Abbreviation	Lens properties
N-Vinyl pyrrolidone	NVP	Gas transmissibility Hydrophilicity Wettability Machineability Color, clarity
Siloxanyl methacrylate	SMA	Hardness Wettability Gas transmissibility

Table 6 FDA Grouping for Soft Hydrophilic Lenses and Generic Names

Group 1 Low water (< 50%H_2O) nonionic polymers	Group 2 High water (> 7.50%H_2O) nonionic polymers	Group 3 Low water (< 50%H_2O ionic polymers	Group 4 High water (> 50%H_2O) ionic polymers
Tefilcon (38%)	Lidofilcon (70%)	Etafilcon (43%)	Bufilcon A (55%)
	Lidofilcon B (79%)		
Tetrafilcon A (43%)	Surfilcon (74%)	Bufilcon A (45%)	Perfilcon (71%)
Grofilcon (39%)	Vilifilcon A (55%)	Deltafilcon A (43%)	Etafilcon A (58%)
Dimefilcon A (38%)	Scafilcon A (71%)	Dronifilcon A (47%)	Ocufilcon C (55%)
Hefilcon A (43%)	Xylofilcon A (67%)	Phenifilcon A (38%)	Phenfilcon A (55%)
		Ocufilcon (44%)	Tetrafilcon B (58%)
Hefilcon B (43%)		Mafilcon (33%)	Methafilcon (55%)
Phenifilcon A (30%)			Vifilcon A (55%)
Isofilcon (36%)			
Polymacon (38%)			
Mafilcon (33%)			

D. Types of Lens Care Products

Contact lens care products can be divided into three categories: cleaners, disinfectants, and lubricants. Improperly cleaned lenses can cause discomfort, irritation, decrease in visual acuity, and giant papillary conjunctivitis (GPC). This latter condition often requires discontinuation of lens wear, at least until the symptoms clear. Deposits can also accumulate preservatives from lens care products and produce toxicity and can act as a matrix for microorganism attachment to the lens [317]. Thus, cleaning with the removal of surface debris, tear components, and contaminating microorganisms is one of the most important steps contributing to the safety and efficacy of successful lens wear [318].

Daily cleaners and weekly cleaners are employed to clean deposits that accumulate on lenses during normal wear. A list of cleaning agents commonly used in daily cleaners is provided in Table 9. Single cleaning agents or combinations of cleaning agents may be used in a cleaner. Surfactant(s), surface-active polymer(s), solvent(s), and complexing agent(s) chosen for cleaner formulations must be capable of solubilizing lens deposits and must have low irritation potential. They must be rinsed easily, leaving very low or nondetectable residue levels on the lens. Many problems that contact lens wearers experience with their lenses are the results of incomplete removal of deposit(s) [319]. Nonionic and amphoteric surfactants are commonly used in daily cleaner products. Because of their toxicity to the cornea and binding to the lenses, anionic and cationic surfactants are avoided. Solvents capable of solubilizing lens deposits without altering the lens polymer properties should be selected carefully. Complexing agents, such as citrates, are included in daily cleaner formulations [320]. They retard the binding of positively charged proteins to the lenses and by ion pairing or salt formation render the proteins more soluble in the media.

Table 7 FDA Grouping of Hydrophobic Hard and Rigid Gas-Permeable Lenses

Lens materials	Generic name	D_k
Cellulose acetate butyrate	Cabufocon A	> 150
	Powfocon A	> 150
	Powfocon B	> 150
t-Butylstyrene	Aufocon A	> 150
Silicone	Elastofilcon A	> 150
	Dimofocon	> 150
	Dilafilcon A	> 150
t-Butylstyrene-silicon acrylate	Pentasilcon P	120
Fluoracrylate	Fluorofocon A	100
Fluoro silicone acrylate	Itafluorofocon A	60
	Porflufocon A	30–92
Silicone acrylate	Pasifocon A	14
	Pasifocon B	16
	Pasifocon C	45
	Itafocon A	14
	Itafocon B	26
	Nefocon A	20
	Telefocon A	15–45
	Amefocon A	40

Table 8 Major Proteins of the Tear Film

Name	Total protein (%)	Function
Lysozyme	30–40	Antimicrobial, collagenase regulator
Lactoferin	2–3	Bacteriostatic, anti-inflammatory
Albumin	30–40	Anti-inflammatory
Immunoglobins	0.1	Immunological, anti-inflammatory

Mechanical force is a key aspect in the cleaning process. For daily cleaning, mechanical force is generally provided through the rubbing action of the fingers over the lens during the actual cleaning process. Rubbing typically removes 1.7 ± 0.5 log of microorganisms, rinsing the lens removes 1.9 ± 0.5 log of microorganisms, and cleaning and rinsing the lens removes 3.7 ± 0.5 log of microorganisms of a typical challenge by 10^6 colony-forming units (cfu)/mL [320]. Abrasive particles are included in products to enhance the mechanical force applied to the lens during the cleaning process [321]. The abrasive properties are evaluated by testing the hardness of the included abrasive particles. Typically particles that have Rockwell hardness lower than the hardness of the lens polymers are used. If the hardness of abrasive particles is higher than the hardness of the lens polymer, it is possible that the lens would be damaged. Some contact lenses are reported to require special treatment. Abrasive particles may alter surface treatment effects even when their hardness is lower than that of the lens polymer. Development of potent preservative systems and the use of complexing agents like citrates have led to the availability of multi-purpose solutions. These single-solution products are carefully designed to meet the cleaning and microbiological requirements without a lens rubbing step.

Enzymatic cleaners contain enzymes derived from animals, plants, or microorganisms. Plant and microorganism-derived enzymes may cause sensitization in many lens wearers [322]. A list of commonly used enzymes is provided in Table 10. All of these enzymes are effective in removing deposits from the contact lens surface [323]. They are biochemical catalysts that are specific for catalyzing certain chemical reactions. Those

Table 9 Cleaning Agents Commonly Used in Daily Cleaners

Class	Trade name	Chemical name
Abrasive particles	Nylon 11	11-Aminoundecanoic acid
	Silica	Silicon dioxide
Complexing agents	Citric acid	2-Hydroxy-1,2,3-propane tri-carboxylic acid
Solvents	Isopropyl alcohol	2-Propanol
	Propylene glycol	1,2-Propanediol
	Hexamethylene glycol	1,6-Hexanediol
Surfactants (nonionic)	Tween 21	Polysorbate 21
	Tween 80	Polysorbate 80
	Tyloxapol	4-(1,3,3-Tetramethylbutyl)-phenol polymer with formaldehyde and oxirane
	Pluronic	Poloxamer
	Tetronic	Poloxamine
Surfactants (ionic)	Miracare	Cocoamphocarboxy-glycinate

Table 10 Enzymes Commonly Used in Weekly Cleaners

Name	Origin	Active against	Active at pH
Pancreatin	Animal (Porcine)		
Proteases		Proteins	7.0
Lipase		Lipids	8.0
Amylase		Carbohydrates	6.7–7.2
Papain	Plant (papaya)	Proteins	5.0
Subtilisin A	Microorganisms	Proteins	8–10
Subtilisin B	Microorganisms	Proteins	8–10

that aid in removing debris from contact lenses are protease (protein-specific enzyme), lipase (lipid-specific enzyme), and amylase (polysaccharide-specific enzyme). Such enzymes catalyze breakdown of substrate molecules—protein, lipid, and mucin—into smaller molecular units. This process yields fragments that are readily removed by mechanical force and rinsing.

In the past, only tablet dosage forms of enzymatic cleaners were available. They required soaking lenses in solutions prepared from a tablet for a period of 15 minutes to more than 2 hours before disinfecting the lenses. Although this process provided sufficient time for cleaning, it was a cumbersome process and required multiple steps. Complicated or cumbersome processes inevitably lead to poor user compliance. Enzymes in aqueous liquid compositions are inherently unstable. New technological advances have led to the stabilization of enzymes in liquid vehicles which are compatible with soft and RGP contact lenses [324]. The newer products are either in a tablet or a solution product form. Simultaneous cleaning and disinfection can be achieved, which reduces care time and the need for multiple steps [325].

Contact lenses are contaminated with microorganisms during lens handling and lens wear. They must be disinfected to prevent ocular infections, especially from pathogenic microorganisms. The two disinfection methods used are thermal and chemical. In thermal disinfection systems, lenses are placed in preserved or unpreserved solution in a lens case and then heated sufficiently by a device to kill the microorganisms. The current FDA requirement for thermal disinfection requires heating at a minimum of 80°C for 10 minutes. The unpreserved salines are either packaged in a unit-dose or an aerosol container, and they do have some antimicrobial activity [326]. Preservatives must be used in salines packaged in nonaerosol multidose containers. The types and names of preservatives and antimicrobial disinfectants commonly used in lens care products are listed in Table 11. Thimerosal and sorbic acid are commonly used preservatives in these products; however, concerns of sensitization potential and discoloration of lenses have led to the introduction of new

Table 11 Antimicrobial Agents Commonly Used in Lens Care Products

Class	Generic	Molecular weight	Used in lens type	
			Soft	RGP, PMMA
Acids	Benzoic acid	122	No	Yes
	Boric acid	62	Yes	Yes
	Sorbic acid	112	Yes	Yes
Alcohols	Benzyl alcohol	108	No	Yes
	Phenyl ethyl alcohol	122	No	Yes
Biguanides	Chlorhexidine	505	Yes	Yes
	Polyaminopropyl biguanide	~1200	Yes	Yes
Mercurial	Thimerosal	404	Yes	Yes
	Phenylmercuric nitrate	634	Yes	Yes
Oxidizing	Hydrogen peroxide	34	Yes	No
	Sodium dichloroisocyanurate	220	Yes	No
Quaternary	Tris(2-hydroxyethyl) tallow ammonium chloride	≈424	Yes	No
	Benzalkonium chloride	≈363	No	Yes
	Benzethonium chloride	448	No	Yes
	Polyquaternium-1	≈6000	Yes	Yes

and safer molecules like Polyquad (a polymeric quaternary ammonium compound) and Dymed. Specifically, Polyquad is resistant to absorption into the lenses; thus, there is little to diffuse out of the lens into the eye, leading to corneal toxicity, an inherent problem associated with nonpolymeric quaternary ammonium compounds. FDA and the USP have specific standards for preservative effectiveness that these products must meet. The FDA standards detailing the method were published in 1985 [327]. Oxidizing agents and nonoxidizing chemical disinfectants that are nontoxic at product concentrations are used to disinfect lenses chemically. Hydrogen peroxide is used primarily as an oxidizing agent [328]. It is used in concentrations of 0.6–3.0%. Peroxides are very toxic to the cornea of the eye. After the disinfection cycle, and before placing the lens in the eye, hydrogen peroxide must be completely neutralized by reducing agents, catalase, or transition metals, such as platinum.

An ideal chemical-disinfecting agent would have the following properties: (a) it should be nonirritating, nonsensitizing, and nontoxic in tests for cytotoxicity; (b) it should have an adequate antimicrobial spectrum and be able to kill ocular pathogens during a short lens-soaking period; (c) it should not bind to the lens surface; and (d) it should be compatible with the lens and not cause lens discoloration or alter the tint of colored contact lenses. Polyquad and Dymed have most of these characteristics. They have been introduced recently into the marketplace and are performing to expectations [329,330].

Contact lens wearers may experience increasing awareness of their lenses during the day owing to ocular dryness [331]. With some lens materials, this increase in awareness may arise from a decrease in the wettability of the lens surface. Dehydration of the lens or accumulation of debris on the lens surface can cause similar symptoms [332]. The lens wearer may achieve relief from these symptoms with periodic administration of lubricating rewetting drops [333]. These solutions contain polymers or surfactants that enhance the wettability of the surface, facilitate the spreading of tears, and improve the stability of the tear film. They may also provide cushioning and lubrication actions, thereby reducing the frictional force between the eyelids and the lens. Some products are specifically designed to rehydrate the lens. These products are unpreserved and packaged in a unit-dose. However, a preservative is required for a multidose product.

The emphasis that patients place on convenience has led to the development of single-bottle care products referred to as "multi-purpose solutions." Such products do not require a separate cleaner and in some instances can be used as a rewetting drop. However, they require rubbing and rinsing lenses in order to achieve adequate cleaning. Recent advances in technology along with careful selection of formulation components have resulted in a product that does not require a rubbing step [334]. This product has met all the microbiological and cleaning efficacy requirements, including those proposed in the ISO Guidelines.

Table 12 Types of Tests and Requirements Proposed by FDA for Product Development

I. Chemistry/manufacturing
- A. Solution/container descriptions
- B. Solution stability testing
- C. Lens group selection for solution testing

II. Toxicology
- A. Solution testing
  1. Acute oral toxicity assessment
  2. Acute systemic toxicity assessment
  3. Acute ocular irritation and cytotoxicity assessment
  4. Sensitization/allergic response assessment
     - a. Preservative uptake and release test
     - b. Guinea pig maximization testing
- B. Container/accessory testing
  1. In vitro testing
  2. Systemic toxicity testing
  3. Primary ocular irritation testing

III. Microbiology
- A. Sterilization of the solution by the manufacturer
  1. Validation of the sterilization cycle
  2. USP sterility tests
  3. USP type preservative effectiveness test
  4. USP microbial limits test
- B. Shelf life testing requirements
  1. Shelf life sterility
  2. Shelf life preservative effectiveness
  3. Extension of shelf life protocol
- C. Disinfection of the lens
  1. Chemical disinfection systems
     - a. Contribution of elements test
     - b. D-value determinations
     - c. Multi-item microbial challenge test

IV. Clinical
- A. Patient characteristics
- B. Number of eyes duration and number of investigators
- C. Initial patient visit parameters

D. Summary

Generally, contact lens products are sterile solutions or suspensions. Formulators for these products must have training in technologies practiced during development of sterile pharmaceutical products, such as injectable and large-volume intravenous fluids. The products must be effective and compatible with a wide range of lens materials. Components of the formulations should not accumulate in the lens or change the lens properties. They must be preserved adequately and be well tolerated by the sensitive ocular tissues. The products should also be simple to use in order to assure good compliance on the part of lens wearers. Additionally, they should be developed following the guidelines enumerated in Table 12.

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