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Chapter 43
Ophthalmic Preparations

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INTRODUCTION[1]

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

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

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

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

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

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

From the time of belladonna collyria, ophthalmic technology progressed at a pharmaceutical snail's pace until after World War II. Before World War II and into the 1950s, ophthalmic preparations were mostly compounded by the pharmacist for immediate use. Not until 1953 was there a legal requirement by the US Food and Drug Administration (FDA) that all manufactured ophthalmic solutions be sterile. The range of medicinal agents to treat eye disorders was limited, as was the state of eye surgery and vision correction, which was limited to eyeglasses. In the past 50 years, a modern pharmaceutical industry specializing in ophthalmic preparations has developed to support the advances in diagnosis and treatment of eye diseases, in eye surgery, and in contact lens design and use. Because of the variety of ophthalmic products readily available commercially, the pharmacist now is rarely required to compound a patient's ophthalmic prescription. More important, however, is that the pharmacist appreciate even subtle differences in formulations that may impact efficacy, comfort, compatibility, or suitability of a preparation for particular patients.

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

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

ANATOMY AND PHYSIOLOGY OF THE EYE

In many ways the human eye is an ideal organ for studying drug administration and disposition, organ physiology, and function. Unlike many bodily organs, most of its structure can be inspected without surgical intervention. Its macroscopic responses can be investigated by direct observation. Its miraculous function, so intricate and complex, converting a physical electromagnetic stimulus into a chemical signal that is coupled to distant neurons for signal processing by an electrochemical wave, is detectable by sensitive instruments attached to external tissues. The basis for the function and protection of this important organ that links humans to their external environment is the tissues composing it. The structures to be described are illustrated in Figures 43-1 to 43-3. Figure 43-1 provides a horizontal section of the eyeball identifying the major structures and their interrelationships.[5] Figures 43-2 shows in greater detail the anterior portion of the eye and eyelids, in vertical section, emphasizing some of the structures associated with tear apparatus.[6] Figure 43-3 emphasizes the flow of tears into the nasal structures.[6] This brief introduction will focus on the anatomical structures composing the eye and their function.

EYELIDS

Eyelids serve two purposes: mechanical protection of the globe and creation of an optimum milieu for the cornea. The inner surfaces of the eyelids and the outermost surfaces of the eye are lubricated by the tears, a composite of secretions from both lacrimal glands and specialized cells residing in both the bulbar (covering the sclera) and palpebral (covering the inner surface of the lids) conjunctiva. The antechamber has the shape of a narrow cleft directly over the front of the eyeball, with pocket-like extensions upward and downward. The pockets are called the superior and inferior fornices (vaults), and the entire space, the conjunctival cul-de-sac. The elliptical opening between the eyelids is called the palpebral fissure, and the corner of the eyes where the eyelids meet are the canthi.

OVERVIEW OF STRUCTURE AND FUNCTION OF THE EYEBALL

Structure

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

OUTER FIBROUS LAYER

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

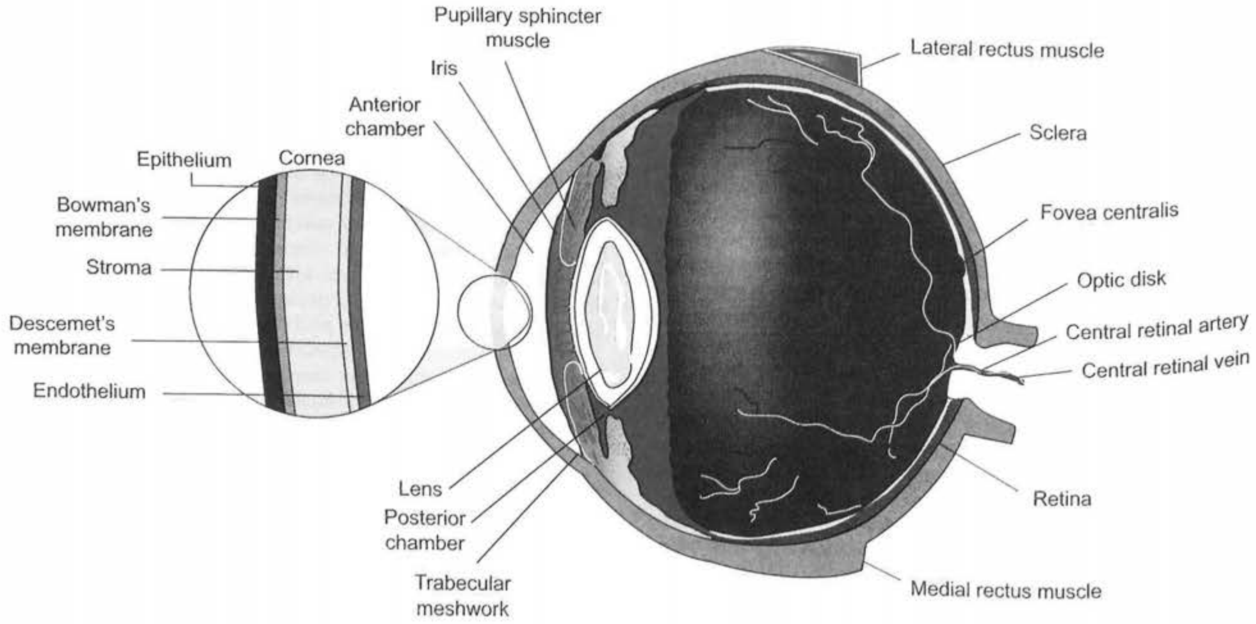

Figure 43-1. A cutaway horizontal section of the eyeball, illustrating the important anatomic structures and their interrelationships diagrammatically. The different layers of the cornea are illustrated in the magnified view. Relative sizes are suggestive and not proportional. The diameter of

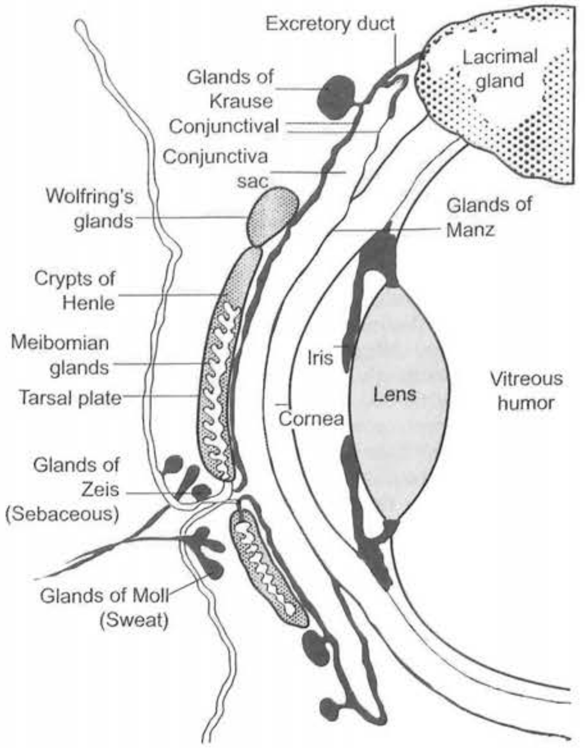

Figure 43-2. The front half of the eye, in vertical section, identifying the important structures associated with cornea and the front of the eye, including the eyelids and the glands associated with tears.

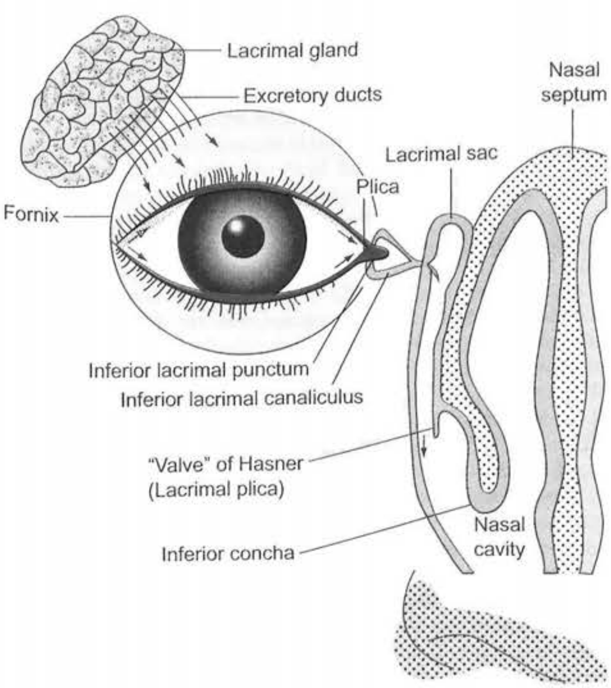

Figure 43-3. The structures associated with the tears and lacrimal flow and access to the nasolacrimal system.

water content so carefully adjusted that it acts as a transparent window. It is devoid of blood vessels. Over the remaining two thirds of the globe, the fibrous collagen-rich coat is opaque (the *white* of the eye) and is called the sclera. It contains the segment, and is usually white except when irritated vessels become dilated.

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

MIDDLE VASCULAR LAYER

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

NEURAL RETINA

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

OCULAR CORE

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

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

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