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CHAPTER 89

Ophthalmic Preparations

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

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

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

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

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

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

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

The sterility requirements for ophthalmic ointments ap-

ophthalmic ointment. This probably was due to the difficulty (at that time) of testing for sterility in such nonaqueous systems and also for the anticipated difficulties in sterilizing and maintaining sterile conditions during the manufacture and filling of ointments on a large scale.

Anatomy and Physiology of the Eye

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

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

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

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

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

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

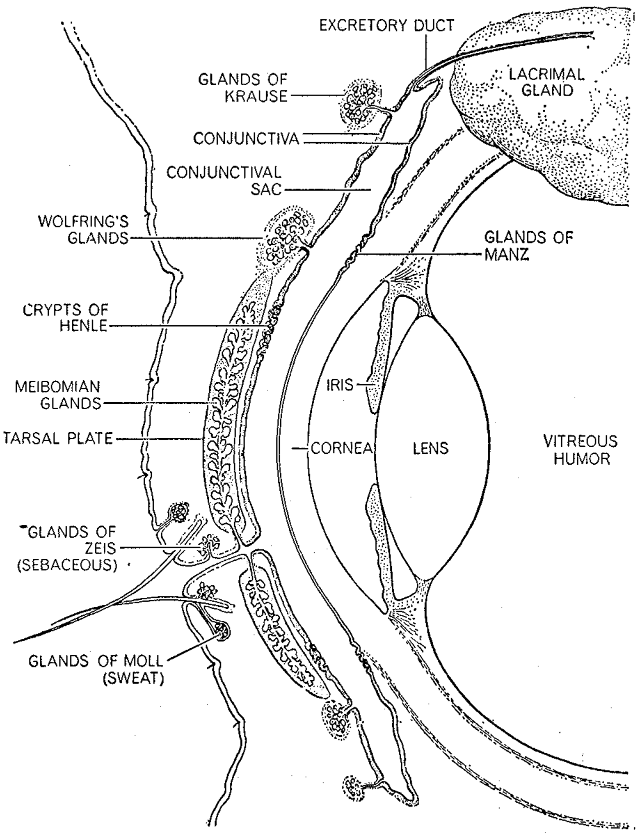
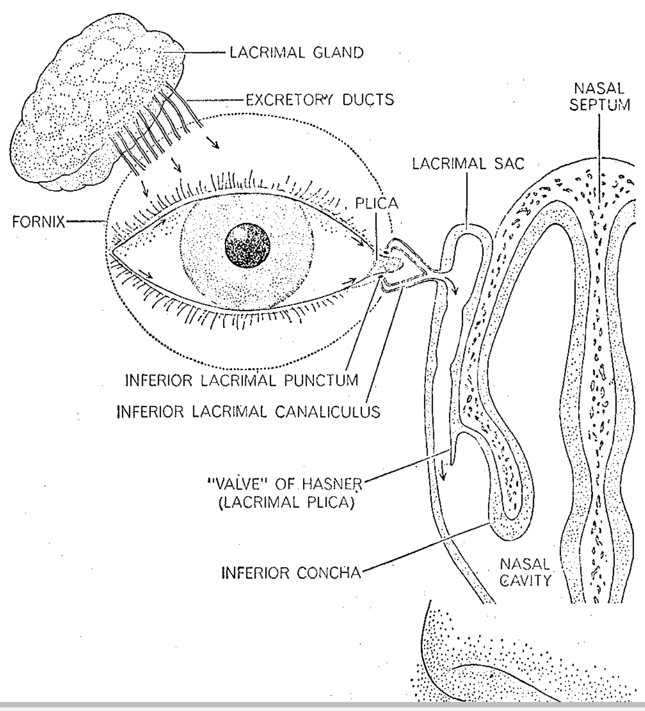


Fig 1. The eye: vertical section.[1]

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



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

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

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

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

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

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

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

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