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

Anatomy and Physiology of the Eye

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

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

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

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

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

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

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

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