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Ophthalmic Preparations

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ABSTRACT General chapter [Ophthalmic Ointments](#) [⟨ 771 ⟩](#) is being revised and renamed [Ophthalmic Preparations—Quality Tests](#) [⟨ 771 ⟩](#) and will include descriptions of and quality tests for all dosage forms that can be applied in the eye. A companion chapter, [Ophthalmic Preparations—Quality Tests](#) [⟨ 771 ⟩](#), will address performance tests such as dissolution and drug release. This *Stimuli* article presents the rationale for these changes, along with descriptions and characteristics related to novel ophthalmic dosage forms.

1. INTRODUCTION

USP general chapter [Ophthalmic Ointments](#) [⟨ 771 ⟩](#) (1) addresses some parameters and characteristics such as added substances, containers, metal particles and leakage for only ophthalmic ointments. In an effort to modernize this general chapter and align it to the other USP general chapters related to pharmaceutical dosage forms, the general chapter [⟨ 771 ⟩](#) is being revised to include the description and quality tests for all dosage forms that can be applied in the eye. This chapter is being renamed to [Ophthalmic Preparations—Quality Tests](#) [⟨ 771 ⟩](#). The chapter will cover only the ophthalmic dosage forms available in the USA at the time of its publication and it is going to be revised when new ophthalmic dosage forms are approved by FDA. As a consequence of the revision to the current version of [⟨ 771 ⟩](#), the general chapter [Metal Particles in Ophthalmic Ointments](#) [⟨ 751 ⟩](#) is being proposed for omission since its content was transferred to the new version of [⟨ 771 ⟩](#) and updated. All monographs that cross-reference [⟨ 751 ⟩](#) are being updated to cross-reference [⟨ 771 ⟩](#). The performance tests (dissolution and drug release) for ophthalmic preparations will be discussed in the new general chapter [Ophthalmic Preparations—Performance Tests](#) [⟨ 1771 ⟩](#). This *Stimuli* article presents the rationale and additional information to support the revisions. Additionally, the article contains description and characteristics related to novel ophthalmic pharmaceutical dosage forms.

2. EYE

2.1 Anatomy of the Eye

The human eye can be generally divided into the anterior and the posterior segments. The anterior segment includes the cornea, conjunctiva, iris, ciliary body, aqueous humor and lens while the posterior segment comprises sclera, choroid, retina and vitreous humor ([Figure 1](#)). The cornea, the outermost transparent multilayered membrane of the eye, is devoid of blood supply and acquires its nourishment from the aqueous humor and limbal blood capillaries. The human cornea is comprised of five layers i.e. corneal epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium. The aqueous humor is a fluid present in the anterior segment of the eye. It is the major source of nutrition to the crystalline lens and cornea. The iris is the colored portion of the eye comprising pigmented epithelial cells and circular muscles (constrictor iridial sphincter muscles). The opening in the middle of the iris is called the pupil. The iris sphincter and dilator muscles help in adjusting the pupil size which regulates the amount of light entering the eye. The ciliary body, a ring-shaped muscle attached to the iris, comprises ciliary muscles. Contraction and relaxation of the ciliary muscle controls the shape of the lens. The lens is a crystalline and flexible unit consisting of layers of tissue enclosed in a capsule. It is suspended from the ciliary muscles by very thin fibers called the zonules. The conjunctiva is a clear mucous membrane that lines the inside of the eyelids and spreads from the anterior surface of the sclera up to the limbus. It facilitates lubrication in the eye by generating mucus and helps adherence of the tear film. The sclera is a white sheath surrounding the eyeball and is called “white of the eye”. It acts as a principal shield to protect the internal organs. The sclera is juxtaposed by a highly vascularized tissue known as the choroid, which is sandwiched between the retina and the sclera. The choroid provides nourishment to the photoreceptor cells in the retina. The retina is a multi-layered sensory, light sensitive tissue that lines the back of the eye. It contains millions of photoreceptors or photosensitive elements that capture light rays and convert them into electrical impulses. These impulses travel along the optic nerve to the brain, where they are converted into an image. The vitreous humor is a jelly-like substance or a hydrogel matrix, distributed between retina and lens (2,3).

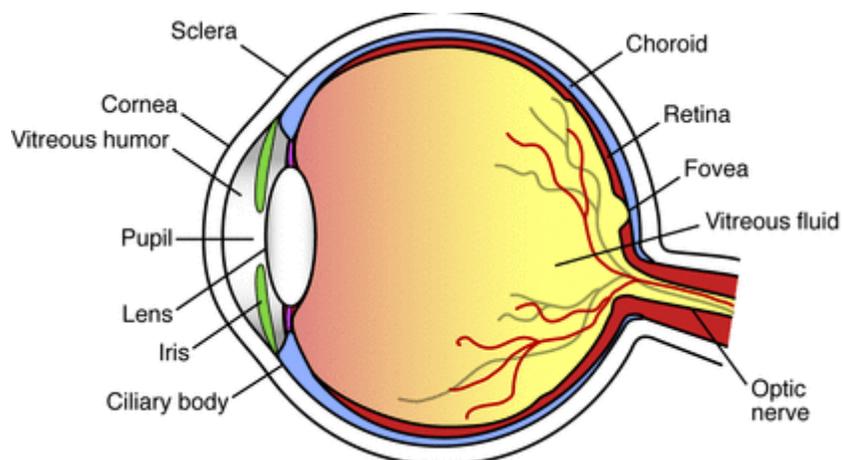


Figure 1. Anatomy of the human eye.

2.2 Routes of Administration into the Eye

Compared with drug delivery to other parts of the body, ocular drug delivery must overcome important challenges posed by various ocular barriers. Many of these barriers are inherent and unique to ocular anatomy and physiology making it a challenge to deliver the appropriate dose at the appropriate place (3,4).

Ophthalmic drug delivery is used only for the treatment of local conditions of the eye and cannot be used as a portal of drug entry to the systemic circulation. Significant advances have been made to optimize the localized delivery of medication to the eye, so that the route is now

associated with highly sophisticated drug delivery techniques. Some of these technologies are unique to the eye and many are also found in other delivery routes (5).

The bioavailability of traditional ocular drug delivery systems such as eye drops is very poor because the eye is protected by a series of complex defense mechanisms that make it difficult to achieve an effective drug concentration within the target area of the eye. The anatomy and physiology of the eye is one of the most complex and unique systems in the human body. Lachrymation, effective drainage by the nasolacrimal system, the inner and outer blood-retinal barrier, the impermeability of the cornea, and inability of other non-corneal structures to absorb compounds make the eye exceedingly impervious to foreign substances. While these innate barriers are advantageous for hindering the invasion of undesired molecules, pathogens, and particulates, they pose significant challenges to the delivery of ocular drugs (6).

Some of routes of administration to the eye are shown in [Figure 2](#).

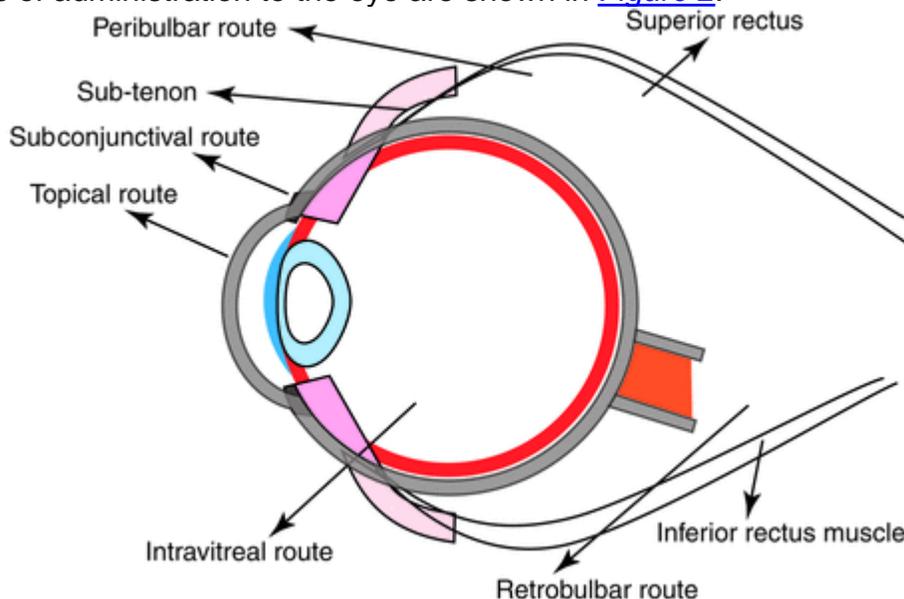


Figure 2. Some of the routes of administration in the eye.

2.2.1 Topical administration

Topical administration is employed mostly in the form of eye drops, ointments, gels, or emulsions, to treat anterior segment diseases. Topical application has remained the most preferred method due to the ease of administration and low cost. For most of the topically applied drugs, the site of action is usually different layers of the cornea, conjunctiva, sclera, and the other tissues of the anterior segment such as the iris and ciliary body (anterior uvea). Upon administration, precorneal factors and anatomical barriers negatively affect the bioavailability of topical formulations. Precorneal factors include solution drainage, blinking, tear film, tear turn over, and induced lacrimation. Human tear volume is estimated to be 7 μL , and the cul-de-sac can transiently contain around 30 μL of fluid. However, tear film displays a rapid restoration time of 2–3 min, and most of the topically applied solutions are washed away within 15–30 s after instillation. Considering all the precorneal factors, contact time with the absorptive membranes is low, which is considered to be the primary reason for less than 5% of the applied dose reaching the intraocular tissues.

The cornea, the most anterior layer of the eye, is a mechanical barrier that limits the entry of exogenous substances into the eye and protects the ocular tissues. It is considered as a major barrier for ocular drug delivery. The cornea can be divided mainly into the epithelium, stroma, and endothelium. Each layer offers a different polarity and a potential rate-limiting structure for drug permeation. The highly hydrated structure of the stroma poses a significant barrier to

permeation of lipophilic drugs.

Routes of absorption that lead to the removal of drugs from the precorneal area and do not result in direct ocular uptake, are referred to as nonproductive (7). Compared to that in the cornea, conjunctival drug absorption is considered to be nonproductive due to the presence of conjunctival blood capillaries and lymphatics that can cause significant drug loss into the systemic circulation thereby lowering ocular bioavailability (3,4,6–10).

Viscosity is another factor that can regulate nonproductive absorption, as well as ocular absorption. Increasing viscosity may decrease drainage rate, prolong precorneal residence time, and increase ocular absorption (7).

2.2.2 Systemic (Parenteral) Administration

Following systemic administration, the blood-aqueous barrier and blood-retinal barrier are the major barriers for the anterior segment and posterior segment ocular drug delivery, respectively. Even though it is ideal to deliver the drug to the retina via systemic administration, it is still a challenge because of the blood-retina barrier, which strictly regulates drug permeation from blood to the retina. Hence, specific oral or intravenous targeting systems are needed to transport molecules through the choroid into deeper layers of the retina.

2.2.3 Oral Administration

Oral delivery alone or in combination with topical delivery has been investigated for different reasons. Topical delivery alone failed to produce therapeutic concentrations in the posterior segment. Also, oral delivery was studied as a possible noninvasive and patient-preferred route to treat chronic retinal diseases as compared to the parenteral route. However, restricted accessibility to many of the targeted ocular tissues limits the utility of oral administration which necessitates high dosage to achieve significant therapeutic efficacy. Such doses can result in systemic side effects. Hence, parameters such as safety and toxicity need to be considered when trying to obtain a therapeutic response in the eye upon oral administration.

2.2.4 Periocular and Intravitreal Administration

Although not very appealing to patients, these routes are employed partly to overcome the inefficiency of topical and systemic delivery to the posterior segment. The periocular route includes subconjunctival, subtenons, retrobulbar, and peribulbar administration and is comparatively less invasive than the intravitreal route. Subconjunctival injection bypasses the conjunctival epithelial barrier, which is a rate-limiting barrier for the permeation of water-soluble drugs. Drug solutions are placed in close proximity to the sclera, which results in high retinal and vitreal concentrations.

Unlike periocular injections, the intravitreal injection offers distinct advantages as the molecules are directly inserted into the vitreous. This method involves injection of the solution containing the drug directly into the vitreous via pars plana using a 30-gauge needle. Unlike other routes, intravitreal injection delivers higher drug concentrations to the vitreous and retina. However, drug distribution in the vitreous is nonuniform. Small molecules can rapidly distribute through the vitreous, whereas the diffusion of larger molecules is restricted. This distribution also depends on the pathophysiological condition and molecular weight of the administered drug. Similarly, mobility of nanoparticles in the vitreous depends on their structure and surface charge (3,4,6).

3. DOSAGE FORMS APPLIED TO THE EYE

Common to all ophthalmic dosage forms is the critical requirement for sterility of the finished product as well as consideration of the sensitivity of ocular tissue to irritation (7).

3.1 Solutions

Ophthalmic solutions are sterile solutions intended for instillation in the eye. Included in this dosage form category are solid preparations that, when reconstituted according to the label

instructions, result in a solution. In addition to sterility, these dosage forms require the careful consideration of such other pharmaceutical factors as the need for antimicrobial agents, osmolarity, buffering, viscosity, and proper packaging.

The corneal contact time of topical ophthalmic solutions increases with the viscosity of the formulations up to 20 centipoise (cP). Further increases result in reflex tearing and blinking in order to regain the original viscosity of the lacrimal fluid (1.05–5.97 cP). The bioavailability increase associated with this longer precorneal permanence allows the frequency of drug application to be reduced. Synthetic polymers, such as polyvinylalcohol (PVA), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), polyacrylic acid (PAA), and many cellulose derivatives, are commonly employed as viscosity enhancers because of their physiologic compatibility and satisfactory physicochemical properties. A more sophisticated approach consists of using polymers that provide the liquid formulation with semisolid consistency only when it is placed in the conjunctival or corneal area. In this way, easy instillation of the solution is followed by prolonged permanence as a result of the viscoelastic properties of the formed hydrogel. This *in situ* gelling phenomenon is caused by a change in the conformation of the polymer(s) that can be triggered by external stimuli such as temperature, pH, ionic content and lacrimal fluid upon delivery into the eye. Additionally, some polymers can interact, via noncovalent bonds, with conjunctival mucin and maintain the formulations in contact with corneal tissues until mucin turnover leads to their removal. Two of the major drawbacks of viscous and mucoadhesive formulations are blurring and an unpleasant sticky feeling in the eye. As consequence, patients may find compliance with treatment schedules difficult (7,9–11).

3.2 Suspensions

Ophthalmic suspensions may be used to increase the corneal contact time of a drug substance and thus provide a more sustained action. Included in this dosage form category are those solid preparations that, when reconstituted according to the label instructions, result in a suspension. An ophthalmic suspension may be required when the active ingredient is insoluble in the desired vehicle or is unstable in solution (12).

Suspensions are required to be made with the insoluble drug in a micronized form to prevent irritation or scratching of the cornea (7). Suspensions are commonly formulated by dispersing micronized drug powder (less than 10 μm in diameter) in a suitable aqueous vehicle. Ophthalmic suspensions, particularly for the steroids, are thought to be acceptable as delivery systems since it is assumed that drug particles persist in the conjunctival sac giving rise to a sustained-release effect. However, suspensions have a disadvantage that the concentration of dissolved drug cannot be manipulated due to their relative insolubility in the vehicle.

Particle size in suspensions for ocular drug delivery is important. An increase in drug particle size enhances the ocular bioavailability. Unfortunately, a particle size above 10 μm in diameter may result in a foreign body sensation in the eye following ocular application, causing reflex tearing. A reduction in particle size generally improves the patient comfort and acceptability of suspension formulations (5,9,11). The potential for any changes in particle size due to Ostwald ripening or particle agglomeration needs to be evaluated through stability testing.

Surfactants may be included in an ophthalmic suspension to disperse the drug effectively during manufacture and during product use. Nonionic surfactants are generally preferred because they tend to be less toxic. The level of surfactant included in the formulation should be carefully evaluated, as excessive amounts can lead to irritation in the eye, foaming during manufacture and upon shaking the product, or interactions with other excipients.

Consideration must be given to establishing good physical stability of a suspension. If the particles settle and eventually produce a cake at the bottom of the container, they must redisperse readily to achieve dosage uniformity. Viscosity-enhancing agents can be used to keep the particles suspended. Preparation of flocculated suspensions is not recommended

because the larger flocs may irritate the eye (10,11).

Ophthalmic suspensions must possess the same characteristic of sterility as ophthalmic solutions, with proper consideration given also to preservation, osmolarity, buffering, viscosity and packaging. Additionally, ophthalmic suspensions must contain particles of such chemical characteristics and small dimensions that they are nonirritating to the eyes. The ophthalmic suspension must be appropriately formulated so that the suspended particles do not agglomerate into larger ones upon storage.

Suspensions may pose challenges during manufacturing to achieve a sterile product. The possibilities of either degradation or morphological changes occurring during the sterilization process exist and must be prevented (8,12).

Sterile powders for reconstitution (resulting in a solution or suspension, after reconstitution) are useful for drugs that have limited stability in liquid form. The sterile powder can be manufactured by lyophilization in the individual container. In powdered form the drug may have a much longer shelf life than in solution or suspension. Usually, a separately packaged sterile diluent is provided with the sterile powder (7).

3.3 Ointments

Ophthalmic ointments must be sterile. Like suspensions, ointments can be more difficult to manufacture in sterile form. They can be terminally sterilized, or, alternatively, they must be manufactured from sterile ingredients in an aseptic environment. Filtration through a suitable membrane or dry heat sterilization is often used.

The ointment base selected for an ophthalmic ointment must be nonirritating to the eye and must permit the diffusion of the active ingredient throughout the secretions bathing the eye. Ointment bases utilized for ophthalmics have a melting or softening point close to body temperature.

Ophthalmic ointments have a longer ocular contact time when compared to many ophthalmic solutions. Studies have shown that the ocular contact time is two to four times greater when ointments are used than when a saline solution is used. One disadvantage to ophthalmic ointments is the blurred vision that occurs as the ointment base melts and is spread across the lens (7,10–12).

3.4 Gels

Ophthalmic gels are composed of mucoadhesive polymers that provide localized delivery of an active ingredient to the eye. Such polymers have a property known as bioadhesion meaning attachment of a drug carrier to a specific biological tissue. These polymers are able to extend the contact time of the drug with the biological tissues and thereby improve ocular bioavailability. The choice of the polymer plays a critical role in the release kinetics of the drug (s) from the dosage form. Several bioadhesive polymers are available with varying degree of mucoadhesive performance. Some examples are carboxymethylcellulose, carbopol, polycarbophil, and sodium alginate (11).

3.5 Emulsions

Topical ophthalmic emulsions generally are prepared by dissolving or dispersing the active ingredient(s) into an oil phase, adding suitable emulsifying and suspending agents and mixing with water vigorously to form a uniform oil-in-water emulsion. Each phase is typically sterilized prior to or during charging into the mixing vessel. High-shear homogenation may be employed to reduce oil droplet size to sub-micron size which may improve the physical stability of the oil micelles so they do not coalesce. The resulting dosage form should contain small oil droplets, uniformly suspended.

Limited aqueous solubility of the drug substance(s) is the most common rationale for developing an ophthalmic emulsion. The drug substance(s) can be added to the phase in which it is soluble at the beginning of the manufacturing process, or it can be added after the emulsion

is prepared by a suitable dispersion process.

To prevent flocculation, creaming and coalescence of the emulsions, manufacturers commonly add surfactants to increase the kinetic stability of the emulsion so that the emulsion does not change significantly with time.

Emulsions may exhibit three types of instability: flocculation, creaming, and coalescence. Flocculation describes the process by which the dispersed phase comes out of suspension in the form of flakes. Coalescence is another form of instability in which small droplets within the media continuously combine to form progressively larger droplets. Emulsions can also undergo creaming, where one of the phases migrate to the top (or the bottom, depending on the relative densities of the two phases) of the emulsion.

3.6 Strips

Ophthalmic strips are made of filter paper and are individually packed to ensure sterility until the time of use. They can be used in the measurement of tear production in dry eye conditions. In this case, they are gauged for easy reading of the measurement. They can be impregnated with certain drugs such as fluorescein sodium (used as a diagnostic strips to visualize defects or aberrations in the corneal epithelium by staining the areas of cellular loss; to evaluate hard contact lens fitting and to evaluate applanation tonometry); lissamine green (used to stain damaged or devitalized cells and to indicate dry patches as well as any mucus-deficient or damaged corneal epithelial cells); and rose bengal (used to stain degenerating epithelium in the outer layer of cornea as well as mucous filaments).

3.7 Injections

While injections are considered a dosage form for nomenclature purposes, they are not treated as a dosage form in this paper. Instead, refer to the appropriate physical form, such as solution, suspension, etc., for general information.

3.8 Inserts

Ophthalmic inserts and ocular systems are solid dosage forms of appropriate size and shape that are placed in the conjunctival fornix, in the lachrymal punctum ([Figure 3](#)) or on the cornea. They can be classified as erodible (soluble) and nonerodible (insoluble). These devices allow accurate dose delivery, can avoid the use of preservatives, and can notably increase ocular bioavailability. Drug release from soluble inserts involves two steps: 1—fast release of a portion of the drug as the tear fluid penetrates into the system; and 2—slow release as a gel layer is formed on the surface of the insert. As the initial dissolution step is usually fast, the solubilized components can often cause blurred vision. Collagen shields made from porcine sclera collagen or bovine corium tissue, and devices obtained by molding, extrusion or compression (minitablets) of gelling polymers, belong to this category. Bioerodible polymers (e.g. cross-linked gelatin derivatives, poly vinyl alcohol, hypromellose, and polyesters) can be used to prepare erodible inserts. These matrices act as simple reservoirs or interact with the drug molecules through labile bonds; the ease with which these bonds can be broken regulates release of the drug. They can dissolve within 12–24 h. As the erosion rate is largely dependent on the conditions of the physiologic environment, drug release profiles usually show a high inter- and intraindividual variability. Finally, insoluble inserts can have a reservoir or matrix structure. They release the drug for longer periods of time. Despite the remarkable therapeutic advantages of these inserts, difficulties with handling, the sensation of a foreign body in the eye, and the high risk of accidental expulsion greatly limit their practical use. (7,9,10,13).

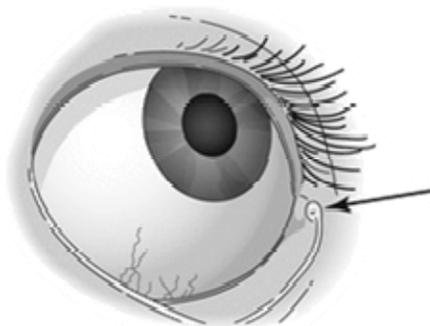


Figure 3. Lachrimal punctum.

3.8.1 Contact Lenses

Contact lenses can be a way of providing extended release of drugs into the eye. Current challenges in this mode of drug delivery are to sustain drug release for longer periods and also to incorporate sufficient drug amounts in the lens matrix (4, 14). Conventional hydrogel soft contact lenses have the ability to absorb some drugs and release them into the postlens lacrimal fluid, minimizing clearance and sorption through the conjunctiva. Their ability to be a drug reservoir strongly depends on the water content and thickness of the lens, the molecular weight of the drug, the concentration of the drug loading solution and the time the lens remains in it. However, the ability of contact lens to load drugs and to control their release is in general inadequate and the following approaches, based on modifications of the polymer network, are under evaluation: (1) covalent binding of the drug to the lens network via labile bonds; (2) inclusion of the drug in colloidal structures that are dispersed in the lens and are responsible for controlling drug release; (3) functionalization of the network with chemical groups that work as ion-exchange resins; and (4) creation in the lens structure of imprinted pockets that memorize the spatial features and bonding preferences of the drug and provide the lens with a high affinity and selectivity for a given drug (4,9, 14).

3.9 Implants

Implants have been widely employed to extend the release of drugs in ocular fluids and tissues particularly in the posterior segment. Implants can be broadly classified into two categories based on their degradation properties: (1) biodegradable and (2) nonbiodegradable. With implants, the delivery rate could be modulated by varying polymer composition. Implants can be solids, semisolids or particulate-based delivery systems (4).

Biodegradable polymers can be used to form solid or injectable implants, or they can be used to encapsulate particular systems as nano- and microparticles. Particulate systems can be injected through thin needles and have different behavior and distribution in the ocular media depending on their size and composition. Polymers can be devised as viscous or semisolid materials that can be localized within the eye and used as a slow-release intraocular implant after a simple injection.

Biodegradable polymers include poly lactic acid (PLA), poly glycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA). Once implanted, bulk erosion occurs causing a burst of encapsulated drug. This phenomenon takes place following the cleavage of polymeric chains by enzymatic and nonenzymatic hydrolysis. These devices can be manufactured in various shapes including rods, plugs, pellets, discs, and sheets. Accordingly, they can be implanted into the anterior chamber, the vitreous cavity through the pars plana, or into the intrascleral space. Degradation of polycaprolactones (PCL) by cleavage of the ester bond produces small polymeric fragments that diffuse from the matrix and undergo phagocytosis. Drug release from PCL porous reservoir can be obtained for more than 250 days with zero-order kinetics. Polyanhydrides are degraded by surface erosion and have very good biocompatibility (15, 16). Scleral plugs are an example of

a matrix implant made for intraocular insertion and delivery of drug into the vitreous cavity. These implants are composed of a matrix of PLGA and drug and are constructed by a compression-molding technique to 1 mm in diameter (13).

Examples of nonbiodegradable polymers used in solid implants are: polyvinyl alcohol (PVA), poly ethylene vinyl acetate (EVA), and silicon. The mechanism of action of these polymers is based on diffusion of a fluid (water) into the device dissolving the drug, creating a saturated solution released to the medium by diffusion out of the device. As long as the inside solution is saturated with drug, the release rate is constant. The nonbiodegradable polymer devices do not produce an initial burst of drug. Very long-lasting (more than a year) and controlled release has been achieved using this type of implant, with higher concentrations measured in the vitreous than in the aqueous humor and very low serum concentrations. The major drawbacks for the use of this type of device are the need for a surgical implantation and the need to remove it after it empties. Polysulfone is a water-impermeable polymer permeable to lipophilic as well as hydrophilic compounds. This polymer has deep macrovoids in the outer membrane which increase the surface area for drug diffusion and release. These implants can be sterilized, but they have to be removed once emptied (13,15).

Poly(ortho esters) (POE) are viscous injectable polymers that are degraded by surface erosion confined to the polymer-water interface which follow a zero-order kinetics when placed in a biological environment. This type of drug release is controlled by gradual surface degradation of the polymer and drug release rather than drug diffusion. Some families of POE have been synthesized. POE I and POE II families were not used for in vivo ophthalmic studies. The third generation of POE is, at room temperature, in a gel-like conformation. This state of the polymer allows the incorporation of therapeutic agents by simple mixing without the need of solvents. Moreover these viscous POE can be injected directly into the eye with an appropriate needle. Since POE contain pH-sensitive links in the polymeric backbone, the degradation rate of the polymer can be controlled by incorporating acidic substances into the polymer matrix to increase the erosion rate, or on the contrary, basic ones to stabilize the polymer backbone. Classic gamma irradiation sterilization induces POE III polymer degradation. Therefore, aseptic preparation of the polymer is recommended (15,16).

3.10 Drug Device Combination Products

An ophthalmic drug device combination product is constituted, in most cases, of two components. One is a pharmaceutical dosage form containing the active ingredient(s) and the other is a device that will activate, or facilitate the penetration of the active ingredient(s) from the dosage form into a particular region of the eye. Some examples of these devices are those that generate waveforms (heat or light). One ophthalmic drug device combination product recently approved by FDA is verteporfin for injection, which is associated with a nonthermal red light activation used in the treatment of age-related macular degeneration.

General chapters [Ophthalmic Preparations—Quality Tests](#) (771) and [Ophthalmic Preparations—Performance Tests](#) (1711) will be applicable only to the pharmaceutical dosage form component of the ophthalmic drug device combination product. The appropriate FDA regulations on medical devices should be used for the device component.

3.11 Novel Ophthalmic Dosage Forms

3.11.1 Colloidal Systems

Colloidal dosage forms have been widely studied and employed in the field of ocular drug delivery. These dosage forms include liposomes, nanoparticles, microemulsions, nanoemulsions, etc. Advantages of colloidal dosage forms include sustained and controlled release of the drug at the targeted site, reduced frequency of administration, and ability to overcome blood-ocular barriers. Further, these carriers can also bypass or overcome various

stability-related problems of drug molecules, e.g., proteins and peptides (3,4). Encapsulation of drugs in these colloidal carriers can also significantly enhance permeation across the membrane and prevent degradation by the ocular enzymes. Such biodegradable carriers can be developed as an alternative to the implants prepared from nonbiodegradable polymers, which has to be removed surgically after a certain period of time (4, 11, 15, 17).

Although very promising, commercial development of these colloidal systems remains limited because of the complexity of their manufacture, particularly in relation to stability problems during sterilization, which are not offset by substantial improvements in pharmacokinetic and pharmacologic performance (9). Temperatures required for autoclaving can cause irreversible damage to colloidal systems, while filtration is only applicable to microparticulates with a size less than 0.2 μm (10).

Microemulsions

Microemulsions are dispersion of water and oil facilitated by a combination of surfactant and cosurfactant in a manner to reduce interfacial tension. These systems are usually characterized by higher thermodynamic stability, small droplet size (approximately 100 nm) and clear appearance. Their transparent appearance is due to the high level of dispersion of the internal phase, the size of it ranges from 100–1000 angstroms (18). Apart from solubility, microemulsion systems have also been exploited to improve permeation across the cornea. Such formulations often provide extended drug release thereby reducing frequency of the drug administration. Although microemulsions have excellent advantages, limitations in the selection of surfactant/cosurfactant system and potential toxicity associated with higher concentrations of surfactant/cosurfactant often restricts its use (4, 18).

Nanosuspensions

Nanosuspensions can be defined as sub-micron colloidal systems that consist of poorly water-soluble drug, suspended in an appropriate dispersion medium stabilized by surfactants. Usually nanosuspensions consist of colloidal carriers like polymeric resins which are inert in nature. They help in enhancement of drug solubility and thus bioavailability. Unlike microemulsions, they are non irritant. Charge on the surface of nanoparticles facilitates their adhesion to the cornea.

Nanoparticles

They can be defined as particles with a diameter of less than 1 μm , comprising of various biodegradable or non biodegradable polymers, lipids, phospholipids or metals. They can be classified as nanospheres or nanocapsules depending upon whether the drug has been uniformly dispersed or coated within polymeric material. The uptake and distribution of nanoparticles depend on its size.

Liposomes

Liposomes are lipid vesicles containing aqueous core and have been widely exploited in ocular delivery for various drug substances. Depending on the nature of the lipid composition selected, liposomes can provide extended release of the drug.

Niosomes

Niosomes are bilayered structural vesicles made up of nonionic surfactant and are capable of encapsulating both lipophilic and hydrophilic compounds. They can release the drug independent of pH, enhancing ocular bioavailability (4). Niosomes are microscopic lamellar structures that are formed on the admixture of nonionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. Structurally niosomes are similar to liposomes, in that they are also made up of a bilayer. However, the bilayer in the case of niosomes is made up of nonionic surface-active agents rather than phospholipids as in the case of liposomes. Niosomes may be unilamellar or multilamellar

depending on the method used to prepare them. They are capable of entrapping hydrophilic and hydrophobic solutes. They possess great stability and lack many disadvantages associated with liposomes such as high cost and the variable purity of phospholipids (19,20).

Dendrimers

Dendrimers are macromolecular compounds made up of a series of branches around a central core. Their nanosize, ease of preparation, functionalization, and possibility to attach multiple surface groups render them suitable alternative vehicles for ophthalmic extended drug delivery. This system of branched polymers represents unique architecture and can entrap both hydrophilic and lipophilic drugs into their structure. Selection of functional group on the surface (amine, carboxylate and hydroxyl), size and molecular weight of the dendrimer are important parameters to be considered in designing a delivery system (4).

3.11.2 Hydrogels

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of taking in large amounts of water or biological fluids. Residence time can be significantly enhanced with a hydrogel formulation. The gelation can be obtained by changing temperature and pH. Poloxamers, the most widely used polymer, contains the hydrophobic part in the centre surrounded by a hydrophilic part. Though they are widely employed to enhance the residence time, they suffer from a major drawback of having weak mechanical strength, rapid erosion, and nonbiodegradability. In case of cellulose derivative like hypromellose, gelation is a result of interaction of hydrophobic components at higher temperature. Another approach is having the polymer dissolved in a suitable carrier. The polymer and carrier are both biodegradable and biocompatible. Once injected into the subcutaneous space, water in surrounding tissues causes the precipitation of polymer which immediately entraps the drug and releases it in a controlled manner (4).

3.11.3 Microneedle-, Ultrasound-, and Iontophoresis-Based Ocular Drug Delivery Systems

All these delivery systems are noninvasive methods designed to deliver drugs to intraocular regions, mainly for the treatment of posterior segment diseases. Drug-coated microneedles have been developed with a length of 500–750 μm . The drug to be delivered can be coated on the solid metal. Following administration, coated molecules dissolve rapidly, and subsequently, microneedles are removed from the tissue. This delivery system generates a much higher concentration compared to a free-drug solution (3,4).

Similarly, ultrasound-mediated drug delivery has also received attention in recent years. Delivery of beta-blockers such as atenolol and timolol, was attempted with ultrasound application (20 kHz for 1 h) across cornea in the treatment of glaucoma. Corneal permeability of these compounds has been significantly enhanced with ultrasound.

Ocular iontophoresis has received a lot of attention in recent years, particularly to deliver drugs across cornea and sclera. Some active ingredients such as ciprofloxacin hydrochloride, gentamicin, dexamethasone, were successfully delivered using this technique (3).

4. CONTAINER CLOSURE SYSTEMS

Traditionally, ophthalmic liquid products were packed in glass containers fitted with an eye dropper. Today, glass containers have limited use where product stability or compatibility issues exclude the use of flexible plastic containers made of polyethylene or polypropylene. Most liquid ophthalmic products on the market are packaged in plastic containers fitted with nozzles from which, by gentle squeezing, the contents may be delivered as drops.

Plastic containers have several advantages over the glass-dropper combination such as minimizing the risk of the contents being contaminated with microorganisms by the replacement of the dropper which may have become contaminated by touching the infected eye or any other surfaces. Also, plastic containers are cheap, light in weight, more robust to handle and easier to

use than glass-dropper type containers.

However, there are some disadvantages of plastic eye-drop containers. Some plastic materials such as polyethylene can absorb some antimicrobial preservatives (e.g. benzalkonium chloride), or some drugs. They may also leach plasticizers into the product, or printing inks from the label can migrate through the plastic into the product. It is necessary to conduct compatibility and stability studies to ascertain whether this is likely to be a problem. Alternatives are to use glass or a preservative-free product. The challenge is to develop a packaging system for preservative-free products that maintains the sterility of the product throughout its shelf-life and during use.

Unit-dose systems offer the easiest technical solution to this problem but have the disadvantage of higher cost of manufacture and of not being as compact as a multidose product containing equivalent doses. An alternative approach is to develop a multidose preservative-free system. The container is required to be collapsible, and the suck-back of air, which could contain bacteria, has to be avoided. Containers are being developed that contain a valve mechanism to achieve this.

Due to the safety and regulatory concerns raised by preservatives used in ophthalmic product, there have been efforts to develop new eye-drop packaging systems that can remove the preservative from the formulation during administration. Benzalkonium chloride is the most common preservative used in commercial eye-drops, and yet there are reports of side-effects caused by its frequent use in ophthalmic products. Plastic containers can also be permeable to water vapor and oxygen over prolonged periods of storage. This can lead to gradual loss of liquid product or oxidation of an unstable drug over time.

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Polyethylene containers are not able to withstand autoclaving and are usually sterilized by ethylene oxide or by irradiation before being filled aseptically with presterilized product. Polypropylene containers can be autoclaved, but are not as flexible as polyethylene for eye-dropper use.

Semi-solid products have been traditionally packed in collapsible tin tubes. Metal tubes are a potential source of metal particles in ophthalmic products, and so the tubes have to be cleaned carefully prior to sterilization. Also, the final product must meet limits for the number of metal particles found. Plastic tubes are not suitable because of their noncollapsible nature, which causes air to enter the tube after withdrawal of each dose. However, collapsible tubes made from laminates of plastic, aluminum foil and paper are good alternative to tin tubes. Laminate tubes fitted with polypropylene caps can be sterilized by autoclaving, whereas tubes fitted with polyethylene caps are sterilized by gamma irradiation. The tubes are usually filled aseptically, sealed with an adhesive and then crimped (7,10).

5. DRUG PRODUCT QUALITY TESTS AND DRUG PRODUCT PERFORMANCE TESTS

Procedures and acceptance criteria for testing ophthalmic preparations are divided into two categories: (1) those that assess general quality attributes, for example, identification, potency, purity, (and impurities), sterility and particulate matter, and (2) those that assess in vitro product performance, i.e., dissolution or drug release of the active drug substance from the drug product. Quality tests assess the integrity of the dosage form, whereas the performance tests assess drug release and other attributes that relate to in vivo drug performance. Taken together, quality and performance tests assure the identity, strength, quality, purity and efficacy of the drug product.

In the new version of general chapter [\(771\)](#) the division of the product quality tests in universal tests and specific tests does not strictly follow the ICH guidance Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products:

Chemical substances (available at www.ich.org). Universal tests in this chapter mean the tests that are applicable to all ophthalmic products regardless of the dosage form type.

5.1 Drug Product Quality Tests—Universal Tests

5.1.1 Description

A qualitative description of the drug product is part of the product manufacturer's specification. The acceptance criteria should contain the final acceptable appearance, including clarity and color, of the dosage form and packaging. If color changes during storage, a quantitative procedure may be appropriate.

5.1.2 Identification

Identification tests should establish the identity of the drug or drugs present in the drug product and should discriminate between compounds of closely related structures that are likely to be present. Identity tests should be specific for the drug substance(s) (e.g., infrared spectroscopy). Near infrared (NIR) or Raman spectrophotometric techniques also could be acceptable for the identification of the drug product (see [Near-infrared Spectroscopy](#) { 1119 } (21) and [Raman Spectroscopy](#) { 1120 } (22)). The most used identification procedure for drug substance(s) contained in pharmaceutical dosage forms is by chromatography with comparison with the appropriate standards (see [Chromatography](#) { 621 } (23) and [Thin-layer Chromatographic Identification Test](#) { 201 } (24)). Identification solely by a single chromatographic retention time is not specific.

5.1.3 Assay

A specific and stability-indicating test should be used to determine the strength (content) of the drug product. In cases when the use of a nonspecific assay test is justified, other supporting analytical procedures should be used to achieve overall specificity. A specific procedure should be used when there is evidence of excipient interference with the nonspecific assay test.

Additional information on specific assays may be found in [Antibiotics—Microbial Assays](#) { 81 } (25), [Chromatography](#) { 621 } (23), [Spectrophotometry and Light scattering](#) { 851 } (26) and [Ion Chromatography](#) { 1065 } (27).

5.1.4 Impurities

Process impurities, synthetic by-products, and other inorganic and organic impurities may be present in the drug substance and excipients used in the manufacture of the drug product. These impurities are controlled by the drug substance and excipients compendial monographs. Organic impurities arising from the degradation of the drug substance in the drug product and those arising during the manufacturing process of the drug product should be monitored. All articles meet the requirements in [Elemental Impurities—Limits](#) { 232 } (28) and [Residual Solvents](#) { 467 } (29).

5.1.5 pH

The pH and buffering capacity of an ophthalmic preparation are 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.

In addition to stability effects, pH adjustment can influence comfort, safety, and activity of the product. Eye irritation is normally accompanied by an increase in tear fluid secretion as a defense mechanism to restore the 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 the drug may occur with a probable reduction in the therapeutic response (7).

Normal tears have a pH of about 7.4, but it varies; for example, tears are more acidic in contact lens wearers (8). Tears possess some buffer capacity. The introduction of a medicated product into the eye stimulates the flow of tears, which neutralize any excess hydrogen or hydroxyl ions introduced. Intraocular hyperosmotic solutions may elicit some transient desiccation of the anterior chamber tissues whereas intraocular hypotonic solutions may cause edema that could lead to corneal clouding (7). Normally, the buffering action of the tears is capable of neutralizing the topically applied product and is thereby able to prevent marked discomfort. For maximum comfort, an ophthalmic preparation should have the same pH as the lacrimal fluid. However, this is not pharmaceutically possible because at pH 7.4 many drugs are insoluble in water. The pH that permits greatest activity may also be the pH at which the drug is least stable. For this reason, a compromise pH is generally selected and maintained by buffers to permit the greatest activity while maintaining stability (8, 10, 12). 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 and is another reason that ophthalmic products are usually only lightly buffered (7).

For pH test procedures see [pH](#) (791) (30).

5.1.6 Osmolarity

In formulating ophthalmic preparations, it is more important to consider the sterility, stability, and preservative aspects, and not jeopardize these aspects to obtain a precisely isotonic solution. In certain instances, the therapeutic concentration of the drug will require using what might otherwise be considered an unacceptable tonicity (7). In practice, the tonicity limits may range from 0.5%–5% sodium chloride, equivalent to a range from about 171 mOsm/kg to about 1711 mOsm/kg, without marked discomfort to the eye.

For procedures to evaluate osmolarity, see [Osmolality and Osmolarity](#) (785) (31).

5.1.7 Particulate and Foreign Matter

Particles administered topically have the potential to damage the epithelial layer, which may lead to infection and scarring. Although the total effect of particulates on intraocular tissue is not completely known, some possible results in the anterior chamber have been postulated. 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 results from particulates in large-volume parenterals. Equally important, particulate matter can block the canals of Schlemm, disrupting the outflow mechanism for the aqueous humor and leading to a rapid increase in intraocular pressure and the onset of an acute attack of glaucoma. Particulates may originate from raw materials as well as glass fragments produced in glass ampoule fracture or elastomeric particles generating during stopper penetration (7).

All ophthalmic preparations including solutions, suspensions, emulsions and implants intended for ophthalmic injection must be inspected to the extent possible for the presence of observable foreign and particulate matter. Qualification of the inspection process should be performed with reference to particulates in the visible range of a type that might emanate from the manufacturing or filling process. The inspection for visible particulates may take place when inspecting for other critical attributes, such as molding abnormalities, cracked or defective containers or seals, or when characterizing the appearance of a lyophilized product.

Ophthalmic preparations, including solutions, suspensions, emulsions and implants, and their packaging should be developed and manufactured in a manner designed to exclude foreign visible particulate matter and to minimize the content of foreign subvisible particulate matter, as appropriate for the dosage form. Containers for ophthalmic use must be evaluated for cleanliness and shown to be free of hard particulate matter such as metal or glass.

Specifically for ophthalmic solutions, 100% inspection of all final packages is required and may

also utilize alternate methods to evaluate the presence of visible particles that may not be evident within translucent to opaque packages, as defined in [Visible Particulate Matter](#) [〈 790 〉](#) (32). Further, subvisible particulate matter content must be determined by the methods and limits defined in [Particulate Matter in Ophthalmic Solutions](#) [〈 789 〉](#) (33). The limits found in [〈 789 〉](#) (33) were developed for these products in order to provide greater assurance that ophthalmic solution batches will be essentially free of visible particles due to the inability for direct examination of the product fill within translucent to opaque containers. Preparations for direct injection into the eye must comply with the limits in [〈 789 〉](#) (33). Ophthalmic products may need to be dissolved in a suitable particle free-solvent prior to conducting suitable electronic or microscopic particle determination. Visible particulate matter present must be noted as part of such determination. All ophthalmic preparations should not exceed predetermined particle limits throughout the intended shelf life.

5.1.8 Sterility and Antimicrobial Preservative

Every ophthalmic product must be manufactured under conditions validated to render it sterile in its final container for the shelf life of the product (7).

All ophthalmic preparations should be sterile when dispensed, and whenever possible, a suitable preservative should be added to ensure sterility during the course of use. Ophthalmic preparations intended to be used during surgery or in the traumatized eye generally do not contain preservative agents because they are irritating to the tissues within the eye. These preparations are usually packaged in single-dose containers and any unused material is discarded (7, 12).

The sterilization procedure to be used will depend upon the nature of the dosage form (12). The most used methods of achieving a sterile product are: steam sterilization (autoclaving), dry heat sterilization, gas sterilization, sterilization by ionizing radiation, sterilization by filtration, and aseptic processing. A combination of two or more of these six methods is routinely used for ophthalmic products packaged in plastic containers (7). Although it is preferable to sterilize ophthalmics in their final container by autoclaving, this method may be precluded by thermal instability of the formulation. As an alternative, other sterilization procedures such as bacterial filters or irradiation may be used, provided their compatibility with the formulation has been investigated. Another option is to manipulate all the sterilized components of the formulation under aseptic conditions (7, 8, 10).

Ophthalmic dosage forms shall meet the requirement of [Sterility Tests](#) [〈 71 〉](#) (34). If the specific ingredients used in the formulation do not lend themselves to routine sterilization techniques, ingredients that meet the sterility requirements described under [Sterility Tests](#) [〈 71 〉](#) (34), along with aseptic manufacture, may be used. The immediate container for ophthalmic preparations shall be sterile at the time of filling and closing.

It is mandatory that the immediate containers for ophthalmic preparations be sealed and tamper-proof so that sterility is ensured at the time of first use.

Ophthalmic preparations to be used on eyes with intact corneal membranes may be packaged in multiple-dose containers. Even though sterile when dispensed, these preparations should contain a rapidly effective, topically nonirritating antimicrobial agent or a mixture of such agents to prevent the growth of, or to destroy, microorganisms accidentally introduced into the product when the container is opened during use. These antimicrobial agents have limitations with respect to stability, chemical compatibility with the other components of the formulation and packaging material, and their concentration should be properly evaluated. These agents have to be effective throughout the entire shelf life of the product (7, 8, 10, 12).

Antimicrobial agents must be added to preparations that are packaged in containers that allow for the withdrawal or administration of multiple doses, unless one of the following conditions

prevails: (1) there are different directions in the individual compendia monograph; (2) the substance contains a radionuclide with a physical half-life of less than 24 h; (3) the drug product without additional agents is sufficiently microbicidal to meet the requirements of [Antimicrobial Effectiveness Testing](#) (51) (35). Substances must meet the requirements of [Antimicrobial Effectiveness Testing](#) (51) (35) and [Antimicrobial Agents—Content](#) (341) (36). Acceptance criteria for antimicrobial preservative content in multidose products should be established throughout the entire shelf life of the product.

5.1.9 Bacterial Endotoxins

All injected ophthalmic drug products shall be prepared in a manner designed to minimize bacterial endotoxins as defined in [Bacterial Endotoxins Test](#) (85) (37) and [Pyrogen Test](#) (151) (38).

5.1.10 Uniformity of Dosage Units

This test is applicable for dosage forms packaged in single-unit containers. Uniformity of dosage units typically is demonstrated by one of two procedures: content uniformity or weight variation (see [Uniformity of Dosage Units](#) (905) (39)).

5.1.11 Uniformity in Containers

Semisolid dosage forms such as ointments, lotions, creams, and emulsions may show physical separation during manufacturing processes and/or during the shelf life. To ensure the integrity of the drug product, it is essential to evaluate the uniformity of the finished product throughout its assigned shelf life. See *Uniformity in Containers*, under [Topical and Transdermal Drug Products—Product Quality Tests](#) (3) (40).

5.1.12 Container Content

Container contents of ophthalmic products should be determined (see [Minimum Fill](#) (755) (41)).

5.1.13 Leachables and Extractables

The packaging system used with ophthalmic preparations should not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity of the drug product. The packaging system should meet the applicable requirements under [Elastomeric Closure for Injections](#) (381) (42), [Containers—Glass](#) (660) (43), [Plastic Materials of Construction](#) (661.1) (44) and [Plastic Packaging Systems for Pharmaceutical Use](#) (661.2) (45). Further information regarding packaging systems testing may be found in [Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems](#) (1663) (46) and [Assessment of Leachables Associated with Pharmaceutical Packaging/Delivery systems](#) (1664) (47).

5.1.14 Container Closure Integrity

The packaging system should be closed or sealed in such a manner as to prevent contamination or loss of contents. Validation of container integrity must demonstrate no penetration of microbial contamination or chemical or physical impurities (see [Sterile Product Packaging—Integrity Evaluation](#) (1207) (48)).

5.2 Drug Product Quality Tests—Specific Tests

5.2.1 Viscosity

In the preparation of ophthalmic solutions a suitable thickening agent is frequently added to increase the viscosity. 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 most of the thickening agents is a lubricating effect.

Numerous studies have shown that increasing the viscosity of ophthalmic products increases contact time and pharmacological effect, but there is a plateau reached after which further increases in viscosity produce only slight or no increases in effect. The location of the plateau is drug and formulation dependent (7).

Viscosity for ophthalmic solutions is considered optimal in the range of 15–25 cp (8,10).

For testing procedures see [Viscosity—Capillary Viscometer Methods](#) (911) (49), [Rotational Rheometer Methods](#) (912) (50), and [Rolling Ball Viscometer Method](#) (913) (51). As viscosity is formulation dependent, it is not part of a compendial monograph for ophthalmic products but it is part of the manufacturer's specification of the drug product.

5.2.2 Antioxidant Content

Stabilizers are ingredients added to a formulation to decrease the rate of decomposition of the drug(s) present in the product. Antioxidants are the principal stabilizers added to some ophthalmic products, primarily those containing epinephrine and other oxidizable drugs (7). If antioxidants are present in the drug product, tests of their content should be established unless oxidative degradation can be detected by another test method such as impurity testing. Acceptance criteria for antioxidant content should be established. They should be based on the levels of antioxidant necessary to maintain the product's stability at all stages throughout its proposed usage and shelf life.

5.2.3 Resuspendibility/Redispersability

An important aspect of any suspension is the ability to resuspend easily any settled particles prior to instillation in the eye and ensure a uniform dose is delivered. It would be ideal to formulate a suspension that does not settle. 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, allowing complete settling between doses, usually leads to a dense layer of agglomerated particles that are difficult to resuspend (7).

The resuspendibility/redispersability of any suspension should be evaluated throughout the entire shelf life of the product.

5.2.4 Particle Size and Particle Size Distribution

The potential for any changes in particle size of ophthalmic suspensions and emulsions needs to be evaluated through stability testing (see [Light Diffraction Measurement of Particle Size](#) (429) (52)).

5.2.5 Drop Size

The volume of a drop is dependent on the physicochemical properties of the formulation, particularly surface tension, the design and geometry of the dispensing orifice, and the angle at which the dispenser is held in relation to the receiving surface. Manufacturing controls must be in place to provide a uniform drop size throughout the shelf life of the product (7). Drop sizes may typically range from 20–70 µL.

5.2.6 Added Substances

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.

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

forms.

Some agents commonly used in topical ocular drugs can be used only sparingly or not at all for intraocular use, and pH and buffering capacity must be taken into account.

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. 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. The use of surfactants is greatly restricted in formulating ophthalmic products (7).

The use of unnecessary ingredients is to be avoided, and the use of ingredients solely to impart a color (1,7), odor, or flavor is prohibited (7).

6. DISSOLUTION/DRUG RELEASE TESTS

The procedures for testing dissolution/drug release for ophthalmic preparations are described in the new general chapter [Ophthalmic Preparations—Performance Tests](#) (1771).

These tests are conducted to ascertain the drug release from the product matrix. In the case of semi-solid dosage forms such as ointments, gels, emulsions, etc., the test can be performed according to the USP general chapter [Semisolid Drug Products—Performance Tests](#) (1724) (53). This chapter contains the description of the equipment and instructions on how to perform the test using equipments such as vertical diffusion cell, immersion cell, and a special cell to be used with the USP Apparatus 4 (flow-through cell). A special cell for USP Apparatus 4 was developed to evaluate the drug release from colloidal systems (54). Depending on the design and release mechanism of the dosage form, the dissolution/drug release test can be developed using the conditions described in USP general chapters [Dissolution](#) (711) (55) or [Drug release](#) (724) (56). Novel dosage forms may require the use of non compendial equipment and/or conditions (e.g. the equipment used in the dissolution test in the USP monograph for *Minocycline Periodontal System* (57)). The dissolution/drug release test should be discriminative for the critical quality attributes of the product and should be properly validated (see USP general chapter [The Dissolution Procedure—Development and Validation](#) (1092) (58)).

REFERENCES

1. USP. *USP 36–NF 31, Ophthalmic Ointments* (771). Rockville, MD: USP; 2013.
2. Vadlapudi AD, Patel A, Cholkar K, Mitra AK. Recent patents on emerging therapeutics for the treatment of glaucoma, age related macular degeneration and uveitis. *Recent Patents Biomed Eng.* 2012; 5(1):83–101.
3. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. *AAPS J.* 2010; 12(3):348–360.
4. Gaudana R, Jwala j, Boddu SHS, Mitra AK. Recent perspectives in ocular drug delivery. *Pharm Res.* 2009; 26(5):1197–1216.
5. Wilson CG, Zhu YP, Kurmala P, Rao LS, Dhillon B. Ophthalmic drug delivery. In: Hillery AM, Lloyd AW, Swarbrick J. *Drug Delivery and Targeting*. New York: Taylor & Francis; 2001:329–354.
6. Palani S, Nisha MJ, Goda CC, Zachariah A, Ayenew Z. Ocular drug delivery: a review. *Int J Pharm Sci Res.* 2010; 1(3):1–11.
7. Missel PJ, Lang JC, Rodeheaver DP, Jani R, Chowhan MA, Chastain J, Dagnon T. Design and evaluation of ophthalmic pharmaceutical products. In: Florence, AT, Siepmann J. *Modern Pharmaceutics—Applications and Advances*. New York: Informa; 2009:101–189.

8. Allen LV, Popovich NG, Ansel HC. *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*, Baltimore: Lippincott Williams & Wilkins; 2005:540–569.
9. Lorenzo CA, Hiratani H, Concheiro A. Contact lens for drug delivery. Achieving sustained release with novel systems. *Am J Drug Deliv*. 2006; 4(3):131–151.
10. Gibson M. Ophthalmic Dosage Forms In: Gibson M—*Pharmaceutical Preformulation and Formulation*. New York: Informa; 2007:459–489.
11. Ali Y, Lehmuusaari K.—Industrial perspective in ocular drug delivery. *Adv Drug Deliv Rev*. 2006; 58: 1258–1268.
12. Ansel HC—*Introduction to Pharmaceutical Dosage Forms*. 4th ed. Philadelphia: Lea & Febiger; 1985:321–336.
13. Lee SS, Yuan P, Robinson MR. Ocular implants for drug delivery. In: Wnek GE, Bowlin GL— *Encyclopedia of Biomaterials and Biomedical Engineering*. New York: Marcel Dekker, 2004:1105–1119.
14. White CJ, Tieppo A, Byrne ME. Controlled drug release from contact lenses: a comprehensive review from 1965–present. *J Drug Del Sci Tech*. 2011; 21(5):369–384.
15. Bourges JL, Bloquel C, Thomas A, Froussart F, Bochot A, Azan F, Gurny R, BenEzra D, Behar-Cohen F. Intraocular implants for extended drug delivery: therapeutical applications. *Adv Drug Deliv Rev*. 2006; 58:1182–1202.
16. Yasukawa T, Ogura Y, Kimura H, Sakurai E, Tabata Y. Drug delivery from ocular implants. *Expert Opin Drug Deliv*. 2006; 3(2):261–273.
17. Amrite AC, Kompella UB—Nanoparticles for ocular drug delivery. In: Amrite AC, Kompella UB. *Nanoparticle Technology for Drug Delivery*. New York: Informa; 2006:319–360.
18. Vandamme TF. Microemulsions as ocular drug delivery systems: recent developments and future challenges. *Prog Retinal Eye Res*. 2002; 21:15–34.
19. Wagh VD, Deshmukh OJ. Niosomes as ophthalmic drug delivery systems: a review. *J Pharm Res*. 2010; 3(7):1558–1563. www.jpronline.info Accessed 15 March 2013.
20. Kaur H, Dhiman S, Arora S. Niosomes: a novel drug delivery system. *Int J Pharm Sci Rev Res*. 2012; 15(1):113–120.
21. USP. *USP 36–NF 31, [Near-Infrared Spectroscopy](#) < 1119 >*. Rockville, MD: USP; 2013:801–806.
22. USP. *USP 36–NF 31, [Raman Spectroscopy](#) < 1120 >*. Rockville, MD: USP; 2013:806–812.
23. USP. *USP 36–NF 31, [Chromatography](#) < 621 >*. Rockville, MD: USP; 2013:268–275.
24. USP. *USP 36–NF 31, [Thin-Layer Chromatographic Identification Test](#) < 201 >*. Rockville, MD: USP; 2013:139–140.
25. USP. *USP 36–NF 31, [Antibiotics—Microbial Assays](#) < 81 >*. Rockville, MD: USP; 2013:76–90.
26. USP. *USP 36–NF 31, [Spectrophotometry and Light-Scattering](#) < 851 >*. Rockville, MD: USP; 2013:420–426.
27. USP. *USP 36–NF 31, [Ion Chromatography](#) < 1065 >*. Rockville, MD: USP; 2013:666–668.
28. USP. *USP 36–NF 31, [Elemental Impurities—Limits](#) < 232 >*. Rockville, MD: USP; 2013:151–153.
29. USP. *USP 36–NF 31, [Residual Solvents](#) < 467 >*. Rockville, MD: USP; 2013:195–207.
30. USP. *USP 36–NF 31, [pH](#) < 791 >*. Rockville, MD: USP; 2013:354–355.
31. USP. *USP 36–NF 31, [Osmolality and Osmolarity](#) < 785 >*. Rockville, MD: USP;

- 2013:345–347.
32. USP. [Visible Particulate Matter](#) [〈 790 〉](#). Pharmacopeial Forum. 2012; 38(6). www.usppf.com (Accessed 09 April 2013).
 33. USP. USP 36–NF 31, [Particulate Matter in Ophthalmic Solutions](#) [〈 789 〉](#). Rockville, MD: USP; 2013:353.
 34. USP. USP 36–NF 31, [Sterility Tests](#) [〈 71 〉](#). Rockville, MD: USP; 2013:71–76.
 35. USP. USP 36–NF 31, [Antimicrobial Effectiveness Testing](#) [〈 51 〉](#). Rockville, MD: USP; 2013:54–55.
 36. USP. USP 36–NF 31, [Antimicrobial Agents—Content](#) [〈 341 〉](#). Rockville, MD: USP; 2013:164–166.
 37. USP. USP 36–NF 31, [Bacterial Endotoxins](#) [〈 85 〉](#). Rockville, MD: USP; 2013:90–94.
 38. USP. USP 36–NF 31, [Pyrogen Test](#) [〈 151 〉](#). Rockville, MD: USP; 2013:130–131.
 39. USP. USP 36–NF 31, [Uniformity of Dosage Units](#) [〈 905 〉](#). Rockville, MD: USP; 2013:431–433.
 40. USP. USP 36–NF 31, [Topical and Transdermal Drug Products—Product Quality Tests](#) [〈 3 〉](#). Rockville, MD: USP; 2013:37–41.
 41. USP. USP 36–NF 31, [Minimum Fill](#) [〈 755 〉](#). Rockville, MD: USP; 2013:335.
 42. USP. USP 36–NF 31, [Elastomeric Closures for Injections](#) [〈 381 〉](#). Rockville, MD: USP; 2013:168–172.
 43. USP. USP 36–NF 31, [Containers—Glass](#) [〈 660 〉](#). Rockville, MD: USP; 2013:282–286.
 44. USP. [Plastic Materials of Construction](#) [〈 661.1 〉](#). Pharmacopeial Forum, 2013; in press.
 45. USP. [Plastic Packaging Systems for Pharmaceutical Use](#) [〈 661.2 〉](#). Pharmacopeial Forum, 2013; in press.
 46. USP. [Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems](#) [〈 1663 〉](#). Pharmacopeial Forum, 2013; in press.
 47. USP. Assessment of Leachables Associated with [Pharmaceutical Packaging/Delivery Systems](#) [〈 1664 〉](#). Pharmacopeial Forum, 2013; in press.
 48. USP. USP 36–NF 31, [Sterile Product Packaging—Integrity Evaluation](#) [〈 1207 〉](#). Rockville, MD: USP; 2013:963–964.
 49. USP. USP 36–NF 31, [Viscosity—Capillary Viscometer Methods](#) [〈 911 〉](#). Rockville, MD: USP; 2013:434–435.
 50. USP. USP 36–NF 31, [Rotational Rheometer Methods](#) [〈 912 〉](#). Rockville, MD: USP; 2013:435–438.
 51. USP. USP 36–NF 31, [Rolling Ball Viscometer Method](#) [〈 913 〉](#). Rockville, MD: USP; 2013:439.
 52. USP. USP 36–NF 31, [Light Diffraction Measurement of Particle Size](#) [〈 429 〉](#). Rockville, MD: USP; 2013:185–189.
 53. USP. USP 36–NF 31, First Supplement, [Semisolid Drug Products – Performance Tests](#) [〈 1724 〉](#). Rockville, MD: USP; 2013:5778–5788.
 54. Bhardwaj U, Burgess DJ. A novel USP apparatus 4 based release testing method for dispersed systems. *Int J Pharm.* 2010; 388(1–2):287–294.
 55. USP. USP 36–NF 31, [Dissolution](#) [〈 711 〉](#). Rockville, MD: USP; 2013:307–313.
 56. USP. USP 36–NF 31, [Drug Release](#) [〈 724 〉](#). Rockville, MD: USP; 2013:314–317.
 57. USP. USP 36–NF 31, *Minocycline Periodontal System*. Rockville, MD: USP;

2013:4376–4378.

58. USP. *USP 36–NF 31, [The Dissolution Procedure—Development and Validation](#) (1092)*. Rockville, MD: USP; 2013:735–741.

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^c The views presented in this article do not necessarily reflect those of the FDA. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

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