Liquid Ophthalmic Drug Products: Physicochemical Properties, Formulations, and Manufacturing Considerations

Hovhannes J. Gukasyan and Richard Graham

Abstract Liquid ophthalmic drug products are the most common presentation for pharmacotherapy used to treat a variety of anterior and posterior segment diseases of the eye. Their attributes largely mirror those of parenteral formulations, but specifically consider certain qualities for drug substance and product from a perspective of compatibility and delivery to a biologically and physiologically distinct environment in and around the eye. Features such as formulation pH and osmolarity, or properties of all inactive ingredients, play a critical role when considering the route of ocular administration. This chapter provides an overview of physical chemistry, formulation, and manufacturing considerations as they relate to the anatomical characteristics and physiology of the eye from a pragmatic, historical, case-study-driven, and biosystem-based perspective.

Keywords Sterile liquid · pH · Osmolarity · Ocular tolerability · Sterile manufacturing · Anterior segment · Posterior segment

Abbreviations

AMD	Age-related macular degeneration
DCE-GS	*S*-(1,2-dicarboxyethyl)glutathione
FDA	Food and Drug Administration
GSH	Glutathione
IOP	Intraocular pressure
K_{sp}	Equilibrium constant for a solubility product
p*I*	Isoelectric point

H. J. Gukasyan (✉) · R. Graham
Pharmaceutical Development, Allergan plc, Irvine, CA, USA
e-mail: gukasyan@usc.edu

S. Neervannan, U. B. Kompella (eds.), *Ophthalmic Product Development*,
AAPS Advances in the Pharmaceutical Sciences Series 37,
https://doi.org/10.1007/978-3-030-76367-1_11

pK_a	Acid dissociation constant
pK_b	Base dissociation constant
$P_{o/w}$	Oil/water partition coefficient
ROS	Reactive oxygen species
TRIS	Triethanolamine
USP	United States Pharmacopeia
UVA	Ultraviolet long-wavelength light radiation
UVB	Ultraviolet short-wavelength light radiation
β	Buffering capacity

Preface

Liquid ophthalmic products are categorized as parenteral formulations; however, they are within a highly specialized subclass of their own. To provide a sensible and comprehensive analysis of physical chemistry, compounding pharmacy or formulation, and manufacturing science that's entailed within the larger scope of all liquid ophthalmic drug products, the objectives of this chapter are twofold: first, to briefly visit key topics and critical attributes, which in turn (second) provide examples with references to benefit newcomers into the field for subsequent development of deeper expertise. Liquid ophthalmic drug products can be defined and classified by several differentiating attributes from other dosage forms that are administered into the body. From a global perspective, these characteristics stem out of three ocular biopharmaceutics blueprint attributes. Features include the qualities of drug substance or active pharmaceutical ingredient; the drug product or formulation from a perspective of aqueous solution pH, total concentration of osmolytes, and properties related to the actual vehicle composition taking into account all inactive ingredients (e.g., excipients); and finally, precise route of administration into the eye (e.g., topical eye drops vs. intraocular or periorbital injections) as it relates to the anatomical characteristics and physiology of this organ.

Considerations for Drug Substance

Relating to the active ingredient or drug substance, an inclusive examination of precedence in liquid ophthalmic products (see Table 1) suggests existence of two general categories. There are some liquid ophthalmic products that stem from pure leads. In other words, they contain an active ingredient that was discovered and developed solely for an ophthalmic indication. Moreover, most liquid ophthalmic products are carefully designed reformulations of existing active ingredients repurposed from other therapeutic indications. Molecular-drug profiling for ophthalmic repositioning, in this case, involves development of a preexisting compound into a

Table 1 Commercial liquid ophthalmic products and some off-label used parenterals‖ in an ocular setting and their critical formulation attributes (PDR Network LLC. 2016; Physicians' desk reference for ophthalmic medicines 2000; Lexi-Comp Inc. and American Pharmacists Association)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Acular LS® (ketorolac tromethamine)	Acular LS® ophthalmic solution is supplied as a sterile isotonic aqueous 0.4% solution, with a pH of approximately 7.4. Acular LS® ophthalmic solution contains a racemic mixture of R-(+) and S-(−)- ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pK_a of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light. The osmolality of Acular LS® ophthalmic solution is 290 mOsmol/kg. Each mL of Acular LS® ophthalmic solution contains active, ketorolac tromethamine 0.4%; preservative, benzalkonium chloride 0.006%; and inactives, edetate disodium 0.015%, octoxynol 40, purified water, sodium chloride, and hydrochloric acid and/or sodium hydroxide to adjust the pH		Ophthalmic solution is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery
Acular® (ketorolac tromethamine)	Acular® ophthalmic solution is supplied as a sterile isotonic aqueous 0.5% solution, with a pH of 7.4. Acular® ophthalmic solution contains a racemic mixture of R-(+) and S-(−)- ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pK_a of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light. The molecular weight of ketorolac tromethamine is 376.41. The osmolality of Acular® ophthalmic solution is 290 mOsmol/kg. Each mL of Acular® ophthalmic solution contains active, ketorolac tromethamine 0.5%; preservative, benzalkonium chloride 0.01%; and inactives, edetate disodium 0.1%, octoxynol 40, purified water, sodium chloride, hydrochloric acid, and/or sodium hydroxide to adjust the pH		Ophthalmic solution is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and also indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Acuvail® (ketorolac tromethamine)	Acuvail solution is supplied as a sterile isotonic aqueous 0.45% preservative-free solution, with a pH of approximately 6.8. Acuvail solution contains a racemic mixture of R-(+) and S-(−)- ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pK_a of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light. The osmolality of Acuvail solution is approximately 285 mOsmol/kg. Each mL of Acuvail ophthalmic solution contains active, ketorolac tromethamine 0.45%, and inactives, carboxymethylcellulose sodium, sodium chloride, sodium citrate dehydrate, and purified water with sodium hydroxide and/or hydrochloric acid to adjust the pH		Ophthalmic solution is indicated for the treatment of pain and inflammation following cataract surgery
AK-con-A®	Naphazoline hydrochloride, an ocular vasoconstrictor, is an imidazoline derivative sympathomimetic amine. It occurs as a white, odorless crystalline powder having a bitter taste and is freely soluble in water and in alcohol. Active: Naphazoline HCl 1 mg (0.1%). Preservative: Benzalkonium chloride 0.1 mg (0.01%) Inactives: Boric acid, edetate disodium, purified water, sodium chloride, sodium carbonate, and hydrochloric acid may be added to adjust the pH (5.5–7.0)		Naphazoline constricts the vascular system of the conjunctiva. It is presumed that this effect is due to direct stimulation of the drug upon the alpha-adrenergic receptors in the arterioles of the conjunctiva, resulting in decreased conjunctival congestion. Naphazoline belongs to the imidazoline class of sympathomimetics
Akten® (lidocaine hydrochloride)	Akten® contains 35 mg of lidocaine hydrochloride per mL as the active ingredient. It also contains hypromellose, sodium chloride, and water for injection as inactive ingredients in the 1 mL tube configuration. Akten® contains hypromellose, sodium chloride, and water for injection as inactive ingredients in the 5 mL in 10 mL bottle configuration. The pH may be adjusted to 5.5–7.5 with hydrochloric acid and/or sodium hydroxide		Indicated for ocular surface anesthesia during ophthalmologic procedures

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Alaway® (ketotifen fumarate)	Ketotifen 0.025% (equivalent to ketotifen fumarate 0.035%), benzalkonium chloride 0.01%, glycerin, hydrochloric acid and/or sodium hydroxide, water for injection		Temporary relief of itchy eyes due to ragweed, pollen, grass, animal hair and dander
Alocril® (nedocromil sodium)	Each mL contains active, nedocromil sodium 20 mg/mL (2%); preservative, benzalkonium chloride 0.01%; and inactives, edetate disodium 0.05%, purified water, and sodium chloride 0.5%. It has a pH range of 4.0–5.5 and an osmolality range of 270–330 mOsm/kg		Indicated for the treatment of itching associated with allergic conjunctivitis
Alomide® (lodoxamide tromethamine)	Each mL of Alomide® (lodoxamide tromethamine ophthalmic solution) 0.1% contains active, 1.78 mg lodoxamide tromethamine equivalent to 1 mg lodoxamide; preservative, benzalkonium chloride 0.007%; and inactive, mannitol, hypromellose 2910, sodium citrate, citric acid, edetate disodium, tyloxapol, hydrochloric acid and/or sodium hydroxide (adjust pH), and purified water		Indicated in the treatment of the ocular disorders referred to by the terms vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis
Alphagan P® (brimonidine tartrate)	In solution, Alphagan® P (brimonidine tartrate ophthalmic solution) has a clear, greenish-yellow color. It has an osmolality of 250–350 mOsmol/kg and a pH of 7.4–8.0 (0.1%) or 6.6–7.4 (0.15%). Brimonidine tartrate appears as an off-white to pale-yellow powder and is soluble in both water (0.6 mg/mL) and in the product vehicle (1.4 mg/mL) at pH 7.7. Each mL of Alphagan® P contains the active ingredient brimonidine tartrate 0.1% (1.0 mg/mL) or 0.15% (1.5 mg/mL) with the inactive ingredients sodium carboxymethylcellulose, sodium borate, boric acid, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, PURITE® 0.005% (0.05 mg/mL) as a preservative, purified water, and hydrochloric acid and/or sodium hydroxide to adjust the pH		An alpha-adrenergic agonist indicated for lowering intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Alrex® (loteprednol etabonate)	Each mL contains active, loteprednol etabonate 2 mg (0.2%), and inactives, edetate disodium, glycerin, povidone, purified water, and tyloxapol. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. The suspension is essentially isotonic with a tonicity of 250–310 mOsmol/kg. Preservative added: Benzalkonium chloride 0.01%		Ophthalmic suspension indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis
Altacaine® (tetracaine hydrochloride)	Tetracaine hydrochloride 0.5% is a sterile topical ophthalmic solution useful in producing surface anesthesia of the eye. Active: Tetracaine hydrochloride 0.5%. Preservative: Chlorobutanol. Inactive: Boric acid, edetate disodium, potassium chloride, water for injection, USP. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH		For procedures in which a rapid and short-acting topical ophthalmic anesthetic is indicated such as in tonometry, gonioscopy, removal of corneal foreign bodies, conjunctival scraping for diagnostic purposes, suture removal from the cornea or conjunctiva, and other short corneal and conjunctival procedures
Amikin® (amikacin sulfate)‖	Vials contain 250 mg of active and 50 mg sodium citrate and 4.8 mg sodium metabisulfite, according to pharmaceutical details provided in package inserts from certain countries *(*no pH or osmolarity spec.)*	Treatment of infections due to gram-negative bacteria, treatment of *Mycobacterium avium complex* (oral inhalation)	Bacterial endophthalmitis by intravitreal injection (Jackson and Williamson 1999)
Ancef®, Kefzol® (cefazolin)	Intraocular dosage, adults 100 mg by subconjunctival injection or 1–2.5 mg by intracameral injection, is optional at the end of the procedure. Perioperative antisepsis with povidone-iodine is recommended. Preservative-free, pH 4.0–6.0, 290 mOsm/kg, as a sodium salt		For ophthalmic surgical infection prophylaxis

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Artificial tears®	Polyvinyl alcohol 1.4%; carboxymethylcellulose sodium 1%; glycerin 0.2%, hypromellose 0.2%, polyethylene glycol 400 1%; benzalkonium chloride, edetate disodium, NaCl, sodium phosphate, dibasic anhydrous sodium phosphate, monobasic, anhydrous, water, NaOH/HCl		Eye lubricants
Avastin® (bevacizumab)‖	Bevacizumab has an approximate molecular weight of 149 kDa and is produced in a mammalian cell (Chinese hamster ovary) expression system. Avastin (bevacizumab) injection for intravenous use is a sterile, clear to slightly opalescent, colorless to pale brown solution. Avastin is supplied in 100 and 400 mg preservative-free, single-dose vials to deliver 4 or 16 mL of Avastin (25 mg/mL) The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and water for injection, USP. The 400 mg product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and water for injection, USP *(*no pH or osmolarity spec.)*	Metastatic colorectal cancer	Neurovascular age-related macular degeneration (Bevacizumab (Avastin). Lower cost does not justify taking risks 2015; Lalwani et al. 2008)

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Azopt® (brinzolamide)	Azopt (brinzolamide ophthalmic suspension) 1% is supplied as a sterile, aqueous suspension of brinzolamide which has been formulated to be readily suspended and slow settling, following shaking. It has a pH of approximately 7.5 and an osmolality of 300 mOsm/kg. Each mL of Azopt (brinzolamide ophthalmic suspension) 1% contains active ingredient,brinzolamide 10 mg; preservative, benzalkonium chloride 0.1 mg; and inactives, mannitol, carbomer 974P, tyloxapol, edetate disodium, sodium chloride, and purified water, with hydrochloric acid and/or sodium hydroxide to adjust the pH		A carbonic anhydrase inhibitor indicated for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma
Bepreve™ (bepotastine besilate)	Bepreve™ ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8 and osmolality of approximately 290 mOsm/kg Each mL of Bepreve™ (bepotastine besilate ophthalmic solution) 1.5% contains active, bepotastine besilate15 mg (equivalent to 10.7 mg bepotastine); preservative, benzalkonium chloride 0.005%; and inactives monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust the pH, and water for injection, USP		Treatment of itching associated with allergic conjunctivitis

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Besivance™ (besifloxacin)	Besivance™ (besifloxacin ophthalmic suspension) 0.6% is a sterile ophthalmic suspension of besifloxacin formulated with DuraSite® (polycarbophil, edetate disodium dihydrate, and sodium chloride). Each mL of Besivance™ contains 6.63 mg besifloxacin hydrochloride equivalent to 6 mg besifloxacin base. Active: Besifloxacin 0.6% (6 mg/mL). Preservative: Benzalkonium chloride 0.01%. Inactives: Polycarbophil, mannitol, poloxamer 407, sodium chloride, edetate disodium dihydrate, sodium hydroxide, and water for injection. Besivance™ is an isotonic suspension with an osmolality of approximately 290 mOsm/kg		Quinolone antimicrobial indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: CDC coryneform group G, *Corynebacterium pseudodiphtheriticum*, *Corynebacterium striatum*, *Haemophilus influenzae*, *Moraxella lacunata*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Staphylococcus lugdunensis*, *Streptococcus mitis* group, *Streptococcus oralis*, *Streptococcus pneumoniae*, and *Streptococcus salivarius*
Betagan® (levobunolol hydrochloride)	Betagan® (levobunolol hydrochloride ophthalmic solution, USP) sterile is a noncardioselective beta-adrenoceptor blocking agent for ophthalmic use. The solution is colorless to slightly light yellow in appearance with an osmolality range of 250–360 mOsm/kg. The shelf life pH range is 5.5–7.5. Contains active levobunolol HCl 0.5%. Preservative: Benzalkonium chloride 0.004%. Inactives: Edetate disodium; polyvinyl alcohol 1.4%; potassium phosphate, monobasic; purified water; sodium chloride; sodium metabisulfite; sodium phosphate, dibasic; and hydrochloric acid or sodium hydroxide to adjust the pH		Effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma or ocular hypertension

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Betimol® (timolol)	Betimol® (timolol ophthalmic solution), 0.25% and 0.5%, is a non-selective beta-adrenergic antagonist for ophthalmic use. Each mL of Betimol® 0.25% contains 2.56 mg of timolol hemihydrate equivalent to 2.5 mg timolol Each mL of Betimol® 0.5% contains 5.12 mg of timolol hemihydrate equivalent to 5.0 mg timolol. Inactive ingredients: Monosodium and disodium phosphate dihydrate to adjust the pH (6.5–7.5) and water for injection, benzalkonium chloride 0.01% added as preservative. The osmolality of Betimol® is 260–320 mOsmol/kg		Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma
Betoptic S® (betaxolol hydrochloride)	Ophthalmic suspension contains 0.25% betaxolol hydrochloride in a sterile resin suspension formulation. Each mL of Betoptic S® ophthalmic suspension contains active, betaxolol HCl 2.8 mg equivalent to 2.5 mg of betaxolol base; preservative, benzalkonium chloride 0.01%; and inactive, mannitol, poly(styrene-divinylbenzene) sulfonic acid, carbomer 934P, edetate disodium, hydrochloric acid or sodium hydroxide (to adjust the pH), and purified water		Treatment of elevated intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension
Bleph-10® (sulfacetamide sodium)	Bleph®-10 (sulfacetamide sodium ophthalmic solution, USP) 10% is a sterile, topical antibacterial agent for ophthalmic use. Contains active, sulfacetamide sodium 10% (100 mg/mL); preservative, benzalkonium chloride 0.005%; and inactives edetate disodium, polysorbate 80, polyvinyl alcohol 1.4%, purified water, sodium phosphate dibasic, sodium phosphate monobasic, sodium thiosulfate, hydrochloric acid, and/or sodium hydroxide to adjust the pH (6.8–7.5)		Indicated for the treatment of conjunctivitis and other superficial ocular infections due to susceptible microorganisms and as an adjunctive in systemic sulfonamide therapy of trachoma: *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus* (viridans group), *Haemophilus influenzae*, *Klebsiella* species, and *Enterobacter* species

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Blephamide® (prednisolone acetate, sulfacetamide sodium)	Blephamide® ophthalmic suspension is a sterile, topical anti-inflammatory/anti-infective combination product for ophthalmic use. Each mL of Blephamide® ophthalmic suspension contains actives sulfacetamide sodium 10% and prednisolone acetate (microfine suspension) 0.2%. Inactives: Benzalkonium chloride (0.004%); edetate disodium; polysorbate 80; polyvinyl alcohol 1.4%; potassium phosphate, monobasic; purified water; sodium phosphate, dibasic; sodium thiosulfate; hydrochloric acid and/or sodium hydroxide to adjust the pH (6.6–7.2)		Blephamide® ophthalmic suspension is a steroid/anti-infective combination drug indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. Ocular corticosteroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of corticosteroid use in certain infective conjunctivitis is accepted to obtain diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation, or thermal burns or penetration of foreign bodies
Blink tears®	Polyethylene glycol 400 0.25%; boric acid; calcium chloride; magnesium chloride; potassium chloride; water; sodium borate; sodium chloride; sodium chlorite; hyaluronate sodium		Lubricating eye drops
Boiron, Optique 1®	Eye drops, single-use doses; purified water and 0.9% sodium chloride; HPUS ingredients officially included in the homeopathic Pharmacopœia of the United States—Calcarea fluorica, calendula officinalis, cineraria maritima, euphrasia officinalis, kali muriaticum, magnesia carbonica, silicea		Temporary relief of minor eye irritation due to fatigue or airborne irritants such as ragweed, other pollens, and dust; soothes red, dry, itchy, gritty, burning or tired eyes

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
CEQUA® (cyclosporine A)	Cequa (cyclosporine ophthalmic solution) 0.09% contains a topical calcineurin inhibitor immunosuppressant. Cequa is supplied as a sterile, clear, colorless ophthalmic solution for topical ophthalmic use. It has an osmolality of 160–190 mOsmol/kg and a pH of 6.5–7.2. Each mL of Cequa contains active, cyclosporine 0.09%, and inactives: Polyoxyl hydrogenated castor oil, Octoxynol-40, polyvinylpyrrolidone, sodium phosphate monobasic dihydrate, sodium phosphate dibasic anhydrous, water for injection, and sodium hydroxide or hydrochloric acid to adjust the pH		Cequa ophthalmic solution is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye)
Ciloxan® (ciprofloxacin hydrochloride)	Ciloxan® (ciprofloxacin HCL ophthalmic solution) is a synthetic, sterile, multiple dose, antimicrobial for topical use. Each mL of Ciloxan ophthalmic solution contains active, ciprofloxacin HCl 3.5 mg equivalent to 3 mg base; preservative, benzalkonium chloride 0.006%; and inactives, sodium acetate, acetic acid, mannitol 4.6%, edetate disodium 0.05%, hydrochloric acid and/or sodium hydroxide (to adjust the pH), and purified water. The pH is approximately 4.5 and the osmolality is approximately 300 mOsm		Ciprofloxacin is a fluoroquinolone antibacterial active against a broad spectrum of gram-positive and gram-negative ocular pathogens

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Combigan® (brimonidine tartrate, timolol maleate)	In solution, Combigan® (brimonidine tartrate/timolol ophthalmic solution) 0.2%/0.5% has a clear, greenish-yellow color. It has an osmolality of 260–330 mOsmol/kg and a pH during its shelf life of 6.5–7.3. Brimonidine tartrate appears as an off-white or white to pale-yellow powder and is soluble in both water (1.5 mg/mL) and in the product vehicle (3 mg/mL) at pH 7.2. Timolol maleate appears as a white, odorless, crystalline powder and is soluble in water, methanol, and alcohol. Each mL of Combigan® contains the active ingredients brimonidine tartrate 0.2% and timolol 0.5% with the inactive ingredients benzalkonium chloride 0.005%; sodium phosphate, monobasic; sodium phosphate, dibasic; purified water; and hydrochloric acid and/or sodium hydroxide to adjust the pH		Combigan® is an alpha-adrenergic receptor agonist with a beta-adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP; the IOP lowering of Combigan® dosed twice a day was slightly less than that seen with the concomitant administration of timolol ophthalmic solution, 0.5% dosed twice a day, and brimonidine tartrate ophthalmic solution 0.2% dosed three times per day
Cosopt® Dorzolamide hydrochloride with timolol maleate	Cosopt is supplied as a sterile, clear, colorless to nearly colorless, isotonic, buffered, slightly viscous, aqueous solution. The pH of the solution is approximately 5.65, and the osmolarity is 242–323 mOsM. Each mL of Cosopt contains 20 mg dorzolamide (22.26 mg of dorzolamide hydrochloride) and 5 mg timolol (6.83 mg timolol maleate). Inactive ingredients are sodium citrate, hydroxyethyl cellulose, sodium hydroxide, mannitol, and water for injection. Benzalkonium chloride 0.0075% is added as a preservative		Cosopt® is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP determined after multiple measurements over time). The IOP lowering of Cosopt administered twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol administered twice a day and 2% dorzolamide administered three times a day

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Cromolyn® (cromolyn sodium)	Cromolyn sodium ophthalmic solution USP, 4%, is a clear, colorless, sterile solution intended for topical ophthalmic use. Each mL contains active, cromolyn sodium 40 mg (4%); preservative, benzalkonium chloride 0.01%; and inactives, edetate disodium 0.1% and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH (4.0–7.0)		Mast cell stabilizer indicated in the treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis
Cyclogyl® (cyclopentolate hydrochloride)	Each mL of Cyclogyl® (cyclopentolate hydrochloride ophthalmic solution, USP) contains active, cyclopentolate hydrochloride 0.5%, 1%, or 2%; preservative, benzalkonium chloride 0.01%; and inactives boric acid, edetate disodium, potassium chloride (except 2% strength), sodium carbonate and/or hydrochloric acid (to adjust the pH), and purified water. The pH range is between 3.0 and 5.5		Used to produce mydriasis and cycloplegia
Cystaran® (cysteamine)	Cystaran is a sterile ophthalmic solution containing 6.5 mg/mL of cysteamine hydrochloride, equivalent to 4.4 mg/mL of cysteamine (0.44%) as the active ingredient. Cysteamine is a cystine-depleting agent which lowers the cystine content of cells in patients with cystinosis. Each milliliter of Cystaran contains active, cysteamine 4.4 mg (equivalent to cysteamine hydrochloride 6.5 mg); preservative, benzalkonium chloride 0.1 mg; and inactive ingredients sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust the pH to 4.1–4.5), and purified water		A cystine-depleting agent indicated for the treatment of corneal cystine crystal accumulation in patients with cystinosis
Durezol® (difluprednate)	Durezol (difluprednate ophthalmic emulsion) 0.05% is a sterile, topical, anti-inflammatory corticosteroid for ophthalmic use. Each mL of Durezol contains active, difluprednate 0.5 mg (0.05%); inactive, boric acid, castor oil, glycerin, polysorbate 80, water for injection, sodium acetate, edetate disodium, and sodium hydroxide (to adjust the pH to 5.2–5.8) (the emulsion is essentially isotonic with a tonicity of 304 to 411 mOsm/kg); and preservative, sorbic acid 0.1%		For the treatment of inflammation and pain associated with ocular surgery and endogenous anterior uveitis

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Elestat® (epinastine hydrochloride)	Each mL contains active, epinastine HCl 0.05% (0.5 mg/mL) equivalent to epinastine 0.044% (0.44 mg/mL); preservative, benzalkonium chloride 0.01%; and inactives, edetate disodium, purified water, sodium chloride, sodium phosphate (monobasic), and sodium hydroxide and/or hydrochloric acid (to adjust the pH). Elestat® has a pH of approximately 7 and an osmolality range of 250–310 mOsm/kg		Indicated for the prevention of itching associated with allergic conjunctivitis
Emadine® (emedastine difumarate)	Each mL of Emadine® (emedastine difumarate ophthalmic solution) 0.05% contains active, 0.884 mg emedastine difumarate equivalent to 0.5 mg emedastine; preservative, benzalkonium chloride 0.01%; and inactives, tromethamine, sodium chloride, hypromellose, hydrochloric acid/sodium hydroxide (adjust pH), and purified water. It has a pH of approximately 7.4 and an osmolality of approximately 300 mOsm/kg		Indicated for the temporary relief of the signs and symptoms of allergic conjunctivitis
EYLEA® (aflibercept)	EYLEA (aflibercept) injection is a sterile, clear, and colorless to pale-yellow solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution for intravitreal injection in a single-dose, glass vial designed to deliver 0.05 mL (50 µl) of solution containing 2 mg of EYLEA (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2)		Age-related macular degeneration, diabetic macular edema, diabetic retinopathy, macular edema following retinal vein occlusion
FML Forte® (solution) Fluorometholone (0.25%)	Active: Fluorometholone 0.25%. Preservative: Benzalkonium chloride 0.005%. Inactives: Edetate disodium; polysorbate 80; polyvinyl alcohol 1.4%; purified water; sodium chloride; sodium phosphate, dibasic; sodium phosphate, monobasic; and sodium hydroxide to adjust the pH. FML Forte® suspension is formulated with a pH from 6.2 to 7.5		Indicated for the treatment of corticosteroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
FML® (solution) Fluorometholone (0.1%)	Active: Fluorometholone 0.1%. Preservative: Benzalkonium chloride 0.004%. Inactives: Edetate disodium; polysorbate 80; polyvinyl alcohol 1.4%; purified water; sodium chloride; sodium phosphate, dibasic; sodium phosphate, monobasic; and sodium hydroxide to adjust the pH. FML® suspension is formulated with a pH from 6.2 to 7.5. It has an osmolality range of 290–350 mOsm/kg		Indicated for the treatment of corticosteroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe
Fortaz® (ceftazidime) ‖	Fortaz in sterile crystalline form is supplied in vials equivalent to 500 mg, 1 g, 2 g, or 6 g of anhydrous ceftazidime and in ADD-vantage® vials equivalent to 1 or 2 g of anhydrous ceftazidime. Solutions of Fortaz range in color from light yellow to amber, depending on the diluent and volume used. The pH of freshly constituted solutions usually ranges from 5 to 8. Fortaz is available as a frozen, isosmotic, sterile, nonpyrogenic solution with 1 or 2 g of ceftazidime as ceftazidime sodium premixed with approximately 2.2 or 1.6 g, respectively, of hydrous dextrose, USP. Dextrose has been added to adjust the osmolality. Sodium hydroxide is used to adjust the pH and neutralize ceftazidime pentahydrate free acid to the sodium salt. The pH may have been adjusted with hydrochloric acid. Solutions of premixed Fortaz range in color from light yellow to amber. The solution is intended for intravenous (IV) use after thawing to room temperature. The osmolality of the solution is approximately 300 mOsmol/kg, and the pH of thawed solutions ranges from 5 to 7.5	Bacterial septicemia, bone and joint infections, CNS infections, empiric therapy in immuno compromised patient, gynecologic infections, intra-abdominal infections, lower respiratory tract infections, skin and skin-structure infections, urinary tract infections	Bacterial endophthalmitis by intravitreal injection (Jackson and Williamson 1999)

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Genteal® (hydroxypropyl methylcellulose)	Dextran 70 0.1%, glycerin 0.2%, and hypromellose 0.3% all acting as lubricants		Temporary relief of burning and irritation due to dryness of the eye, as a protectant against further irritation, and temporary relief of discomfort due to minor irritations of the eye or to exposure to wind or sun
HUMIRA® (adalimumab)	Adalimumab is a tumor necrosis factor blocker. It consists of 1330 amino acids and has a molecular weight of approximately 148 kDa Each 80 mg/0.8 mL prefilled syringe or prefilled pen delivers 0.8 mL (80 mg) of drug product. Each 0.8 mL of HUMIRA contains adalimumab (80 mg), mannitol (33.6 mg), polysorbate 80 (0.8 mg), and water for injection, USP Each 40 mg/0.4 mL prefilled syringe or prefilled pen delivers 0.4 mL (40 mg) of drug product. Each 0.4 mL of HUMIRA contains adalimumab (40 mg), mannitol (16.8 mg), polysorbate 80 (0.4 mg), and water for injection, USP. HUMIRA® (adalimumab) citrate-free is specifically indicated for ophthalmic use, although not clear what is the final pH or osmolarity. General description says, "the solution of HUMIRA is clear and colorless, with a pH of about 5.2"		HUMIRA is indicated or the treatment of noninfectious intermediate, posterior, and panuveitis in adults and pediatric patients 2 years of age and older
Iopidine® (apraclonidine hydrochloride)	Each mL of Iopidine 0.5% ophthalmic solution contains active, apraclonidine hydrochloride 5.75 mg equivalent to apraclonidine base 5 mg, and inactives: Sodium chloride, sodium acetate, sodium hydroxide and/or hydrochloric acid (pH 4.4–7.8), purified water, and benzalkonium chloride 0.01% (preservative)		Relatively selective alpha2-adrenergic agonist that reduces elevated, as well as normal, intraocular pressure, whether or not accompanied by glaucoma

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Isopto Carpine® (pilocarpine hydrochloride)	Each mL of Isopto Carpine® (pilocarpine hydrochloride ophthalmic solution) contains active: Pilocarpine hydrochloride 1% (10 mg/mL), 2% (20 mg/mL), or 4% (40 mg/mL)		Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension management of acute angle-closure glaucoma prevention of postoperative elevated IOP associated with laser surgery induction of miosis
ISOPTO® atropine (atropine sulfate)	Each mL of ISOPTO® atropine 1% contains 10 mg of atropine sulfate monohydrate equivalent to 9.7 mg/mL of atropine sulfate or 8.3 mg of atropine. pH of 3.5–6.0. Preservative: Benzalkonium chloride 0.01%. Inactive ingredients: Hypromellose, boric acid, sodium hydroxide and/or hydrochloric acid (to adjust the pH), purified water		A muscarinic antagonist indicated for mydriasis, cycloplegia, penalization of the healthy eye in the treatment of amblyopia
Jetrea® (ocriplasmin)	Ocriplasmin is a recombinant truncated form of human plasmin with a molecular weight of 27.2 kDa produced by recombinant DNA technology in a *Pichia pastoris* expression system. Jetrea is a sterile, clear, and colorless solution with no preservatives in a single-use glass vial containing 0.5 mg ocriplasmin in 0.2 mL solution for intravitreal injection after dilution Each vial contains 0.5 mg ocriplasmin (active) and 0.21 mg citric acid, 0.75 mg mannitol, sodium hydroxide (for pH adjustment), and water for injection. The pH of the solution is 3.1		Proteolytic enzyme indicated for the treatment of symptomatic vitreomacular adhesion
Kenalog® (triamcinolone acetonide)‖	Each mL of the sterile aqueous suspension provides 40 mg triamcinolone acetonide, with 0.65% sodium chloride for isotonicity, 0.99% (w/v) benzyl alcohol as a preservative, 0.75% carboxymethylcellulose sodium, and 0.04% polysorbate 80. Sodium hydroxide or hydrochloric acid may be present to adjust the pH to 5.0–7.5. At the time of manufacture, the air in the container is replaced by nitrogen	Rheumatoid arthritis	Treatment of sympathetic ophthalmia, temporal arteritis, and uveitis, diabetic macular edema (Fazelat and Lashkari 2011; Kovacs et al. 2012; Young et al. 2001)

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Lastacaft® (alcaftadine)	Active: Alcaftadine 0.25% (2.5 mg/mL) Inactives: Benzalkonium chloride 0.005% as a preservative; edetate disodium; sodium phosphate, monobasic; Purified water; sodium chloride; sodium hydroxide and/or hydrochloric acid (to adjust the pH). The drug product has a pH of approximately 7 and an osmolality of approximately 290 mOsm/kg		Lastacaft® is an H1 histamine receptor antagonist indicated for the prevention of itching associated with allergic conjunctivitis
Latisse® (bimatoprost)	Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. Latisse® is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg. Contains active bimatoprost 0.3 mg/mL, preservative benzalkonium chloride 0.05 mg/mL, and inactives sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust the pH. The pH during its shelf life ranges from 6.8 to 7.8		A prostaglandin analog indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness
Lotemax® (solution, loteprednol etabonate)	Each mL contains active loteprednol etabonate 5 mg (0.5%); inactives edetate disodium, glycerin, povidone, purified water, and tyloxapol (hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. The suspension is essentially isotonic with a tonicity of 250–310 mOsmol/kg); and preservative added benzalkonium chloride 0.01%		Indicated for the treatment of steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, and selected infective conjunctivitis, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation, and for the treatment of postoperative inflammation following ocular surgery

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Lucentis® (ranibizumab)	Sterile, colorless, to pale-yellow solution in a single-use glass vial. Lucentis is supplied as a preservative-free, sterile solution in a single-use glass vial designed to deliver 0.05 mL of 10 mg/mL Lucentis (0.5 mg dose vial) or 6 mg/mL Lucentis (0.3 mg dose vial) aqueous solution with 10 mM histidine HCl, 10% α,α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5		Neovascular (wet) age-related macular degeneration, macular edema following retinal vein occlusion, diabetic macular edema
Lumify® (brimonidine tartrate)	Active ingredient: Brimonidine tartrate (0.025%). Inactive ingredients: Benzalkonium chloride, boric acid, calcium chloride dihydrate, glycerin, potassium chloride, sodium borate decahydrate, sodium chloride, water for injection. Hydrochloric acid and/or sodium hydroxide may be used to adjust the pH		Redness reliever, over the counter
Lumigan® (bimatoprost)	Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. Lumigan® 0.01% and 0.03% is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg. Lumigan® 0.01% contains active bimatoprost 0.1 mg/mL, preservative benzalkonium chloride 0.2 mg/mL, and inactives sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust the pH. The pH during its shelf life ranges from 6.8 to 7.8		A prostaglandin analog indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Luxturna® (voretigene neparvovec-rzyl)	Each single-dose (preservative-free) vial of LUXTURNA contains 5E12 vector genomes (vg) per mL, and the excipients 180 mM sodium chloride, 10 mM sodium phosphate, and 0.001% Poloxamer 188 (pH 7.3), in a 0.5 mL extractable volume. Luxturna requires a 1:10 dilution prior to administration. After dilution, each dose of Luxturna consists of 1.5E11 vg in a deliverable volume of 0.3 mL. Luxturna may also contain residual components of HEK293 cells including DNA and protein and trace quantities of fetal bovine serum		Adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s)
Macugen® (pegaptanib sodium)	Sterile, aqueous solution containing pegaptanib sodium for intravitreal injection is formulated to have an osmolality of 280–360 mOsm/kg and a pH of 6–7, supplied in a single-dose, prefilled syringe, as a 3.47 mg/mL solution measured as the free acid form of the oligonucleotide. The active ingredient is 0.3 mg of the free acid form of the oligonucleotide without polyethylene glycol, in a nominal volume of 90 µL. This dose is equivalent to 1.6 mg of pegaptanib sodium (pegylated oligonucleotide) or 0.32 mg when expressed as the sodium salt form of the oligonucleotide moiety. The product is a sterile, clear, preservative-free solution containing sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, hydrochloric acid, and/or sodium hydroxide to adjust the pH and water for injection		Treatment of neovascular (wet) age-related macular degeneration

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Maxidex® (dexamethasone)	Each mL contains active dexamethasone 0.1%, preservative benzalkonium chloride 0.01%, vehicle hypromellose 0.5%, and inactives: Sodium chloride, dibasic sodium phosphate, polysorbate 80, edetate disodium, citric acid and/or sodium hydroxide (to adjust the pH), and purified water		Inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies
Maxitrol® (neomycin sulfate, polymyxin B sulfate, dexamethasone)	Each mL of Maxitrol® (neomycin and polymyxin B sulfates and dexamethasone ophthalmic suspension) contains actives neomycin sulfate equivalent to neomycin 3.5 mg, polymyxin B sulfate 10,000 units, and dexamethasone 0.1% and inactives: Hypromellose 2910 0.5%, sodium chloride, polysorbate 20, hydrochloric acid and/or sodium hydroxide (to adjust the pH), purified water, and benzalkonium chloride 0.004% (preservative)		For steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial infection exists. Ocular corticosteroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of corticosteroids use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Miochol®-E (acetylcholine chloride intraocular solution)	Packaged in a blister pack containing one vial and one ampoule. The vial contains 20 mg acetylcholine chloride and 56 mg mannitol. The accompanying ampoule contains 2 mL of a modified diluent of sodium acetate trihydrate, potassium chloride, magnesium chloride hexahydrate, calcium chloride dihydrate, and sterile water for injection. The reconstituted liquid will be a sterile isotonic solution (275–330 milliosmoles/kg) containing 20 mg acetylcholine chloride (1:100 solution) and 2.8% mannitol. The pH range is 5.0–8.2		Obtain miosis of the iris in seconds after delivery of the lens in cataract surgery, in penetrating keratoplasty, iridectomy, and anterior segment surgery where rapid miosis may be required
MOXEZA™ (moxifloxacin hydrochloride ophthalmic solution)	Each mL of MOXEZA™ solution contains 5.45 mg moxifloxacin hydrochloride, equivalent to 5 mg moxifloxacin base. Inactives: Sodium chloride, xanthan gum, boric acid, sorbitol, tyloxapol, purified water, and hydrochloric acid and/or sodium hydroxide to adjust the pH. MOXEZA™ is a greenish-yellow, isotonic solution with an osmolality of 300–370 mOsm/kg and a pH of approximately 7.4. Moxifloxacin hydrochloride is a slightly yellow to yellow crystalline powder		Indicated for the treatment of bacterial conjunctivitis caused by susceptible strains
Muro-128® (solution)	Sodium chloride 2%		Temporary relief of corneal edema

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Mydfrin® (phenylephrine HCl)	Medicinal ingredient: Phenylephrine HCl 2.5% w/v. non-medicinal ingredients: Benzalkonium chloride 0.01% w/v (preservative), boric acid, sodium bisulfite, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust the pH), purified water		A vasoconstrictor, decongestant, and mydriatic in a variety of ophthalmic conditions and procedures; for pupillary dilatation in uveitis (to prevent posterior synechia formation), for multiple ophthalmologic surgical procedures (including phacoemulsification, intracapsular and extracapsular cataract extraction, vitrectomy, etc.), and for refraction without cycloplegia (as an adjunct to increase pupillary dilatation); fundoscopy, multiple ophthalmic diagnostic procedures and examination
Mydriacyl® (tropicamide)	Mydriacyl® (tropicamide ophthalmic solution, USP) is an anticholinergic prepared as a sterile topical ophthalmic solution in two strengths. Each mL of Mydriacyl® (tropicamide ophthalmic solution, USP) contains active tropicamide 0.5 or 1%, preservative benzalkonium chloride 0.01%, and inactives: Sodium chloride, edetate disodium, hydrochloric acid and/or sodium hydroxide (to adjust the pH), and purified water; pH range 4.0–5.8		For mydriasis and cycloplegia for diagnostic procedures
Naphcon-A®	Naphazoline hydrochloride 0.025%, redness reliever; pheniramine maleate 0.3%, antihistamine; benzalkonium chloride, boric acid, edetate disodium, purified water, sodium borate, sodium chloride, sodium hydroxide and/or hydrochloric acid		Benzalkonium chloride, boric acid, edetate disodium, purified water, sodium borate, sodium chloride, sodium hydroxide and/or hydrochloric acid

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Neosporin® (solution; neomycin sulfate, polymyxin B sulfate, gramicidin)	Neosporin ophthalmic solution (neomycin and polymyxin B sulfates and gramicidin ophthalmic solution) is a sterile antimicrobial solution for ophthalmic use. Each mL contains neomycin sulfate equivalent to 1.75 mg neomycin base, polymyxin B sulfate equivalent to 10,000 polymyxin B units, and gramicidin 0.025 mg. The vehicle contains alcohol 0.5%, thimerosal 0.001% (added as a preservative), and the inactive ingredients propylene glycol, polyoxyethylene polyoxypropylene compound, sodium chloride, and water for injection		Neosporin ophthalmic solution is indicated for the topical treatment of superficial infections of the external eye and its adnexa caused by susceptible bacteria. Such infections encompass conjunctivitis, keratitis and keratoconjunctivitis, blepharitis, and blepharoconjunctivitis
Neo-Synephrine® (phenylephrine)	(phenylephrine) 2.5% eye drops		This medication is used to dilate the pupils for eye examinations or procedures and to treat certain eye conditions. It belongs to a class of drugs known as decongestants. Phenylephrine works by narrowing the blood vessels
Nevanac® (nepafenac)	Nevanac 0.1% is supplied as a sterile, aqueous suspension with a pH approximately of 7.4. The osmolality of Nevanac 0.1% is approximately 305 mOsm/kg. Each mL of Nevanac 0.1% contains active nepafenac 0.1% and inactives boric acid, propylene glycol, carbomer 974P, sodium chloride, tyloxapol, edetate disodium, benzalkonium chloride 0.005% (preservative), sodium hydroxide and/or hydrochloric acid to adjust the pH, and purified water, USP		Indicated for the treatment of pain and inflammation associated with cataract surgery

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Ocufen® (flurbiprofen sodium)	Contains active flurbiprofen sodium 0.03% (0.3 mg/mL), preservative thimerosal 0.005%, and inactives: Citric acid, edetate disodium, polyvinyl alcohol 1.4%, potassium chloride, purified water, sodium chloride, and sodium citrate. May also contain hydrochloric acid and/or sodium hydroxide to adjust the pH. The pH of Ocufen® ophthalmic solution is 6.0–7.0. It has an osmolality of 260–330 mOsm/kg		A sterile topical nonsteroidal anti-inflammatory product for ophthalmic use indicated for the inhibition of intraoperative miosis
Ocuflox® (ofloxacin)	Contains active ofloxacin 0.3% (3 mg/mL), preservative benzalkonium chloride (0.005%), and inactives sodium chloride and purified water. May also contain hydrochloric acid and/or sodium hydroxide to adjust the pH. Ocuflox® solution is unbuffered and formulated with a pH of 6.4 (range 6.0–6.8). It has an osmolality of 300 mOsm/kg		Ocuflox® ophthalmic solution is indicated for the treatment of infections caused by susceptible strains of certain bacteria in the conditions of conjunctivitis and corneal ulcers
Ocupress® (carteolol hydrochloride)	Each mL contains 10 mg carteolol HCl and the inactive ingredients—Benzalkonium chloride 0.05 mg (0.005%) as a preservative; sodium chloride; sodium phosphate, dibasic; sodium phosphate, monobasic; and water for injection, USP. The product has a pH of 6.2–7.2		Effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma and intraocular hypertension
Omidria® (ketorolac phenylephrine)	Omidria is a sterile aqueous solution concentrate containing phenylephrine hydrochloride 12.4 mg/mL equivalent to 10.16 mg/mL of phenylephrine and ketorolac tromethamine 4.24 mg/mL equivalent to 2.88 mg/mL of ketorolac, as a clear, colorless, sterile solution concentrate with a pH of approximately 6.3. Inactives: Citric acid monohydrate; sodium citrate dihydrate; water for injection; may include sodium hydroxide and/or hydrochloric acid for pH adjustment		Maintain pupil size by preventing intraoperative miosis, and reducing postoperative pain, added to an irrigation solution used during cataract surgery or intraocular lens replacement

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Omnipred® (prednisolone acetate)	Each mL contains active prednisolone acetate 1.0%, preservative benzalkonium chloride 0.01% (prednisolone acetate ophthalmic suspension is an adrenocortical steroid product prepared as sterile ophthalmic suspension), vehicle hypromellose, and inactives: Dibasic sodium phosphate, polysorbate 80, edetate disodium, glycerin, citric acid and/or sodium hydroxide (to adjust the pH), and purified water		Steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies
Opcon-A®	Naphazoline HCl (0.02675%); pheniramine maleate (0.315%); benzalkonium chloride, boric acid, edetate disodium, hypromellose, purified water, sodium borate, sodium chloride. Hydrochloric acid may be used to adjust the pH		Temporarily relieves itching and redness caused by pollen, ragweed, grass, animal hair, and dander
OptiPranolol® (metipranolol hydrochloride)	Metipranolol ophthalmic solution 0.3% is a sterile solution that contains metipranolol, a non-selective beta-adrenergic receptor blocking agent. Each mL of metipranolol ophthalmic solution, for ophthalmic administration, contains 3 mg metipranolol. Inactives: Povidone, glycerol, hydrochloric acid, sodium chloride, edetate disodium, and purified water. Sodium hydroxide may be added to adjust the pH. Preservative added: Benzalkonium chloride 0.004%		Indicated to treat increased intraocular pressure in patients with ocular hypertension or open-angle glaucoma

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Optivar® (azelastine hydrochloride)	Each mL of Optivar® contains active 0.5 mg azelastine hydrochloride, equivalent to 0.457 mg of azelastine base; preservative 0.125 mg benzalkonium chloride; and inactives: Disodium edetate dihydrate, hypromellose, sorbitol solution, sodium hydroxide, and water for injection. It has a pH of approximately 5.0–6.5 and an osmolarity of approximately 271–312 mOsmol/L		A relatively selective histamine H_1 antagonist and an inhibitor of the release of histamine and other mediators from cells (e.g., mast cells) involved in the allergic response
Pataday® (olopatadine hydrochloride)	Each mL of Pataday™ solution contains active 2.22 mg olopatadine hydrochloride equivalent to 2 mg olopatadine and inactives: Povidone, dibasic sodium phosphate, sodium chloride, edetate disodium, benzalkonium chloride 0.01% (preservative), hydrochloric acid/ sodium hydroxide (adjust pH), and purified water. It has a pH of approximately 7 and an osmolality of approximately 300 mOsm/kg		Indicated for the treatment of ocular itching associated with allergic conjunctivitis
Patanol® (olopatadine hydrochloride)	Each mL of Patanol (olopatadine hydrochloride ophthalmic solution) 0.1% contains active 1.11 mg olopatadine hydrochloride equivalent to 1 mg olopatadine, preservative benzalkonium chloride 0.01%, and inactives: Dibasic sodium phosphate, sodium chloride, hydrochloric acid/ sodium hydroxide (adjust pH), and purified water. It has a pH of approximately 7 and an osmolality of approximately 300 mOsm/kg		Indicated for the treatment of the signs and symptoms of allergic conjunctivitis

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Pazeo® (olopatadine hydrochloride)	Each mL of Pazeo solution contains an active ingredient [7.76 mg of olopatadine hydrochloride (7 mg olopatadine)] and the following inactive ingredients: Povidone, hydroxypropyl-gamma-cyclodextrin, polyethylene glycol 400, hypromellose, boric acid, mannitol, benzalkonium chloride 0.015% (preservative), hydrochloric acid/ sodium hydroxide (to adjust the pH), and purified water. Pazeo solution has a pH of approximately 7.2 and an osmolality of approximately 300 mOsm/kg		Indicated for the treatment of ocular itching associated with allergic conjunctivitis
Polytrim® (polymyxin B sulfate, trimethoprim)	Polytrim® (polymyxin B sulfate and trimethoprim ophthalmic solution, USP) is a sterile antimicrobial solution for topical ophthalmic use. It has a pH of 4.0–6.2 and osmolality of 270–310 mOsm/kg. Contains actives polymyxin B sulfate 10,000 units/mL and trimethoprim sulfate equivalent to 1 mg/mL, preservative benzalkonium chloride 0.04 mg/mL, and inactives: Purified water, sodium chloride, and sulfuric acid. May also contain sodium hydroxide to adjust the pH		Indicated in the treatment of surface ocular bacterial infections, including acute bacterial conjunctivitis, and blepharoconjunctivitis, caused by several susceptible strains of microorganisms

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Pred-G® (solution, gentamicin sulfate and prednisolone acetate)	Chemical names: Prednisolone acetate: 11β,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate. Gentamicin sulfate is the sulfate salt of gentamicin C1, gentamicin C2, and gentamicin C1A which are produced by the growth of *Micromonospora purpurea*. Contains actives gentamicin sulfate equivalent to 0.3% gentamicin base and prednisolone acetate (microfine suspension) 1%; preservative benzalkonium chloride 0.005%; and inactives: Edetate disodium; hypromellose; polyvinyl alcohol 1.4%; polysorbate 80; purified water; sodium chloride; and sodium citrate, dihydrate. May contain sodium hydroxide and/or hydrochloric acid to adjust the pH (5.4–6.6). Pred-G® suspension is formulated with a pH from 5.4 to 6.6 and its osmolality ranges from 260 to 340 mOsm/kg		Pred-G® suspension is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists
Prefrin Liquifilm®	The active substance is phenylephrine hydrochloride 1.2 mg/ml. The preservative is benzalkonium chloride 0.005% w/v. the other ingredients are polyvinyl alcohol (Liquifilm), sodium phosphate dibasic anhydrous, sodium phosphate monobasic, disodium edetate, sodium acetate anhydrous, sodium thiosulfate anhydrous, and purified water. Sodium hydroxide or hydrochloric acid may be added to adjust the pH		Lubricating decongestant that whitens the eyes and is used for the relief of minor eye irritations caused by colds, hay fever, dust, smog, hard contact lenses, sun, swimming, and wind, when no infection is present

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Prolensa® (bromfenac)	Each mL of Prolensa contains 0.805 mg bromfenac sodium sesquihydrate (equivalent to 0.7 mg bromfenac free acid). Bromfenac sodium is a yellow to orange crystalline powder. The molecular weight of bromfenac sodium is 383.17. Prolensa ophthalmic solution is supplied as a sterile aqueous 0.07% solution, with a pH of 7.8. The osmolality of Prolensa ophthalmic solution is approximately 300 mOsmol/kg. Each mL contains bromfenac sodium sesquihydrate 0.0805%, which is equivalent to bromfenac-free acid 0.07%. Preservative: Benzalkonium chloride 0.005% Inactives: Boric acid, edetate disodium, povidone, sodium borate, sodium sulfite, tyloxapol, sodium hydroxide to adjust the pH and water for injection, USP		A nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients wWho have undergone cataract surgery
Quixin® (levofloxacin)	Each mL of Quixin® contains 5.12 mg of levofloxacin hemihydrate equivalent to 5 mg levofloxacin. Contains active levofloxacin 0.5% (5 mg/mL), preservative benzalkonium chloride 0.005%, and inactives sodium chloride and water. May also contain hydrochloric acid and/or sodium hydroxide to adjust the pH to approximately 6.5. Quixin® solution is isotonic with an osmolality of approximately 300 mOsm/kg		Indicated for the treatment of corneal ulcer caused by susceptible strains of the following bacteria: Gram-positive bacteria—*Corynebacterium* species *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumonia*, and viridans group streptococci—and gram-negative bacteria *Pseudomonas aeruginosa* and *Serratia marcescens*

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Refresh Liquigel®	Carboxymethylcellulose sodium (1%)		Artificial tear substitute
Refresh Optive gel drops®	Carboxymethylcellulose sodium (1%) and glycerin (0.9%)		Artificial tear substitute
Refresh Optive Mega-3®	Carboxymethylcellulose sodium (0.5%), glycerin (1%), and polysorbate 80 (0.5%)		Artificial tear substitute
Refresh redness relief®	Formula: Redness reliever (phenylephrine, 0.12%) and lubricant		Removes redness and instantly moisturizes to soothe and protect dry, irritated eyes
Refresh repair/ refresh Optive®	Carboxymethylcellulose sodium (0.5%) and glycerin (0.9%)		Artificial tear substitute
Refresh® tears	Active ingredients: Carboxymethylcellulose sodium (0.5%). Purpose: Eye lubricant. Inactive ingredients: Boric acid, calcium chloride, magnesium chloride, potassium chloride, purified water, Purite™ (stabilized oxychloro complex), sodium borate, and sodium chloride. May also contain hydrochloric acid and/or sodium hydroxide to adjust the pH. 260–330 mOsm/kg		Artificial tear substitute
RESTASIS® (cyclosporine A)	RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% contains a topical calcineurin inhibitor immunosuppressant with anti-inflammatory effects. Cyclosporine is a fine white powder. RESTASIS® appears as a white opaque to slightly translucent homogeneous emulsion. It has an osmolality of 230–320 mOsmol/kg and a pH of 6.5–8.0. Each mL of RESTASIS® ophthalmic emulsion contains active, cyclosporine 0.05%; and inactives: Glycerin, castor oil, polysorbate 80, carbomer copolymer type A, purified water, and sodium hydroxide to adjust the pH		Indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Rhopressa® (netarsudil dimesylate)	Rhopressa (netarsudil ophthalmic solution) 0.02% is supplied as a sterile, isotonic, buffered aqueous solution of netarsudil dimesylate with a pH of approximately 5 and an osmolality of approximately 295 mOsmol/kg. It is intended for topical application in the eye. Each mL of Rhopressa contains 0.2 mg of netarsudil (equivalent to 0.28 mg of netarsudil dimesylate). Benzalkonium chloride, 0.015%, is added as a preservative. The inactive ingredients are boric acid, mannitol, sodium hydroxide to adjust the pH, and water for injection		Indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
Rohto cooling eye drops®	Naphazoline hydrochloride 0.012%; polysorbate 80 0.2%; alcohol (0.1%), benzalkonium chloride, boric acid, chlorobutanol, edetate disodium, menthol, purified water, sodium borate		Relieves redness of the eye due to minor eye irritations; temporarily relieves burning and irritation due to dryness of the eye
Tetcaine® (tetracaine hydrochloride)	Tetracaine hydrochloride ophthalmic solution 0.5% has a pH of 3.7–5.5. Active ingredient: Tetracaine hydrochloride 0.5% w/v (equivalent to 0.44% w/v tetracaine). Inactive ingredients: Sodium chloride, sodium acetate trihydrate, acetic acid (to adjust the pH approximately 4.5), water for injection, USP		Tetracaine hydrochloride ophthalmic solution 0.5%, an ester local anesthetic, is indicated for procedures requiring a rapid and short-acting topical ophthalmic anesthetic

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Tetravisc Forte® (tetracaine hydrochloride)	Tetracaine hydrochloride 0.5% is a sterile topical ophthalmic solution useful in producing surface anesthesia of the eye. Boric acid; edetate disodium; hypromellose; potassium chloride; sodium borate; sodium chloride; water for injection USP, hydrochloric acid and/or sodium hydroxide to adjust the pH		For procedures in which a rapid and short-acting topical ophthalmic anesthetic is indicated such as in tonometry, gonioscopy, removal of corneal foreign bodies, conjunctival scraping for diagnostic purposes, suture removal from the cornea or conjunctiva, other short corneal and conjunctival procedures
Tetravisc® (tetracaine hydrochloride)	Tetracaine hydrochloride 0.5% is a sterile topical ophthalmic solution useful in producing surface anesthesia of the eye. Active: Tetracaine HCI 0.5%. Preservative: Benzalkonium chloride (0.01%). Inactive: Boric acid, edetate disodium, hypromellose, potassium chloride, sodium borate, sodium chloride, water for injection USP, hydrochloric acid and/or sodium hydroxide to adjust the pH		For procedures in which a rapid and short-acting topical ophthalmic anesthetic is indicated such as in tonometry, gonioscopy, removal of corneal foreign bodies, conjunctival scraping for diagnostic purposes, suture removal from the cornea or conjunctiva, other short corneal and conjunctival procedures
TheraTears® Lubricant eye drops	Carboxymethylcellulose sodium (0.25%), 170 mOsm/kg; published pH 9.01 and 145 mmol/kg osmolarity (Chen et al. 2009)		Artificial tear substitute

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Timoptic® (timolol maleate)	Timolol maleate ophthalmic solution is supplied in two formulations: Ophthalmic solution Timoptic (timolol maleate ophthalmic solution), which contains the preservative benzalkonium chloride, and ophthalmic solution Timoptic (timolol maleate ophthalmic solution), the preservative-free formulation. Preservative-free ophthalmic solution Timoptic is supplied in OCUDOSE, a unit dose container, as a sterile, isotonic, buffered, aqueous solution of timolol maleate in two dosage strengths: Each mL of preservative-free Timoptic in OCUDOSE 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). The pH of the solution is approximately 7.0, and the osmolarity is 252–328 mOsm. Each mL of preservative-free Timoptic in OCUDOSE 0.5% contains 5 mg of timolol (6.8 mg of timolol maleate). Inactive ingredients: Monobasic and dibasic sodium phosphate, sodium hydroxide to adjust the pH, and water for injection		Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Timoptic-XE® (gel-forming timolol maleate)	Timoptic-XE sterile ophthalmic gel forming solution is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in two dosage strengths. The pH of the solution is approximately 7.0, and the osmolarity is 260–330 mOsm. Each mL of Timoptic-XE 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of Timoptic-XE 0.5% contains 5 mg of timolol (6.8 mg of timolol maleate). Inactive ingredients: Gellan gum, tromethamine, mannitol, and water for injection. Preservative: Benzododecinium bromide 0.012%. The gel-forming solution contains a purified anionic heteropolysaccharide derived from gellan gum. An aqueous solution of gellan gum, in the presence of a cation, has the ability to gel. Upon contact with the precorneal tear film, Timoptic-XE forms a gel that is subsequently removed by the flow of tears		Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma
Tobradex® (dexamethasone, tobramycin)	Tobradex® (tobramycin and dexamethasone ophthalmic suspension) is a sterile, multiple dose antibiotic and steroid combination for topical ophthalmic use. Each mL of Tobradex® (tobramycin and dexamethasone ophthalmic suspension) contains actives, tobramycin 0.3% (3 mg) and dexamethasone 0.1% (1 mg); preservative, benzalkonium chloride 0.01%; and inactives: Tyloxapol, edetate disodium, sodium chloride, hydroxyethyl cellulose, sodium sulfate, sulfuric acid and/or sodium hydroxide (to adjust the pH), and purified water		For steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Travatan Z® (travoprost)	Travatan Z® (travoprost ophthalmic solution) 0.004% is supplied as sterile, buffered aqueous solution of travoprost with a pH of approximately 5.7 and an osmolality of approximately 290 mOsmol/kg Travatan Z® contains active, travoprost 0.04 mg/mL, and inactives: Polyoxyl 40 hydrogenated castor oil, SofZia® (boric acid, propylene glycol, sorbitol, zinc chloride), sodium hydroxide and/or hydrochloric acid (to adjust the pH), and purified water, USP. Preserved in the bottle with an ionic buffered system, SofZia®		Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma
Triesence® (triamcinolone acetonide)	Each mL of the sterile, aqueous suspension provides 40 mg of triamcinolone acetonide, with sodium chloride for isotonicity, 0.5% (w/v) carboxymethylcellulose sodium, and 0.015% polysorbate 80. It also contains potassium chloride, calcium chloride (dihydrate), magnesium chloride (hexahydrate), sodium acetate (trihydrate), sodium citrate (dihydrate), and water for injection. Sodium hydroxide and hydrochloric acid may be present to adjust the pH to a target value 6–7.5		Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids and visualization during vitrectomy
TRUSOPT® (dorzolamide hydrochloride)	TRUSOPT sterile ophthalmic solution is supplied as a sterile, isotonic, buffered, slightly viscous, aqueous solution of dorzolamide hydrochloride the pH of the solution is approximately 5.6, and the osmolarity is 260–330 mOsM. Each mL of TRUSOPT 2% contains 20 mg dorzolamide (22.3 mg of dorzolamide hydrochloride). Inactive ingredients are hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, sodium hydroxide (to adjust the pH), and water for injection. Benzalkonium chloride 0.0075% is added as a preservative		Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Vancocin® (vancomycin)‖	Vancomycin hydrochloride for injection, USP, intravenous, is a chromatographically purified tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly Nocardia orientalis). The molecular weight is 1485.74; 500 mg of the base is equivalent to 0.34 mmol, 750 mg of the base is equivalent to 0.51 mmol, and 1 g of the base is equivalent to 0.67 mmol. When reconstituted with sterile water for injection, USP, vancomycin hydrochloride forms a clear, light to dark tan solution with a pH of 4.0 (2.5–4.5). This product is oxygen sensitive	Endocarditis, enterocolitis, staphylococcal infections	Endophthalmitis (Gan et al. 2001)
Vexol® (rimexolone)	Vexol® 1% ophthalmic suspension is a sterile, multidose topical ophthalmic suspension containing the corticosteroid, rimexolone. Each mL contains active ingredient rimexolone 10 mg (1%); preservative, benzalkonium chloride 0.01%; and inactive ingredients: Carbomer 974P, polysorbate 80, sodium chloride, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust the pH), and purified water. The pH of the suspension is 6.0–8.0 and the tonicity is 260–320 mOsmol/kg		Indicated for the treatment of postoperative inflammation following ocular surgery and in the treatment of anterior uveitis
Viroptic® (trifluridine)	Viroptic sterile ophthalmic solution contains 1% trifluridine in an aqueous solution with acetic acid and sodium acetate (buffers), sodium chloride, and thimerosal 0.001% (added as a preservative). The pH range is 5.5–6.0 and osmolality is approximately 283 mOsm		Activity against herpes simplex virus, types 1 and 2 and vaccinia virus, and some strains of adenoviruses
Visine®	Inactive ingredients: Glycerin, hypromellose, polyethylene glycol 400; in Visine A® 3 mg/mL pheniramine maleate and 0.25 mg/mL naphazoline hydrochloride		Artificial tear substitute or allergy and redness relief

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Visudyne® (verteporfin)	Visudyne® (verteporfin for injection) is a light-activated drug used in photodynamic therapy. The finished drug product is a lyophilized dark green cake. Each mL of reconstituted Visudyne contains active verteporfin, 2 mg, and inactives ascorbyl palmitate, butylated hydroxytoluene, dimyristoyl phosphatidylcholine, egg phosphatidylglycerol, and lactose		Indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia, or presumed ocular histoplasmosis
Voltaren® (diclofenac sodium)	Voltaren ophthalmic (diclofenac sodium ophthalmic solution) 0.1% solution is a sterile, topical, nonsteroidal, anti-inflammatory product for ophthalmic use. Voltaren ophthalmic is available as a sterile solution which contains diclofenac sodium 0.1% (1 mg/mL). Inactive ingredients: Polyoxyl 35 castor oil, boric acid, tromethamine, sorbic acid (2 mg/mL), edetate disodium (1 mg/mL), and purified water. Diclofenac sodium is a faintly yellow-white to light beige, slightly hygroscopic crystalline powder. It is freely soluble in methanol, sparingly soluble in water, very slightly soluble in acetonitrile, and insoluble in chloroform and in 0.1 N hydrochloric acid. Its molecular weight is 318.14. Voltaren ophthalmic 0.1% is an iso-osmotic solution with an osmolality of about 300 mOsmol/1000 g, buffered at approximately pH 7.2. Voltaren ophthalmic solution has a faint characteristic odor of castor oil		Treatment of postoperative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Vyzulta® (latanoprostene bunod)	Vyzulta™ (latanoprostene bunod ophthalmic solution) 0.024% is a prostaglandin analog formulated as a sterile topical ophthalmic solution. Vyzulta contains the active ingredient latanoprostene bunod 0.24 mg/mL, the preservative benzalkonium chloride 0.2 mg/mL, and the following inactive ingredients: Polysorbate 80, glycerin, EDTA, and water. The formulation is buffered to pH 5.5 with citric acid/sodium citrate		Indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
Xiidra® (lifitegrast)	Xiidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist supplied as a sterile, clear, colorless to slightly brownish-yellow colored, isotonic solution of lifitegrast with a pH of 7.0–8.0 and an osmolality range of 200–330 mOsmol/kg. Active: Lifitegrast 50 mg/mL. Inactives: Sodium chloride, sodium phosphate dibasic anhydrous, sodium thiosulfate pentahydrate, sodium hydroxide and/or hydrochloric acid (to adjust the pH), and water for injection		Indicated for the treatment of the signs and symptoms of dry eye disease
Xolair® (omalizumab)‖	Xolair is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with sterile water for injection (SWFI), USP, and administered as a subcutaneous (SC) injection. A Xolair vial contains 202.5 mg of omalizumab, 145.5 mg sucrose, 2.8 mg L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20 and is designed to deliver 150 mg of omalizumab, in 1.2 mL after reconstitution with 1.4 mL SWFI, USP *(*no pH or osmolarity spec.)*	Asthma, chronic idiopathic urticaria	Vernal keratoconjunctivitis (El-Qutob 2016)

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Zaditor® (ketotifen fumarate)	Ketotifen (0.025%) (equivalent to ketotifen fumarate 0.035%); Systane® polyethylene glycol 400 4 mg/mL, propylene glycol 3 mg/mL, benzalkonium chloride 0.01%, glycerol, purified water; boric acid, calcium chloride, hydroxypropyl guar, magnesium chloride, potassium chloride, sodium chloride, zinc chloride. May contain hydrochloric acid and/or sodium hydroxide to adjust the pH		Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair, and dander
Zerviate® (cetirizine hydrochloride)	Each mL of Zerviate contains an active ingredient [cetirizine 2.40 mg (equivalent to 2.85 mg of cetirizine hydrochloride)] and the following inactive ingredients: Benzalkonium chloride 0.010% (preservative); glycerin; sodium phosphate, dibasic; edetate disodium; polyethylene glycol 400; polysorbate 80; hypromellose; hydrochloric acid/sodium hydroxide (to adjust the pH); and water for injection. Zerviate solution has a pH of approximately 7.0 and osmolality of approximately 300 mOsm/kg		A sterile ophthalmic solution containing cetirizine, which is a histamine-1 receptor antagonist, for topical administration to the eyes for the treatment of ocular itching associated with allergic conjunctivitis
Zioptan® (tafluprost)	Zioptan (tafluprost ophthalmic solution) 0.0015% is supplied as a sterile, preservative-free, solution of tafluprost with a pH range of 5.5–6.7 and an osmolality range of 260–0 mOsmol/kg. Zioptan contains active, tafluprost 0.015 mg/ml, and inactives, glycerol, sodium dihydrogen phosphate dihydrate, disodium edetate, polysorbate 80, hydrochloric acid and/or sodium hydroxide (to adjust the pH), and water for injection		Prostaglandin analog indicated for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

(continued)

Table 1 (continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Zirgan® (ganciclovir)	Each gram of gel contains active, ganciclovir 1.5 mg (0.15%); inactives, carbomer homopolymer, water for injection, sodium hydroxide (to adjust the pH to 7.2–7.6), and mannitol; and preservative benzalkonium chloride 0.075 mg (0.0075)		Indicated for the treatment of acute herpetic keratitis (dendritic ulcers)
Zithromax® (azithromycin)‖ AzaSite®	AzaSite (azithromycin ophthalmic solution) is a 1% sterile aqueous topical ophthalmic solution of azithromycin formulated in DuraSite® (polycarbophil, edetate disodium, sodium chloride). AzaSite is an off-white, viscous liquid with an osmolality of approximately 290 mOsm/kg. Preservative: 0.003% benzalkonium chloride. Inactives: Mannitol, citric acid, sodium citrate, poloxamer 407, polycarbophil, edetate disodium (EDTA), sodium chloride, water for injection, and sodium hydroxide to adjust the pH to 6.3	Chancroid, chronic obstructive pulmonary disease, *Mycobacte-rium avium* complex, acute otitis media, community-acquired pneumonia, skin and skin structure infections obtained from *Staphylococcus aureus*, *Streptococcus pyogenes* or *Streptococcus agalactiae*, streptococcal pharyngitis, urethritis, cervicitis	Bacterial conjunctivitis, treatment of meibomian gland dysfunction (Liu et al. 2014)

(continued)

Drug name	Liquid, ophthalmic formulation attributes	Original indications	Ophthalmic indications
Zylet® (loteprednol etabonate, tobramycin)	Each mL contains actives loteprednol etabonate 5 mg (0.5%) and tobramycin 3 mg (0.3%) and inactives edetate disodium, glycerin, povidone, purified water, tyloxapol, and benzalkonium chloride 0.01% (preservative). Sulfuric acid and/or sodium hydroxide may be added to adjust the pH to 5.7–5.9. The suspension is essentially isotonic with a tonicity of 260–320 mOsm/kg		A topical anti-infective and corticosteroid combination for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists; inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, and where the inherent risk of steroid use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation, chronic anterior uveitis, and corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies
Zymaxid® (gatifloxacin)	Zymaxid® is a clear, pale-yellow, sterile, preserved aqueous solution with an osmolality of 260–330 mOsm/kg and a pH of 5.1–5.7. Zymaxid® contains the active ingredient gatifloxacin 0.5% (5 mg/mL) and the inactive ingredients benzalkonium chloride 0.005%, edetate disodium, sodium chloride, and purified water. Zymaxid® may contain hydrochloric acid and/or sodium hydroxide to adjust the pH		Indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: Aerobic gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* mitis group, St*reptococcus oralis*, *Streptococcus pneumoniae)* and aerobic gram-negative bacteria (*Haemophilus influenzae*)

new liquid ophthalmic drug product for use in an ocular disease. Such compound repurposing capitalizes on the fact that approved drugs and many compounds in the pipeline (note that clinical development candidates that are not yet approved could come from active or even abandoned programs in the pipeline) have achieved human testing and are accompanied with an understanding of pharmacology, defined systemic pharmacokinetics and safety data, and possibly a proof (or in vivo validation) of a mechanism of action. While there are close to 600 ophthalmic drug products captured in the current edition of the FDA's Orange Book (https://www.hhs.gov/ 2019), about 80% of these are drug repositioning examples underpinned by the fact that common molecular pathways contribute to different disease phenotypes. Furthermore, approximately the same proportion of *Orange Book* listed ocular products (~80%) are variations on ophthalmic formulations of the same drug or active ingredient, with more than half of those (approximately 200 reference listed drugs) qualifying as liquid ophthalmic drug products (https://www.hhs.gov/ 2019).

Physical and Chemical Considerations

Conventional physicochemical characterization approaches also apply to all active pharmaceutical ingredients used in liquid ophthalmic products; however, other distinctive requirements exist. Physical and chemical properties include those of small organic molecules as well as large macromolecules derived from biotechnology (e.g., biophysical considerations). Understanding of crystal structure and disposition thereof, single crystal data (molecular orientation and long-range packing, or that of salts and hydrates/solvates from the same perspective as isolated from the final step in process chemistry), solid state polymorphisms and solid form as it impacts thermodynamic stability and solubility in aqueous liquids, drug substance morphology including particle size distributions, and other properties which are related to manufacturability of a downstream product—e.g., melting point or glass transition temperature, hygroscopic tendencies, absolute density of substance, and any latent process chemistry or recombinant/fermentation-related impurities (Hilfiker et al. 2006). Intuitively, the aforementioned properties relate to the quality of a downstream product, e.g., controls around stability and purity; however, in some cases they can also directly impact performance and hence potentially affect safety and efficacy. Furthermore, drug substance chemical and biophysical properties in a selected ophthalmic candidate must also be fully characterized as they can relate to and influence the nature of previously listed physical considerations. Chemistry and (bio)physics can also impact the biopharmaceutical aspects which typically address liquid formulations and absorption mechanisms for a given dose and route of ocular delivery: for example, the balance between equilibrium solubility values in an aqueous environment vs. in oil, e.g., the oil/water partition coefficient—$P_{o/w}$ (Schoenwald and Huang 1983b; Wang et al. 1991); the ionization constant if the molecule has one within the relevant ocular physiological pH range (discussed later)—pK_a, pK_b, or pI values for acids, bases, and zwitterions, resp.

(Pawar et al. 2013; Schoenwald and Huang 1983b); and finally, the molecules' absolute or thermodynamic aqueous solubility with a defined pH-dependent solubility profile, or an equilibrium solubility product rate constant (K_{sp}) if ionic drug substance is being considered (Breda et al. 2009; Diehl and Markuszewski 1985; Maren et al. 1990; Pawar et al. 2013; Scozzafava et al. 1999; Shirasaki 2008; Shoghi et al. 2013; Sieg and Robinson 1977; Zhang et al. 2013). For classes of liquid ophthalmic suspension products, e.g., PRED FORTE® (https://www.accessdata.fda.gov/ 1973) 10 mg/mL prednisolone acetate topical microfine suspension indicated for treatment of steroid-responsive inflammation in anterior ocular segment tissues or TRIESSENCE® (https://www.accessdata.fda.gov/ 2007) 40 mg/mL injectable triamcinolone acetonide suspension indicated for posterior ocular inflammatory conditions unresponsive to topical corticosteroids and visualization during vitrectomy, the final particle size distribution plays a key role in precorneal residence time (a combination of turnover due to tear fluid secretion and nasolacrimal drainage) and intensity plus durability of intravitreal exposure, respectively (Missel et al. 2010; Sieg and Robinson 1975). Particle size characterization studies in topical liquid ophthalmic suspensions support the belief that moderate dilution of a suspension of a poorly soluble drug (such as the steroidal anti-inflammatory examples given earlier) does not diminish aqueous humor drug levels or, conversely, that the use of a higher drug particle count within a suspension increases aqueous humor (typical ocular pharmacokinetic sampling compartment) drug concentration-time profiles (Sieg and Robinson 1975). An order-of-magnitude lower dose (vs. PRED FORTE® (https://www.accessdata.fda.gov/ 1973)), 0.1% fluorometholone suspension, compared to a saturated solution of the same drug did not produce sustaining pharmacokinetic effects, suggesting that the conjunctival cul-de-sac retains suspended particles within a topical liquid ophthalmic eye drop and contributes significantly to the overall extent of steroid penetrating across the cornea (Sieg and Robinson 1975). Furthermore, investigations of various particle sizes and concentrations (e.g., 77–428 μm and 40–160 mg/mL) and their effect on intraocular residence time suggested that performance of liquid intravitreal-injectable suspension depots is insensitive to these physical and pharmaceutical parameters (Missel et al. 2010).

Chemical Characteristics

For small molecules, information on the lipophilicity, ionization state, and aqueous solubility forms a trifecta of physicochemical properties relating to the oil/water partition coefficient ($P_{o/w}$ or more commonly reported as log P). A known relationship exists with permeability across various ocular epithelial tissue barriers (note here one must consider the actual physiological route of administration for rationale in the final selection of drug substance for a liquid ophthalmic product design) or in other words absorption into the eye and intraocular target tissues (Chien et al. 1990; Edward and Prausnitz 2001; Friedrich et al. 1997; Hamalainen et al. 1997; Kidron et al. 2010; Pitkanen et al. 2005; Prausnitz and Noonan 1998; Ramsay et al. 2018,

2017; Schoenwald and Huang 1983a, b; Tai et al. 2003; Wang et al. 1991; Yoshida and Topliss 1996; Ahmed et al. 1987; Shirasaki 2008; Gukasyan et al. 2019a, b). The hydrophobic or hydrophilic nature of the active pharmaceutical ingredient can also be carefully used in delivery vehicle design, choice, and respective amounts of inactive ingredients used, and (bio)chemical specifications such as final pH, buffer capacity, and ionic strength or osmolyte content (Breda et al. 2009; He et al. 2003; Leibowitz et al. 1978; Mitra 1993; Palkama et al. 1985; Pawar et al. 2013; Sieg and Robinson 1975, 1977, 1979; Zhang et al. 2013; Singh et al. 2009). Formulation design, at least partly related to choices of inactive ingredient selection, will be discussed in detail in the following sections; however, it is noteworthy to mention that physicochemical properties like log *P* and pK_a (or log *D* which combines log *P* value with an acid or base dissociation constant at a particular pH) are important toward the selection of appropriate solubilizing excipients. Ionization constants (e.g., pK_a or pK_b) are similarly related to multiple biopharmaceutical dimensions as they influence molecules' final dose and overall absorption efficiency into the eye (Gukasyan et al. 2019b; Shirasaki 2008). Chiefly, these include the required dose and its inherent (pH)-solubility ratio, and also dissolved active pharmaceutical ingredient fraction within a total dose that's molecularly and thermodynamically eligible and available to present a chemical driving force (gradient) for flux across ocular tissue barriers (Mortimer and Eyring 1980). It is generally accepted that the neutral form of any drug substance is favored in terms of transcellular flux across biological membrane barriers; hence, within this context the physiological properties of tear fluid and intraocular compartments must be considered in conjunction with formulation attributes and how they would influence the degree of ionization of a molecule (if any) temporally from the time point of introduction into ocular space (Hogben et al. 1959; Kansy et al. 1998; Mortimer and Eyring 1980). This is an important theoretical concept with several practical examples in liquid ophthalmic dosage forms (e.g., those of brimonidine (https://www.accessdata.fda.gov/ 2001, 2006, 1996)) which will be discussed in the drug product pH considerations section.

Since the eye is exposed to direct light, as it relates to the circadian rhythm, diurnal and nocturnal changes in several physiological factors, esp. in topical ocular drug delivery, it is important to understand the chemical photosensitivity of liquid ophthalmic candidates. On a molecular level in solution, the absorbance of sunlight energy in the visible, UVA, and partially UVB radiation range is a common characteristic which can potentially lead to photoirritation and photoallergy. Hence, it is essential to characterize light absorbance profiles of liquid ophthalmic candidates and identify wavelengths within the relevant spectrum which achieve the maximum absorption (e.g., at λ_{max} value the molar extinction coefficient $> 1000\,L \times mol^{-1} \times cm^{-1}$ (https://www.ich.org/products/guidelines/ 2019)), and if needed evaluate the prevalence and phototoxic activity of light-excitable drug substances. Several mechanisms for light-induced ocular drug toxicity have been proposed and are equally helpful in in vitro or in vivo ocular models designed toward simple, inexpensive testing of developmental stage compounds as a screen for their potential ocular phototoxicity (Fishman 1986; Roberts 2002). For example, fluoroquinolone class of

antibiotics commonly used in topical ophthalmic formulations, and via intravitreal or intracameral injections, are known to cause various degrees of phototoxicity (with an established structure activity relationship for their potential to cause photo-instability and photocarcinogenic effect, as well as chemical mechanisms of action) when exposed to ultraviolet (UV) light (Pawar et al. 2013; Thompson 2007). The UV-fluoroquinolone phototoxicity is associated with the formation of reactive oxygen species (ROS), where excitation by light energy produces both singlet oxygen and superoxide, followed by ocular-cellular damage (Thompson 2007). A related (e.g., via ROS mechanism) notable mechanism of action is the effect of such drugs *(or even some inactive ingredients found in liquid ophthalmic compositions, to be discussed in the subsequent section)* in liquid ophthalmic drug products on equilibrium concentrations of reduced glutathione (GSH) within physiological ocular fluids (e.g., tear fluid, aqueous humor, vitreous humor) or cells that comprise tissues which come into immediate contact with the product (Aguirre et al. 2012; Gurbay and Hincal 2004). For example, reduction of tear fluid or aqueous humor GSH concentration is known to trigger undesirable changes in corneal endothelial cell permeability (Green et al. 2001). Similarly, *S*-(1,2-dicarboxyethyl)glutathione (DCE-GS), which is biosynthesized in an enzyme-mediated reaction utilizing reduced glutathione and L-malate, is found at highest known concentrations in mammalian lens tissue and thought to play several key ocular physiological roles (Green et al. 2001; Tsuboi et al. 1990a, b). Within the context of liquid ophthalmic products, the extent of phototoxic damage would be a function of both the drug concentration (which is a known factor for the fluoroquinolone class) and total UV-light dose. Moreover, despite the availability of relatively more photostable fluoroquinolones such as 8-methoxy analogs of gatifloxacin and moxifloxacin vs. the photo-unstable ciprofloxacin, plus a paucity of data supporting human fluoroquinolone-induced photocarcinogenicity, in clinical use an advisory to avoid sunlight exposure for the duration of therapy with these agents is persistent (Thompson 2007; Gurbay and Hincal 2004).

Physical Characteristics

Drug substance solid form is an important consideration for liquid ophthalmic formulation development, and it warrants a brief discussion using a case study to exemplify challenges in drug repurposing for ophthalmic use as well as bridging and bioequivalence understanding form a pharmaco- and toxico-kinetic point of view. Studies with gatifloxacin (Table 1, fluoroquinolone broad-spectrum antibiotic) have provided the pharmaceutical industry with ample reasons and rationale to devote enough attention to identification and understanding of inter-relationships between all possible crystalline solid forms and how the polymorph landscape would impact the desired dosage form and development plans. Gatifloxacin was initially discovered as a hemihydrate crystallized from methanol (Masuzawa et al. 1991). Since this particular crystal form displayed poor characteristics for tableting, e.g., extremely hygroscopic with slow disintegration and dissolution for original

therapeutic indication using enteral delivery route, this directed several subsequent polymorph screens and identification of 14 additional solid forms for gatifloxacin (Matsumoto et al. 1999; Raghaven et al. 2002). Briefly, all these studies added considerable challenges to the overall development pathway of the molecule to an oral product, called Tequin®, which was ironically withdrawn from major markets in 2006 for systemic safety reasons. As an appropriate segue to the next section, a highly soluble sesquihydrate (Raghaven et al. 2002) of gatifloxacin was ultimately chosen/repurposed and utilized for production of ophthalmic topical solutions called Zymar® followed by Zymaxid® (which differs at least based on label claim in active ingredient concentration, 0.3% (3 mg/mL) and 0.5% (5 mg/mL) gatifloxacin, resp., with benzalkonium chloride at 0.005%, EDTA, purified water, and sodium chloride in both), and as the compound went off-patent sometime in 2010, the generic maker Apotex Inc. started using the hemihydrate in their version of the topical drug product (Newman and Wenslow 2016). While several reports exist, the aqueous solubility relationship among known forms of gatifloxacin is understood to parallel its thermodynamic stability, with the pentahydrate having the lowest solubility at 25 °C (Raghaven et al. 2002). As a general best practice, an approach which evaluates (or identifies, if unknown) the risks and benefits associated with all solid forms of a given drug substance being considered for liquid ophthalmic product development should be adopted within the context of the proposed ocular dose and route of delivery. While it would be prudent to identify the form with lowest free energy and propose a process of isolating it from the last step in drug substance synthesis, for liquid ophthalmic products it is also important to address any risks of potentially forming less soluble hydrates or salts from common physiological or buffer ions. A full polymorphic landscape analysis will dictate also the complete interconversion mechanisms between known solid forms, ideally allowing for establishment of tight process controls and analytical methodology to produce crystalline material with high homogeneity (i.e., no detectable presence of other known polymorphs). If lower solubility forms exist than the one used in liquid ophthalmic product development, a potential supersaturated state is rendered and conversion during storage (or after introduction into intraocular compartments) toward lower-soluble forms can occur. While this is a temporally kinetic phenomenon, it is a risk which could impact the quality (e.g., formation of a precipitate) and performance (e.g., dissolution and absorption) of a liquid ophthalmic product. Unless there is a clear reason related to a medical benefit which suggests that a metastable or amorphous form for a drug substance is desired for product development, only the most stable solid form should be selected/developed. If the former exception is not applicable, and a less thermodynamically stable form is used for manufacturing ease (or other nonscience-related or regulatory strategic reasons), then it is incumbent upon the pharmaceutical developer to minimize and mitigate risk to patients from a performance and quality point of view (Singhal and Curatolo 2004).

Drug Product Considerations

The next layer of classification in liquid ophthalmic products relates to the design of delivery vehicle itself. While several strata of complexity exist in liquid ophthalmic formulation design from a physiologically based route of administration perspective, here the focus will be agnostic of site of ocular drug deposition. Progressive understanding of barriers presented by ocular anatomical features on drug delivery impart parallel protective mechanisms that help this organ to perform its primary function of ensuring proper vision. These protective mechanisms include clearance of exogenous chemicals (such as drug molecules) into the systemic circulation via fluid drainage and lacrimation. Liquid ophthalmic formulation design must consider these physiological attributes and find a logical balance between those and physicochemical ones that govern boundaries in product design. While a finite collection of different configurations exists, a deep understanding of all overlapping physiological and physicochemical characteristics is required to nominate possible formulation contenders for initial in vivo prototyping and testing.

All liquid ophthalmic dosage forms face a primary challenge that's related to the limited amount of space available for drug delivery to the eye. A typical eye drop volume is thought to be approximately 30 μL, although reports indicate a range between 25 and 56 μL with a key importance on dropper tip inner/outer diameter (as opposed to liquid formulation properties like viscosity or surface tension) (Brown and Lynch 1986; Lederer and Harold 1986). There is a restricted limit in the size of a dose that can be applied to, injected, and tolerated by ocular sites of drug deposition, and in the duration over which an applied dose stays in contact with absorptive surfaces of the eye (whether they are topical or intraocular). From this perspective, it is important to guarantee through proper liquid formulation design that the complete dose is either solubilized in a liquid product or fully available for accurate delivery in the case of solid, semi-solid, or colloidal suspended particulates within a liquid delivery vehicle. The formulation vehicle composition, e.g., pH, ionic content, and strength, as well as the presence of any inactive ingredients, plays a critical role since the allowed practical volumes for ocular delivery of liquid dosage forms lie within 30–100 μL range (depending on the route of administration) (Ghate and Edelhauser 2006; Lee and Robinson 1986). The three main ocular physiological fluids with which liquid ophthalmic formulations come into contact and mix with are tear fluid, aqueous humor, and vitreous humor, while estimations of the ionic content, nature of electrolytes, and pH of these fluids have been of interest from a basic science perspective for nearly a century according to early published records (Meyer and Palmer 1936). In contrary to initial hypothesis that these biological fluids had origins of dialysates (e.g., from blood circulation), their ionic content, presence of hyaluronic acid, and pH which is generally 0.1–0.3 units lower than that of blood suggested more complex biological regulation mechanisms in these ocular compartments and highlighted the importance of understanding their characteristics for drug delivery purposes (Meyer and Palmer 1936).

pH, Buffers, and Buffering Capacity

Furthermore, the pH range of aqueous preparations for ocular administration requires tight control and optimized buffering capacity (β). The latter, e.g., β, has been investigated in several eye-related fluids and displays considerable intersubject variability in ocular biosystems, depending on the methods used, e.g., acid or base titration. For example, local zones of enhanced buffering by human tear fluid across the entire pH spectrum were identified, reflecting multiple endogenous buffering components, primarily bicarbonate and a heterogeneous tear film protein population, among others (Carney et al. 1989). Baseline tear fluid pH values from several reports indicate a range from 7 to 7.5, which is highly dependent on several factors: diurnal fluctuations, e.g., tears are more acidic as sampled from eyes during waking hours of the day (average pH 7.25) than later in the day (pH 7.45) (Carney and Hill 1976); the dynamics attributed to these fluctuations could be related to metabolic byproducts associated with anaerobic conditions during sleep as well as differences in carbon dioxide activity in the eyelids-open vs. eyelids-closed configurations (1 h eyelid patching resulted in a significant acidic shift from pH 7.20 to 7.06 (Coles and Jaros 1984)), and also gender and age, especially in females where tear film pH increases significantly, e.g., 7.06 vs. 7.28, for <40 years of age vs. >40 years of age, respectively (Coles and Jaros 1984). Vitreous humor pH has been estimated in several instances and species, as it is thought to play a role during intraocular hypoxia, acidosis, and optic nerve cell health. Baseline vitreous pH in normotensive eyes is reported to be approximately 7.3, while it can decrease by as much as 0.4 pH units in cases of acute intraocular pressure (IOP) elevation (however, it is reversible if IOP is returned to normal levels within 2 h) (Lu et al. 2001). While the mechanisms of vitreous humor pH regulation are not well known, the influence of liquid intravitreal-injectable ophthalmic formulations for retinal disease treatment on posterior tissue circulation and vitreous pH is of great importance. Within an exploratory context, liquid intravitreal injections of pH 3–8 range have been evaluated and characterized as acceptable or tolerable from a post-hoc histopathological examination perspective (Aguirre et al. 2012). These studies employed specific buffers (at pH 3–4 range with a relatively low β) and counterions to prepare intravitreal liquid vehicles targeted for delivery of new chemical entities (e.g., small-molecule inhibitors of angiogenesis being repurposed from an oral route of delivery in oncology indications for the treatment of wet neovascular age-related macular degeneration (AMD)) (Aguirre et al. 2012; Marra et al. 2011). Specific counterions entertained within this wide pH range included sulfate, maleate, malate, fumarate, citrate, and phosphate; their molar concentrations were maintained in the 10–30 mM range with the intention to allow for rapid pH adjustment in the vitreous chamber microenvironment as the exact buffering mechanism and capacity of the compartment was not well defined (Aguirre et al. 2012, 2018; Marra et al. 2011). The selection of counterions from ionic chemical drug substances, which could subsequently behave as buffers in liquid ophthalmic formulations, or additional buffering agents for setting and controlling final drug product pH, is another important consideration from an

ocular safety point of view. While traditional selection and use criteria for pharmaceutical salts can be considered as a starting point (Stahl et al. 2011), there are several physiologically unique principles which may be limitations in an ophthalmological setting. For example, in research formulation development work for a potent, selective vascular endothelial growth factor receptor tyrosine kinase inhibitor, PF-00337210, under consideration for the treatment of age-related macular degeneration, twofold changes were made to maximize safety and ocular delivery properties. Switching from an oral immediate release tablet in an oncology indication, PF-00337210 bismaleate (a rapidly dissolving salt form of the original drug substance) was recrystallized as a stable free-base polymorph to avoid use of maleate counterion intravitreally, thought to elicit retinal tissue toxicity partially through GSH depletion (Aguirre et al. 2012). Furthermore, to optimize the unique physicochemical properties of the drug which would allow for a sterile liquid parenteral injectable product to be developed for early testing (i.e., deliver up to 6 mg of PF-00337210 in a 0.1 mL intravitreal injection), the aqueous solubility was increased to >800 mg/mL using crystalline free base in a safer citrate buffer system at pH 3 with low β (10 mM citrate, β 0.001–0.003) to allow for rapid in situ neutralization of pharmaceutical pH (Marra et al. 2011). Buffering zone offered instantaneous intravitreal neutralization (i.e., from pH 3 to 7) of PF-00337210 doses by the endogenous ampholytes present in vitreous humor allowing for a spontaneous in situ formation of a drug substance precipitate which acted as a dose depot to reduce the frequency of intravitreal injections, expected by virtue of known rapid elimination of small molecules from this intraocular compartment (Aguirre et al. 2012; Raghava et al. 2004).

Liquid ophthalmic formulation preparations whose pH or tonicity is non-physiological are known to stimulate tear turnover, changes in aqueous humor dynamics, and transient ion solute exchange, thereby accelerating drug loss or potential compromise of ocular tissue integrity (Ghate and Edelhauser 2006; Mitra 1993; Shen et al. 2018). Early investigations, however largely based on subjective comfort indices, of appropriate formulation pH for ophthalmic use already suggested that deviating away from eyes' physiological pH caused non-productive drug losses as opposed to desirable absorption, accompanied by damage to ocular tissues in extreme cases. Furthermore, various buffering agent effects were studied as a function of lacrimation presumably based on human tolerance (Hind and Goyan 1947; Martin and Mims 1950). Plausibly the earliest quantitative approach which utilized dacryoscintigraphy as a method of detecting lacrimation, in direct proportionality to tear drainage rate constant, showed that alkaline and acid pH in liquid formulations decreased ocular bioavailability—for both nonionizable and ionizable drugs (Conrad et al. 1978). Furthermore, changing aspects (diurnal and nocturnal fluctuations) of tear film and ocular surface pH have been explored, and the mechanisms of tear fluid pH regulation have been carefully studied. pH challenges can affect formulation vehicle toleration, drug effectiveness, and clinical signs in disease-related endpoints. Specifically, the buffering capacity of tears shows considerable differences from those seen in the blood, large intrasubject variability, especially toward acidic-range titration. Local ocular zones of enhanced micro-buffering

across the pH spectrum have been identified, presumably suggesting the existence of multiple buffering components (bicarbonate, protein, and others) present in ocular fluids (Carney et al. 1989; Coles and Jaros 1984). Perfusion of intraocular aqueous humor containing compartments with solutions of varying pH range revealed that outside of the pH range of 6.5–8.5, morphological and cell-physiology-related alterations occur, including direct cellular damage, as well as disruption of tight-junctional complexes, leading to loss in barrier function integrity within ocular and blood-systemic compartments. Furthermore, analysis of the extent of this breakdown has been shown to be dependent upon the magnitude and the exposure time to altered pH (Gonnering et al. 1979).

Estimations of pH have been performed in tears and aqueous and vitreous humor, reported at 7.25–7.45, 7.5, and 7.32, respectively, and the endogenous buffering capacity of each compartment is estimated to be significantly lower than that of blood in terms of the presence of species which act as buffers and recovery turnover time to baseline pH value following an exogenous stressor (Carney and Hill 1976; Carney et al. 1989; Lu et al. 2001; Paterson et al. 1975). Classical pH-partition hypothesis partially explains the influence of physiological pH (specifically the hydrogen ion concentration normally found in tear fluid or other ocular fluids where liquid dosage forms are deposited) for drugs with an acid dissociation constant (e.g., pK_a) on the extent of drug transfer, partitioning, or absorption across the phospholipid bilayer of cells. The concept reasons that when a drug is ionized, it will not be able to get through a lipid membrane, while keeping in mind that the ionized form of a drug is also in a pK_a-governed simultaneous equilibrium with its neutral form (Shore et al. 1957). For liquid ophthalmic drug products, the final pH of the formulation has exclusive control over the ratio of drugs' non-ionized vs. ionized states and therefore has a transient influence on proportion of species with higher lipid solubility. Pioneering reports indicated that the extent of ocular absorption of ionizable drugs must consider pH-dependent lacrimation in addition to the classical pH-partition explanation. Within this context, detailed pharmacokinetic ocular absorption studies of early glaucoma drug, pilocarpine, were able to fully corroborate quantitative estimations illustrating a plateau within the pH-dependent absorption into aqueous humor plot, only by taking into account both lacrimation and pH-partition hypothesis as two opposing effects above physiological pH and pK_a of the drug (Conrad et al. 1978). The enhanced delivery of brimonidine is apparent from a comparison of ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% at a pH of 5.6–6.6 (https://www.accessdata.fda.gov/ 1996) vs. ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% at a pH of 7.4–8.0 (https://www.accessdata.fda.gov/ 2001, 2006), where the 50% lower concentration of brimonidine equivalents in ALPHAGAN® P at a more alkaline pH provides bioequivalence (comparable to aqueous humor, iris ciliary body exposures, and intraocular pressure lowering). By buffering the pH in ALPHAGAN® P to slightly basic and near 7.4–7.8, e.g., at approximately the pK_a of brimonidine (Bhagav et al. 2010), the ocular penetration is further enhanced partially due to the tendency of the drug to efficiently diffuse through lipid membranes under such circumstances where dissolved brimonidine species are predominantly unionized in neutral to alkaline

formulation environments (Olejnik July 14, 2000). Increasing the pH of vehicles can promote increased corneal penetration for pilocarpine as well in accordance with the pH-partition hypothesis (Shore et al. 1957), while analogous series of experiments with nonionizable drugs and glycerin have been reported to give similar results (Sieg and Robinson 1977). Here, there is additional consideration around an extent of pH-induced lacrimation by the liquid topical ophthalmic vehicle, and the effect on precorneal drug concentration was determined to partially increase pilocarpine absorption at neutral to slightly alkaline pH. Comparisons against neutral, nonionizable controls suggested a primary relationship to pilocarpine's unique solubility characteristics coupled with less irritation and lacrimation, rather than a direct pH effect on the molecule (Sieg and Robinson 1977). Analogously, previous studies provided support for further development of L-carnosine as a functionally synergistic buffer for topical ophthalmic use, with pharmaceutical compatibility in the context of dosage forms displaying in situ gel-formation properties following eye drop mixing with resident tear fluid. L-Carnosine was shown to have higher buffering capacity (its buffer capacity, b, ranged from 0.002 to 0.01 at 7.5–44 mM of the dipeptide) when compared to tromethamine (e.g., TRIS) at pH values of 6.5–7.6, and superior stability (L-carnosine appeared to be 3–4 times more resistant to thermal acid/base-driven decomposition under most limiting conditions) when assessed against L-histidine (e.g., a common biologic buffer). For ophthalmic pharmacology and therapeutics, where a broad spectrum of topical (or injectable) ophthalmic agents require chronic dosing because of disease etiology or pharmacological mechanism of action, use of L-carnosine as a buffer was proposed to enable applications of emerging sustained delivery technologies which utilize osmotic or ionic in situ gel formation to slow down the clearance of small molecules or biologics from ocular compartments (Singh et al. 2009). Overall, based on the comparatively lower physiological buffering capacity of ocular fluids than that of blood *(*i.e. *blood, plasma, and red blood cells combined—*e.g.*, the typical central compartment for drug distribution—in contrast have virtually unlimited buffering capacity* (Salenius 1957)*)*, the final pH and chemical buffer content of liquid ophthalmic products have to be carefully controlled. A global examination of known liquid ophthalmic products (Table 1) indicates that pH is targeted close to neutrality and the concentrations of exogenous buffers used in the product are maintained to a level sufficient to guarantee product quality and not interfere with endogenous ocular physiological pH (which can cause irritation and inter-ocular compartment boundary compromise) (Aguirre et al. 2018; Marra et al. 2011; Younis et al. 2008). Limited examples of drug products displaying a final pH (or range) significantly away from 7 exist, and despite the fact that these come with a strong case from a drug product quality point of view, the adequacy of such digressions from guidance criteria set forth by ocular physiological constraints is contextual, i.e., related to the nature of disease conditions and almost exclusively acute duration of treatment (as opposed to chronic conditions).

Osmolarity and Osmolality

In addition to the pH specification in liquid ophthalmic drug products, the final osmolarity of formulations (typically estimated using freezing point depression approach (Tomlinson et al. 2010)) is another essential biophysical and physiological compatibility attribute. Total solute content has been demonstrated to play a key role in injectable and topical ophthalmic liquid products. Formerly called osmolarity, by definition an osmotic concentration is the product of the osmolality and the mass density of water, in which osmolality is the quotient of the negative natural logarithm of the rational activity of water and the molar mass of water (McNaught and Wilkinson 1997, 2006). Conrad et al. published one of the earliest plausible investigations on the influence of tonicity (in addition to previously discussed pH and local ocular or systemic anesthesia) on lacrimation and topical ocular drug bioavailability. Employing the state-of-the-art microscintigraphy monitoring systems at the time, radiotracer signal dilution was detected in the tear film with hypertonic liquid formulations, suggesting considerable increase in lacrimation. The same was not evident with hypotonic formulations. Furthermore, this relationship of osmolarity and lacrimation had a proxy to ocular pharmacokinetic exposures, in an inverse relationship, where greatest ocular bioavailability was observed with deionized formulations containing a probe/drug, and hypertonicity (up to four times isotonic) giving the lowest (Conrad et al. 1978). Additional influential factors over extents and peak exposures elucidated from these studies were found to depend on precorneal contact time and mixing efficiency with the resident tear film (Conrad et al. 1978; Patton and Robinson 1975; Sieg and Robinson 1975, 1977; Singh et al. 2009). Limiting mechanisms which are apparently exerted by total solute concentration in liquid ophthalmic dosage forms are relative to the tonicity of the blood. While several different explanations exist, in the scenario where formulation osmolarity exceeds physiological tonicity, another phenomenon of rapid fluid extraction from ocular compartments into the vicinity of instilled dose can occur, effectively diluting the total dose in situ and decreasing the driving force for passive diffusive mass transfer to surrounding ocular compartments (Maurice 1971, 1980). From a liquid formulation design perspective, this can have implications on maximal amounts of inactive (esp. solubilizers, co-solvents, buffers, cyclodextrins, surfactants) and active ingredients that can act as solutes or osmolytes, which should be considered during ophthalmic safety and efficacy evaluations. Since excipients often make up a majority of the weight to volume ratio in liquid ophthalmic products, their contribution to osmolarity and final pH is also of paramount importance (Aguirre et al. 2018). Prolonged ocular dosing compartment exposure to hypertonic solutions, e.g., topical or intravitreal ophthalmic delivery, has been shown to be benign on epithelial barrier permeability. However, the opposite is true for hypoosmotic compositions introduced to ocular tissue compartments, which are reported to elicit transient increases in epithelial permeability from a topical delivery perspective, or microscopic findings manifesting themselves as mild retinal degeneration with emergence

of eosinophilic bodies from an intravitreal delivery perspective (Aguirre et al. 2018; Maurice 1980).

The ionic content of ocular fluids is known to be modulated on a molecular and cellular level by several endogenous and pharmacological factors of relevance in the eye. Liquid ophthalmic dosage forms which are administered into various compartments of the eye require fine-tuning of their pharmaceutical and pharmacological properties that directly or indirectly influence osmolyte balance to further ensure compatibility, safety, and efficacy. In the anterior segment of the eye, epithelial tissues which line the entire ocular surface and come into full contact with topical liquid ophthalmic dosage forms have been characterized in terms of active and passive net fluid transfer rates across corneal and conjunctival epithelial cells. Chloride is the most abundant physiological anion, and its movement across cell membranes and mucosa/serosa of epithelial tissue layers is known to be tightly coupled to the osmotically driven flux of sodium (an abundant, physiological extracellular cation) (Mobasheri et al. 2005; Pusch and Jentsch 1994). Characterization of active ion transport in the presence and absence of molecules known to affect chloride secretion and sodium absorption in corneal and conjunctival epithelial tissues indicated that the cornea is primarily a sodium absorptive tissue, while the conjunctiva plays a largely chloride secretory role (Chang-Lin et al. 2005; Kompella et al. 1993; Shiue et al. 1998, 2000). This asymmetrical transfer of physiological ions to and from tear fluid by ocular epithelial tissues is thought to modulate composition and concentration of drugs and other solutes within the context of topical ophthalmic liquid dosage forms. While transient perturbation of this osmotic balancing mechanism by extremes in liquid formulation solute content has been shown to result in changes in drug permeability across ocular epithelia (Scholz et al. 2002), the absolute osmolarity of endogenous tear film present on ocular surface is also known to behave as a biomarker for prognosis at various degrees (e.g., mild to moderate) of dry eye disease (Tomlinson et al. 2006; Rocha et al. 2017). Toward addressing the latter, several liquid formulations of secretagogues have been tested in the treatment of ocular surface inflammation relief and tear film dysfunction, most prominent of which maybe diquafosol (Nichols et al. 2004), a purinergic receptor agonist which stimulates chloride coupled net fluid flow into the tear film (Hosoya et al. 2005; Dartt 2002; Shiue et al. 1998; Kompella et al. 1993). Osmotically driven fluid flux also plays a key role in the production of aqueous humor by ciliary epithelial cells. Here, the presence of bicarbonate exchange mechanisms found in the non-pigmented ciliary epithelium has been capitalized pharmaceutically, evidenced by well-documented slowing in the rate of aqueous humor production elicited by carbonic anhydrase inhibitors (e.g., compounds found in liquid ophthalmic drug products like AZOPT® (https://www.accessdata.fda.gov/ 1998) and TRUSOPT® (https://www.accessdata.fda.gov/ 1994)) which reduce the supply of ciliary epithelial cell cytoplasmic bicarbonate (Delamere 2005). Lastly, in the anterior chamber of the eye, fluid (possibly also by virtue of aquaporin water channels (Thiagarajah and Verkman 2002)) coupled anion secretion requires transcorneal endothelial cell net flux of chloride, bicarbonate, and/or lactate, the modulation of which through endogenous factors—such as aging—or exogenous factors which can be introduced

through intracameral introduction of various ophthalmic drug products can play a role in cause or therapy for corneal stromal swelling or edema (Bonanno 2012). In the posterior segment of the eye, hypertonicity in liquid injectable ophthalmic preparations has been shown to exert macroscopic changes on a cellular level in retinal tissues in pathology reports (Aguirre et al. 2018). Furthermore, pharmacological findings suggested that INS37217 (a structural analog diquafosol, a secretagogue discussed earlier in the anterior segment setting) was able to stimulate fluid secretion from vitreous-to-choroid direction by activating similar chloride coupled osmotic movement mechanisms in retinal pigmented epithelial cells enhancing the rates of subretinal fluid reabsorption in certain experimentally induced retinal detachments (Maminishkis et al. 2002). Overall, therapeutic usefulness for selective solute control in liquid ophthalmic drug products within the context of treating a variety of retinal diseases that result in fluid accumulation in various posterior segment tissue compartments requires further study to determine if the described osmolarity linked mechanisms could be additive or synergistic in nature.

Inactive Ingredients Found in Liquid Ophthalmic Products

A high-level, global survey of known liquid ophthalmic drug products (Table 1) suggests that the arsenal of excipients available for use in product development is remarkably sparse (e.g., in comparison to other routes of parenteral drug administration). Selection of optimal route for ocular delivery depends on multiple factors, intuitively including the disease condition being treated, ocular tissue physiology (e.g., retina, choroid, and iris-ciliary body) that is targeted for pharmacological intervention, desired treatment modality or duration, as well as patient-disease demographics. Selection of key excipients in liquid ophthalmic drug products involves stratified rationale considerations. Initially choices may be limited from a pragmatic perspective, for example, precedence of use and prior utilization in a reference listed ophthalmic drug product as found in the Inactive Ingredient Search for Approved Drug Products or the Orange Book (https://www.accessdata.fda.gov/ 2019; https://www.hhs.gov/ 2019), or availability of parenteral and pharmaceutical grade excipient bulk from manufacturers which perform compendia testing on the material. However, ultimate restrictions most often come from a lack of basic scientific understanding about the full tolerability and disposition of the preferred inactive ingredients within an ocular context. Secondly, selections of excipients should be driven by a conventional functional role and appropriate requirement within the context of drug product quality, safety, and consistent performance (Rowe et al. 2012). Several existing reports have done a systematic evaluation of various functional excipients from an in vivo veterinary medicine (observational tests, e.g., the Draize eye test) and post-hoc tissue histopathology perspective, although there is limitation to translation from preclinical species to humans (Abraham et al. 2003; Wilhelmus 2001). Emerging research in this specific area of excipient qualification to enable ophthalmic drug delivery and product development could be highly

helpful and influential in understanding the safety limits around selection of inactive ingredients in liquid ophthalmic products for development of topical eye drops, intravitreal and sub-tenon injections, or other novel routes of administration into this organ (Aguirre et al. 2012, 2018; Blandford et al. 1992; Younis et al. 2008).

Within this context, a unique and specific consideration among preservatives in liquid ophthalmic products is worthwhile to mention. Although preservatives are technically not inactive ingredients in liquid ophthalmic products, particular basic physiological research reports about additional roles (over those of known bactericidal and bacteriostatic activity) preservatives play in liquid eye products are noteworthy. Benzalkonium chloride has probably one of the most lengthy track records of use in topical eye drop products; however, it is not devoid of limitations in safety and tolerability which have over time resulted in the advent of alternatives like Polyquad, Purite®, and SofZia® (Ammar et al. 2010; Kahook and Noecker 2008; Dong et al. 2004). Furthermore, investigations on the influence benzalkonium chloride and commonly co-employed ethylene diamine tetra-acetic acid on the permeability of several ophthalmic drugs used for management of glaucoma showed a general trend in facilitating drug transport across the cornea and conjunctiva. This was partially attributed to some level of toxic effect that benzalkonium chloride has on ocular epithelial cells, permeabilizing them possibly transiently, however not insignificantly (Ashton et al. 1991; Scholz et al. 2002).

Historical accounts of off-label use of triamcinolone acetonide (a steroidal anti-inflammatory drug substance) within liquid ophthalmic drug product space presented as Kenalog-40® (https://www.accessdata.fda.gov/ 1965) provides a compelling retrospective argument supporting the importance of careful excipient selection within this pharmaceutical development space. Before the advent of TRIESENCE™ (https://www.accessdata.fda.gov/ 2007), Kenalog-40® was widely used via intravitreal and sub-tenon injection routes to treat ocular diseases, such as varieties of noninfectious uveitis and diabetic macular edema (Jonas 2006; Kovacs et al. 2012). As Kenalog-40® evolved into the most widely injected liquid parenteral drug product for triamcinolone acetonide application in various intraocular neovascular and edematous diseases, purification of triamcinolone suspension from this product (designed for intramuscular or intra-articular use only (https://www.accessdata.fda.gov/ 1965)) became important. Once it was clear that the solvent agent was better removed, in order to avoid the potential toxic effects of the vehicle, evaluations of different techniques used to reduce benzyl alcohol (~0.9–1%w/v) from commercially prepared triamcinolone acetonide suspensions were researched and published (Garcia-Arumi et al. 2005; Jonas 2006). Subsequent, more thorough histopathological evaluations of benzyl alcohol showed that the lack of toleration following the excipient's use in liquid ophthalmic preparations was manifested as conjunctival swelling, corneal and intraglobal opacities, and corneal lesions arising from multiple concentrations and compendia/purity grades available for testing (Younis et al. 2008). Overall, it is important to take a systematic and deliberate approach in the selection and qualification of all inactive ingredients present in liquid ophthalmic drug products, keeping in mind the physiological considerations around the actual, final physiological route of administration into the eye.

Manufacturing Considerations

As introduced earlier, all liquid ophthalmic products—occurring as solutions, suspensions, or more complex dosage forms of small molecules and compounds derived from biological sources—are specialized parenteral dosage forms, e.g., sterile products, that are intended for application to ocular compartments including locations adjacent to the eye and its immediate surrounding periorbital tissues. Ophthalmic routes of administration for liquid products include, but are not limited to: topical drops, subconjunctival, sub-tenon capsule, subretinal, sub- or suprachoroidal, intracorneal, intrascleral, intravitreal, intracameral, juxtascleral, and retrobulbar injection routes (Ghate and Edelhauser 2006). While Table 1 shows a comprehensive list of liquid ophthalmic products, with several off-label used parenterals in an ocular setting, this section succinctly enumerates consolidated, common liquid ophthalmic product preparation and quality test considerations which would apply for manufacturing. The current, electronic, United States Pharmacopeia chapter 771, with encompassed references, is recommended as a helpful resource for obtaining details on new manufacturing guidelines toward de novo development of liquid ophthalmic drug product monographs (United States Pharmacopeial Convention. Committee of Revision, 1979; United States Pharmacopeial Convention).

Sterilization process considerations add one of several important product development boundaries to selected physical, chemical, and formulation attributes for liquid ophthalmic products. Depending on the drug substance, packaging selection for route of administration and final liquid delivery vehicle composition, degradation, and/or morphological changes can occur to liquid suspensions and colloidal systems during sterilization. A particle size cutoff of <0.2 μm is required to consider filtration as a method of terminal sterilization for a liquid ophthalmic drug product. While aseptic processing remains a feasible option, the manufacture of sterile liquid ophthalmic products within class 10 or 100 clean rooms could be limiting to scale and flexibility. Design considerations for the development of steam-in-place sterilization processes, by introduction of pressurized steam into the internal cavities of a vessel used for liquid ophthalmic product manufacturing, have proven to be an effective means of making sure large, stationery processing equipment is compliant with sterility guidelines. While steam-in-place sterilization has several engineering control nuances, it does offer an advantage by potentially eliminating the need for aseptic processing or individual assembly of component parts within a manufacturing line. The latter can still introduce a risk of equipment contamination due to several possible root causes. Many liquid ophthalmic products, which are unit-dose and unpreserved, are manufactured under steam-in-place system procedures which allow the flexibility of non-aseptic fabrication followed by complete sterilization of the closed system carrying the product (Myers and Chrai 1980, 1981, 1982).

Limited aqueous solubility of drug substances is typically the most common consideration leading toward the development of suspension or colloidal-emulsion ophthalmic products (as opposed to aqueous solutions). Emulsion formulation

manufacture is within a unique complex drug product category, as establishment of pharmaceutical and bioequivalence between two colloidal liquid ophthalmic products carrying the same drug substance is complicated and challenging (if not, in many cases pragmatically impossible). For such liquid ophthalmic complex drug products (e.g., cyclosporin A containing dosage forms of Restasis® (0.5 mg/mL), Ikervis® (1.0 mg/mL), Papilock mini® (1.0 mg/mL), Modusik-A Ofteno® (1.0 mg/mL), Lacrinmune® (0.5 mg/mL), TJ Cyporin® (0.5 mg/mL), Cyporin® (0.5 mg/mL), and Cyclorin® (0.5 mg/mL) (Lallemand et al. 2017)), it has been documented that "the manufacturing process is the product," i.e., a well-controlled and well-understood production and scale-up procedure should be engineered to guarantee reproducible product quality, safety, and performance (de Vlieger et al. 2019; Hussaarts et al. 2017). Topical ophthalmic emulsions are generally prepared by dissolving a drug substance into an oil phase, including a suitable emulsifying agent, considering additional suspending excipients, and mixing with the liquid aqueous phase vigorously to homogenize an oil-in-water emulsion. Essentially two macroscopic phases exist, where each phase—the oil and aqueous—is normally sterilized in advance or concurrently with charging into mixing vessel. High-shear homogenization is one approach which can be used to reduce emulsion droplet sizes to (sub) micron distributions, desirable toward improving physical stability of unit micelles by slowing their coalescing rate.

Once prototypical liquid ophthalmic drug products are manufactured, procedures for testing and accepting them need to be developed. Assessment of general quality attributes, e.g., identification, potency, purity (and impurities), sterility, and particulate matter, and in vitro product performance, i.e., dissolution or drug release of the drug substance from a suspension or colloidal drug product, can be found in USP (United States Pharmacopeial Convention. Committee of Revision. 1979; United States Pharmacopeial Convention.). 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. For example, the aforementioned physicochemical and biophysical considerations around the final pH and solute content, specific to liquid ophthalmic dosage forms, are described in USP ⟨pH 791⟩ and⟨osmolality and osmolarity 785⟩. Additionally, liquid ophthalmic drug products are required to be essentially free of visible foreign (extrinsic or intrinsic) particulates and subvisible particles in intra- or extra-ocular injectables. Besides terminal sterilization considerations discussed earlier, further analyses of effectiveness in antimicrobial preservatives (in the case of multidose liquids ophthalmics) and minimization of bacterial endotoxins (e.g., pyrogen-free) are essential (United States Pharmacopeial Convention. Committee of Revision 1979; United States Pharmacopeial Convention).

Design and validation of specific tests is necessary to build a good understanding and proper.

control over the manufacturing process critical for a reproducible, high-quality liquid ophthalmic drug product. For colloidal systems and some suspensions, development of such tests may pose challenges. Active ingredient release testing conducted on complex liquid colloidal ophthalmic drug products or suspensions

manufactured under boundary conditions and compared to drug products that are intentionally prepared with meaningful variations in formulation and manufacturing sensitive parameters (i.e., particle size distribution, dose or drug loading, types and/or amounts of inactive ingredients) maybe far from predictive in terms of ophthalmic bioequivalence. The extents and degrees of sensitivity analysis require further discussion and research; although it is pragmatically unachievable to ascertain robust in vitro-in vivo correlations with these assays in an ophthalmic setting, some in vitro release tests and in silico simulations and modeling tools still represent promising avenues for evaluating their ability to distinguish performance (de Vlieger et al. 2019; Gukasyan et al. 2019b; Hussaarts et al. 2017). Several additional specific tests which maybe discriminating from a performance of a manufactured liquid ophthalmic product perspective include those around viscosity, particle size distribution, and inactive ingredients. Inclusion of viscosity evaluations in the specification of liquid ophthalmic products should be based on the types of dosage forms and whether changes in product viscosity will affect the overall performance. For example, in liquid suspensions, depending on the vehicles' viscosity, if drug particles settle and cake, they must re-disperse promptly in users' hands to achieve proper dose uniformity and accurate delivery. As mentioned earlier, the opposite is the case for viscosity influence on reliable eye-drop volume dispensing (vs. nozzle engineering) (Brown and Lynch 1986; Lederer and Harold 1986). While particle size and distributions can impact the intensity and duration of ophthalmic pharmacokinetics, the potential for any changes in particle size of ophthalmic suspensions and emulsions also needs to be evaluated. Lastly suitable substances may be added to ophthalmic products to increase stability, provided they are benign in the amounts administered and do not interfere with therapeutic efficacy or with responses to the specified manufacturing-related assays and quality tests (United States Pharmacopeial Convention.; United States Pharmacopeial Convention. Committee of Revision 1979).

In recent years the field of ophthalmic drug discovery and development has witnessed what some experts in the field call a renaissance (Yerxa 2018). With the advent of gene therapies which promise to be thus far the most curative solutions to several genetically inherited retinal diseases, and several new chemical entities being introduced as novel pharmacological mechanisms for management of glaucoma and dry eye disease, the importance of pharmaceutical development of liquid ophthalmic dosage forms remains essential (Gukasyan et al. 2019a). Discovery efforts continue toward treatment of rare genetic ocular diseases, neuroprotection from damage caused by glaucoma at the optic nerve head, and prevention of neovascular wet age-related macular degeneration (AMD) through inhibition and reversal of dry AMD, demand for additional pharmaceutical technology research, and development to support novel drugs in the pipeline. Considerations discussed here for drug substance (any modality), drug product blueprint attributes, and sterile manufacturing guidelines will remain vital and fundamental in clinical testing and commercialization for future progressive liquid ophthalmic drug products.

References

Abraham MH, Hassanisadi M, Jalali-Heravi M, Ghafourian T, Cain WS, Cometto-Muniz JE. Draize rabbit eye test compatibility with eye irritation thresholds in humans: a quantitative structure-activity relationship analysis. Toxicol Sci. 2003;76(2):384–91. https://doi.org/10.1093/toxsci/kfg242.

Aguirre SA, Collette W III, Gukasyan HJ, Huang W. An assessment of the ocular safety of excipient maleic acid following intravitreal injection in rabbits. Toxicol Pathol. 2012;40(5):797–806. https://doi.org/10.1177/0192623312441400.

Aguirre SA, Gukasyan HJ, Younis HS, Huang W. Safety assessment of formulation vehicles following intravitreal administration in rabbits. Pharm Res. 2018;35(9):173. https://doi.org/10.1007/s11095-018-2450-1.

Ahmed I, Gokhale RD, Shah MV, Patton TF. Physicochemical determinants of drug diffusion across the conjunctiva, sclera, and cornea. J Pharm Sci. 1987;76(8):583–6.

Ammar DA, Noecker RJ, Kahook MY. Effects of benzalkonium chloride-preserved, polyquad-preserved, and sofZia-preserved topical glaucoma medications on human ocular epithelial cells. Adv Ther. 2010;27(11):837–45. https://doi.org/10.1007/s12325-010-0070-1.

Ashton P, Podder SK, Lee VH. Formulation influence on conjunctival penetration of four beta blockers in the pigmented rabbit: a comparison with corneal penetration. Pharm Res. 1991;8(9):1166–74.

Bevacizumab (AVASTIN) and age-related macular degeneration. Lower cost does not justify taking risks. Prescrire Int. 2015;24(163):201–4.

Bhagav P, Deshpande P, Pandey S, Chandran S. Development and validation of stability indicating UV spectrophotometric method for the estimation of brimonidine tartrate in pure form, formulations and preformulation studies. Pharm Lett. 2010;2(3):106–22.

Blandford DL, Smith TJ, Brown JD, Pearson PA, Ashton P. Subconjunctival sustained release 5-fluorouracil. Invest Ophthalmol Vis Sci. 1992;33(12):3430–5.

Bonanno JA. Molecular mechanisms underlying the corneal endothelial pump. Exp Eye Res. 2012;95(1):2–7. https://doi.org/10.1016/j.exer.2011.06.004.

Breda SA, Jimenez-Kairuz AF, Manzo RH, Olivera ME. Solubility behavior and biopharmaceutical classification of novel high-solubility ciprofloxacin and norfloxacin pharmaceutical derivatives. Int J Pharm. 2009;371(1–2):106–13. https://doi.org/10.1016/j.ijpharm.2008.12.026.

Brown RH, Lynch MG. Drop size of commercial glaucoma medications. Am J Ophthalmol. 1986;102(5):673–4.

Carney LG, Hill RM. Human tear pH. Diurnal variations. Arch Ophthalmol. 1976;94(5):821–4.

Carney LG, Mauger TF, Hill RM. Buffering in human tears: pH responses to acid and base challenge. Invest Ophthalmol Vis Sci. 1989;30(4):747–54.

Chang-Lin JE, Kim KJ, Lee VH. Characterization of active ion transport across primary rabbit corneal epithelial cell layers (RCrECL) cultured at an air-interface. Exp Eye Res. 2005;80(6):827–36. https://doi.org/10.1016/j.exer.2004.12.012.

Chen SL, Png E, Tong L. Comparison of two artificial tear formulations using aberrometry. Clin Exp Optom. 2009;92(6):519; author reply 519. https://doi.org/10.1111/j.1444-0938.2009.00421.x.

Chien DS, Homsy JJ, Gluchowski C, Tang-Liu DD. Corneal and conjunctival/scleral penetration of p-aminoclonidine, AGN 190342, and clonidine in rabbit eyes. Curr Eye Res. 1990;9(11):1051–9. https://doi.org/10.3109/02713689008997579.

Coles WH, Jaros PA. Dynamics of ocular surface pH. Br J Ophthalmol. 1984;68(8):549–52.

Conrad JM, Reay WA, Polcyn RE, Robinson JR. Influence of tonicity and pH on lacrimation and ocular drug bioavailability. J Parenter Drug Assoc. 1978;32(4):149–61.

Dartt DA. Regulation of mucin and fluid secretion by conjunctival epithelial cells. Prog Retin Eye Res. 2002;21(6):555–76.

Delamere NA. Ciliary body and ciliary epithelium. Adv Organ Biol. 2005;10:127–48. https://doi.org/10.1016/S1569-2590(05)10005-6.

Diehl H, Markuszewski R. Studies on fluorescein-II the solubility and acid dissociation constants of fluorescein in water solution. Talanta. 1985;32(2):159–65.
Dong JQ, Babusis DM, Welty DF, Acheampong AA, Tang-Liu D, Whitcup SM. Effects of the preservative purite on the bioavailability of brimonidine in the aqueous humor of rabbits. J Ocul Pharmacol Ther. 2004;20(4):285–92. https://doi.org/10.1089/1080768041725326.
Edward A, Prausnitz MR. Predicted permeability of the cornea to topical drugs. Pharm Res. 2001;18(11):1497–508.
El-Qutob D. Off-label uses of Omalizumab. Clin Rev Allergy Immunol. 2016;50(1):84–96. https://doi.org/10.1007/s12016-015-8490-y.
Fazelat A, Lashkari K. Off-label use of intravitreal triamcinolone acetonide for diabetic macular edema in a pregnant patient. Clin Ophthalmol. 2011;5:439–41. https://doi.org/10.2147/OPTH.S14584.
FDA. Kenalog®-40 injection. 1965. https://www.accessdata.fda.gov/, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/014901s042lbledt.pdf.
FDA. PRED FORTE®. 1973. https://www.accessdata.fda.gov/, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/017011s047lbl.pdf.
FDA. TRUSOPT®. 1994. https://www.accessdata.fda.gov/, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020408s047lbl.pdf.
FDA. ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%. 1996. https://www.accessdata.fda.gov/, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020613s031lbl.pdf.
FDA. Azopt®. 1998. https://www.accessdata.fda.gov/, https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020816s009lbl.pdf.
FDA. ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% or 0.15%. 2001, 2006. https://www.accessdata.fda.gov/, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021262s020,021770s004lbl.pdf.
FDA. TRIESENCE™. 2007. https://www.accessdata.fda.gov/, https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022223,022048lbl.pdf.
FDA. (2019) Inactive ingredient search for approved drug products. https://www.accessdata.fda.gov/, https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.
Fishman GA. Ocular phototoxicity: guidelines for selecting sunglasses. Surv Ophthalmol. 1986;31(2):119–24.
Food and Drug Administration, Center for Drug Evaluation and Research. Orange book: approved drug products with therapeutic equivalence evaluations. 2019. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.
Friedrich S, Saville B, Cheng YL. Drug distribution in the vitreous humor of the human eye: the effects of aphakia and changes in retinal permeability and vitreous diffusivity. J Ocul Pharmacol Ther. 1997;13(5):445–59. https://doi.org/10.1089/jop.1997.13.445.
Gan IM, van Dissel JT, Beekhuis WH, Swart W, van Meurs JC. Intravitreal vancomycin and gentamicin concentrations in patients with postoperative endophthalmitis. Br J Ophthalmol. 2001;85(11):1289–93. https://doi.org/10.1136/bjo.85.11.1289.
Garcia-Arumi J, Boixadera A, Giralt J, Martinez-Castillo V, Gomez-Ulla F, Corcostegui B, Garcia-Arumi E. Comparison of different techniques for purification of triamcinolone acetonide suspension for intravitreal use. Br J Ophthalmol. 2005;89(9):1112–4. https://doi.org/10.1136/bjo.2005.067744.
Ghate D, Edelhauser HF. Ocular drug delivery. Expert Opin Drug Deliv. 2006;3(2):275–87. https://doi.org/10.1517/17425247.3.2.275.
Gonnering R, Edelhauser HF, Van Horn DL, Durant W. The pH tolerance of rabbit and human corneal endothelium. Invest Ophthalmol Vis Sci. 1979;18(4):373–90.
Green K, Kearse EC, Yokogaki S, Awata T. Human and rabbit corneal endothelial permeability after different chemical forms of glutathione. Ophthalmic Res. 2001;33(3):151–5. https://doi.org/10.1159/000055662.
Gukasyan HJ, Hailu S, Karami TK. Ophthalmic drug discovery and development. Pharm Res. 2019a;36(5):69. https://doi.org/10.1007/s11095-019-2606-7.

Gukasyan HJ, Hailu S, Karami TK, Graham R. Ocular biopharmaceutics: impact of modeling and simulation on topical ophthalmic formulation development. Drug Discov Today. 2019b; https://doi.org/10.1016/j.drudis.2019.04.002.

Gurbay A, Hincal F. Ciprofloxacin-induced glutathione redox status alterations in rat tissues. Drug Chem Toxicol. 2004;27(3):233–42. https://doi.org/10.1081/DCT-120037504.

Hamalainen KM, Kananen K, Auriola S, Kontturi K, Urtti A. Characterization of paracellular and aqueous penetration routes in cornea, conjunctiva, and sclera. Invest Ophthalmol Vis Sci. 1997;38(3):627–34.

He Y, Li P, Yalkowsky SH. Solubilization of fluasterone in cosolvent/cyclodextrin combinations. Int J Pharm. 2003;264(1–2):25–34.

Hilfiker R, Blatter F, von Raumer M. Relevance of solid-state properties for pharmaceutical products, in polymorphism: in the pharmaceutical industry. Weinheim: Wiley; 2006.

Hind HW, Goyan FM. A new concept of the role of hydrogen ion concentration and buffer system in the preparation of ophthalmic solutions. J Am Pharm Assoc Am Pharm Assoc. 1947;36(2):33–41.

Hogben CA, Tocco DJ, Brodie BB, Schanker LS. On the mechanism of intestinal absorption of drugs. J Pharmacol Exp Ther. 1959;125(4):275–82.

Hosoya K, Lee VH, Kim KJ. Roles of the conjunctiva in ocular drug delivery: a review of conjunctival transport mechanisms and their regulation. Eur J Pharm Biopharm. 2005;60(2):227–40. https://doi.org/10.1016/j.ejpb.2004.12.007.

Hussaarts L, Muhlebach S, Shah VP, McNeil S, Borchard G, Fluhmann B, Weinstein V, Neervannan S, Griffiths E, Jiang W, Wolff-Holz E, Crommelin DJA, de Vlieger JSB. Equivalence of complex drug products: advances in and challenges for current regulatory frameworks. Ann N Y Acad Sci. 2017;1407(1):39–49. https://doi.org/10.1111/nyas.13347.

Jackson TL, Williamson TH. Amikacin retinal toxicity. Br J Ophthalmol. 1999;83(10):1199–200. https://doi.org/10.1136/bjo.83.10.1194f.

Jonas JB. Intravitreal triamcinolone acetonide: a change in a paradigm. Ophthalmic Res. 2006;38(4):218–45. https://doi.org/10.1159/000093796.

Kahook MY, Noecker RJ. Comparison of corneal and conjunctival changes after dosing of travoprost preserved with sofZia, latanoprost with 0.02% benzalkonium chloride, and preservative-free artificial tears. Cornea. 2008;27(3):339–43. https://doi.org/10.1097/ICO.0b013e31815cf651.

Kansy M, Senner F, Gubernator K. Physicochemical high throughput screening: parallel artificial membrane permeation assay in the description of passive absorption processes. J Med Chem. 1998;41(7):1007–10. https://doi.org/10.1021/jm970530e.

Kidron H, Vellonen KS, del Amo EM, Tissari A, Urtti A. Prediction of the corneal permeability of drug-like compounds. Pharm Res. 2010;27(7):1398–407. https://doi.org/10.1007/s11095-010-0132-8.

Kompella UB, Kim KJ, Lee VH. Active chloride transport in the pigmented rabbit conjunctiva. Curr Eye Res. 1993;12(12):1041–8.

Kovacs K, Wagley S, Quirk MT, Ceron OM, Silva PA, Singh RJ, Gukasyan HJ, Arroyo JG. Pharmacokinetic study of vitreous and serum concentrations of triamcinolone acetonide after posterior sub-tenon's injection. Am J Ophthalmol. 2012;153(5):939–48. https://doi.org/10.1016/j.ajo.2011.10.021.

Lallemand F, Schmitt M, Bourges JL, Gurny R, Benita S, Garrigue JS. Cyclosporine A delivery to the eye: a comprehensive review of academic and industrial efforts. Eur J Pharm Biopharm. 2017;117:14–28. https://doi.org/10.1016/j.ejpb.2017.03.006.

Lalwani GA, Berrocal AM, Murray TG, Buch M, Cardone S, Hess D, Johnson RA, Puliafito CA. Off-label use of intravitreal bevacizumab (Avastin) for salvage treatment in progressive threshold retinopathy of prematurity. Retina. 2008;28(3 Suppl):S13–8. https://doi.org/10.1097/IAE.0b013e3181644ad2.

Lederer CM Jr, Harold RE. Drop size of commercial glaucoma medications. Am J Ophthalmol. 1986;101(6):691–4.

Lee VH, Robinson JR. Topical ocular drug delivery: recent developments and future challenges. J Ocul Pharmacol. 1986;2(1):67–108.
Leibowitz HM, Kupferman A, Stewart RH, Kimbrough RL. Evaluation of dexamethasone acetate as a topical ophthalmic formulation. Am J Ophthalmol. 1978;86(3):418–23.
Lexi-Comp Inc., American Pharmacists Association. Pediatric & neonatal dosage handbook. Lexi Comp's drug reference handbooks. LexiComp; American Pharmacists Association, Hudson, OH, Washington, DC.
Liu Y, Kam WR, Ding J, Sullivan DA. One man's poison is another man's meat: using azithromycin-induced phospholipidosis to promote ocular surface health. Toxicology. 2014;320:1–5. https://doi.org/10.1016/j.tox.2014.02.014.
Lu DW, Chang CJ, Wu JN. The changes of vitreous pH values in an acute glaucoma rabbit model. J Ocul Pharmacol Ther. 2001;17(4):343–50. https://doi.org/10.1089/108076801753162753.
Maminishkis A, Jalickee S, Blaug SA, Rymer J, Yerxa BR, Peterson WM, Miller SS. The P2Y(2) receptor agonist INS37217 stimulates RPE fluid transport in vitro and retinal reattachment in rat. Invest Ophthalmol Vis Sci. 2002;43(11):3555–66.
Maren TH, Bar-Ilan A, Conroy CW, Brechue WF. Chemical and pharmacological properties of MK-927, a sulfonamide carbonic anhydrase inhibitor that lowers intraocular pressure by the topical route. Exp Eye Res. 1990;50(1):27–36.
Marra MT, Khamphavong P, Wisniecki P, Gukasyan HJ, Sueda K. Solution formulation development of a VEGF inhibitor for intravitreal injection. AAPS PharmSciTech. 2011;12(1):362–71. https://doi.org/10.1208/s12249-011-9591-4.
Martin FN Jr, Mims JL. Preparation of ophthalmic solutions with special reference to hydrogen ion concentration and tonicity. AMA Arch Ophthalmol. 1950;44(4):561–72.
Masuzawa K, Suzue S, Hirai K, Ishizaki T. 8-Alkoxyquinolonecarboxylic acid and salts thereof. US 5,043,450; 1991.
Matsumoto T, Hara M, Miyashita K, Kato Y. 8-Alkoxyquinolonecarboxylic acid hydrate with excellent stability and process for producing the same. US5880283; 1999.
Maurice DM. The tonicity of an eye drop and its dilution by tears. Exp Eye Res. 1971;11(1):30–3.
Maurice DM. Factors influencing the penetration of topically applied drugs. Int Ophthalmol Clin. 1980;20(3):21–32.
McNaught AD, Wilkinson A. IUPAC. Compendium of chemical terminology. 2nd edn (the "gold book"). Blackwell Scientific Publications, Oxford; 1997, 2006. https://doi.org/10.1351/goldbook.
Meyer K, Palmer JW. On the nature of the ocular fluids. Am J Ophthalmol. 1936;19(10):859–65. https://doi.org/10.1016/S0002-9394(36)92723-X.
Missel PJ, Horner M, Muralikrishnan R. Simulating dissolution of intravitreal triamcinolone acetonide suspensions in an anatomically accurate rabbit eye model. Pharm Res. 2010;27(8):1530–46. https://doi.org/10.1007/s11095-010-0163-1.
Mitra AK. Ophthalmic drug delivery systems. Drugs and the pharmaceutical sciences, vol. 58. New York: Dekker; 1993.
Mobasheri A, Barrett-Jolley R, Shakibaei M, Canessa CM, Martin-Vasallo P. Enigmatic roles of the epithelial sodium channel (ENaC) in articular chondrocytes and osteoblasts: mechanotransduction, sodium transport or extracellular sodium sensing? In: Kamkin A, Kiseleva I, editors. Mechanosensitivity in cells and tissues. Moscow: Academia; 2005.
Mortimer RG, Eyring H. Elementary transition state theory of the Soret and Dufour effects. Proc Natl Acad Sci U S A. 1980;77(4):1728–31.
Myers T, Chrai S. Parenteral fundamentals. Basic principles and applications of bioindicators. J Parenter Drug Assoc. 1980;34(3):234–43.
Myers T, Chrai S. Design considerations for development of steam in-place sterilization processes. J Parenter Sci Technol. 1981;35(1):8–12.
Myers T, Chrai S. Steam-in-place sterilization of cartridge filters in-line with a receiving tank. J Parenter Sci Technol. 1982;36(3):108–12.

Newman A, Wenslow R. Solid form changes during drug development: good, bad, and ugly case studies. AAPS Open. 2016;2(1):2. https://doi.org/10.1186/s41120-016-0003-4.
Nichols KK, Yerxa B, Kellerman DJ. Diquafosol tetrasodium: a novel dry eye therapy. Expert Opin Investig Drugs. 2004;13(1):47–54. https://doi.org/10.1517/13543784.13.1.47.
Olejnik OK, E.D.S. Compositions containing α-2-adrenergic agonist components. USA Patent; 14 July 2000.
Palkama A, Uusitalo H, Raij K, Uusitalo R. Comparison of the effects of adrenergic agonists and alpha-, beta 1-, beta 2-antagonists on the intraocular pressure and adenylate cyclase activity in the ciliary processes of the rabbit. Acta Ophthalmol. 1985;63(1):9–15.
Paterson CA, Pfister RR, Levinson RA. Aqueous humor pH changes after experimental alkali burns. Am J Ophthalmol. 1975;79(3):414–9.
Patton TF, Robinson JR. Influence of topical anesthesia on tear dynamics and ocular drug bioavailability in albino rabbits. J Pharm Sci. 1975;64(2):267–71.
Pawar P, Katara R, Mishra S, Majumdar DK. Topical ocular delivery of fluoroquinolones. Expert Opin Drug Deliv. 2013;10(5):691–711. https://doi.org/10.1517/17425247.2013.772977.
PDR Network LLC. PDR drug information handbook. Montvale: PDR, LLC; 2016.
Photosafety evaluation of pharmaceuticals. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. 2019. https://www.ich.org/products/guidelines/.
Physicians' desk reference for ophthalmic medicines. Medical Economics, Montvale; 2000.
Pitkanen L, Ranta VP, Moilanen H, Urtti A. Permeability of retinal pigment epithelium: effects of permeant molecular weight and lipophilicity. Invest Ophthalmol Vis Sci. 2005;46(2):641–6. https://doi.org/10.1167/iovs.04-1051.
Prausnitz MR, Noonan JS. Permeability of cornea, sclera, and conjunctiva: a literature analysis for drug delivery to the eye. J Pharm Sci. 1998;87(12):1479–88.
Pusch M, Jentsch TJ. Molecular physiology of voltage-gated chloride channels. Physiol Rev. 1994;74(4):813–27. https://doi.org/10.1152/physrev.1994.74.4.813.
Raghava S, Hammond M, Kompella UB. Periocular routes for retinal drug delivery. Expert Opin Drug Deliv. 2004;1(1):99–114. https://doi.org/10.1517/17425247.1.1.99.
Raghaven KS, Ranadive SA, Gougoutas JZ, DiMarco JD, Parker WL, Davidovich M, Newman A. Gatifloxacin pentahydrate US6413969; 2002.
Ramsay E, Ruponen M, Picardat T, Tengvall U, Tuomainen M, Auriola S, Toropainen E, Urtti A, Del Amo EM. Impact of chemical structure on conjunctival drug permeability: adopting porcine conjunctiva and cassette dosing for construction of in silico model. J Pharm Sci. 2017;106(9):2463–71. https://doi.org/10.1016/j.xphs.2017.04.061.
Ramsay E, Del Amo EM, Toropainen E, Tengvall-Unadike U, Ranta VP, Urtti A, Ruponen M. Corneal and conjunctival drug permeability: systematic comparison and pharmacokinetic impact in the eye. Eur J Pharm Sci. 2018;119:83–9. https://doi.org/10.1016/j.ejps.2018.03.034.
Roberts JE. Screening for ocular phototoxicity. Int J Toxicol. 2002;21(6):491–500. https://doi.org/10.1080/10915810290169918.
Rocha G, Gulliver E, Borovik A, Chan CC. Randomized, masked, in vitro comparison of three commercially available tear film osmometers. Clin Ophthalmol. 2017;11:243–8. https://doi.org/10.2147/OPTH.S127035.
Rowe RC, Sheskey PJ, Cook WG, Fenton ME, American Pharmacists Association. In: Rowe RC, Sheskey PJ, Cook WG, Fenton ME, editors. Handbook of pharmaceutical excipients. 7th ed. London: APhA/Pharmaceutical Press; 2012.
Salenius P. A study of the pH and buffer capacity of blood, plasma and red blood cells. Scand J Clin Lab Invest. 1957;9(2):160–7.
Schoenwald RD, Huang H-S. Corneal penetration behavior of β-blocking agents I: physicochemical factors. J Pharm Sci. 1983a;72(11):1266–72. https://doi.org/10.1002/jps.2600721108.
Schoenwald RD, Huang HS. Corneal penetration behavior of beta-blocking agents I: physiochemical factors. J Pharm Sci. 1983b;72(11):1266–72.

Scholz M, Lin JE, Lee VH, Keipert S. Pilocarpine permeability across ocular tissues and cell cultures: influence of formulation parameters. J Ocul Pharmacol Ther. 2002;18(5):455–68. https://doi.org/10.1089/10807680260362731.

Scozzafava A, Menabuoni L, Mincione F, Briganti F, Mincione G, Supuran CT. Carbonic anhydrase inhibitors. Synthesis of water-soluble, topically effective, intraocular pressure-lowering aromatic/heterocyclic sulfonamides containing cationic or anionic moieties: is the tail more important than the ring? J Med Chem. 1999;42(14):2641–50. https://doi.org/10.1021/jm9900523.

Shen J, Lu GW, Hughes P. Targeted ocular drug delivery with pharmacokinetic/pharmacodynamic considerations. Pharm Res. 2018;35(11):217. https://doi.org/10.1007/s11095-018-2498-y.

Shirasaki Y. Molecular design for enhancement of ocular penetration. J Pharm Sci. 2008;97(7):2462–96. https://doi.org/10.1002/jps.21200.

Shiue MH, Kim KJ, Lee VH. Modulation of chloride secretion across the pigmented rabbit conjunctiva. Exp Eye Res. 1998;66(3):275–82. https://doi.org/10.1006/exer.1997.0459.

Shiue MH, Kulkarni AA, Gukasyan HJ, Swisher JB, Kim KJ, Lee VH. Pharmacological modulation of fluid secretion in the pigmented rabbit conjunctiva. Life Sci. 2000;66(7):PL105–11.

Shoghi E, Fuguet E, Bosch E, Rafols C. Solubility-pH profiles of some acidic, basic and amphoteric drugs. Eur J Pharm Sci. 2013;48(1–2):291–300. https://doi.org/10.1016/j.ejps.2012.10.028.

Shore PA, Brodie BB, Hogben CA. The gastric secretion of drugs: a pH partition hypothesis. J Pharmacol Exp Ther. 1957;119(3):361–9.

Sieg JW, Robinson JR. Vehicle effects on ocular drug bioavailability i: evaluation of fluorometholone. J Pharm Sci. 1975;64(6):931–6.

Sieg JW, Robinson JR. Vehicle effects on ocular drug bioavailability II: evaluation of pilocarpine. J Pharm Sci. 1977;66(9):1222–8.

Sieg JW, Robinson JR. Vehicle effects on ocular drug bioavailability III: shear-facilitated pilocarpine release from ointments. J Pharm Sci. 1979;68(6):724–8.

Singh SR, Carreiro ST, Chu J, Prasanna G, Niesman MR, Collette Iii WW, Younis HS, Sartnurak S, Gukasyan HJ. L-carnosine: multifunctional dipeptide buffer for sustained-duration topical ophthalmic formulations. J Pharm Pharmacol. 2009;61(6):733–42. https://doi.org/10.1211/jpp/61.06.0005.

Singhal D, Curatolo W. Drug polymorphism and dosage form design: a practical perspective. Adv Drug Deliv Rev. 2004;56(3):335–47. https://doi.org/10.1016/j.addr.2003.10.008.

Stahl PH, Wermuth CG, International Union of Pure and Applied Chemistry. Handbook of pharmaceutical salts: properties, selection, and use. 2nd rev ed. Weinheim: Wiley-VCH; 2011.

Tai MC, Lu DW, Chiang CH. Corneal and scleral permeability of quinolones--a pharmacokinetics study. J Ocul Pharmacol Ther. 2003;19(6):547–54. https://doi.org/10.1089/108076803322660468.

Thiagarajah JR, Verkman AS. Aquaporin deletion in mice reduces corneal water permeability and delays restoration of transparency after swelling. J Biol Chem. 2002;277(21):19139–44. https://doi.org/10.1074/jbc.M202071200.

Thompson AM. Ocular toxicity of fluoroquinolones. Clin Exp Ophthalmol. 2007;35(6):566–77. https://doi.org/10.1111/j.1442-9071.2007.01552.x.

Tomlinson A, Khanal S, Ramaesh K, Diaper C, McFadyen A. Tear film osmolarity: determination of a referent for dry eye diagnosis. Invest Ophthalmol Vis Sci. 2006;47(10):4309–15. https://doi.org/10.1167/iovs.05-1504.

Tomlinson A, McCann LC, Pearce EI. Comparison of human tear film osmolarity measured by electrical impedance and freezing point depression techniques. Cornea. 2010;29(9):1036–41. https://doi.org/10.1097/ICO.0b013e3181cd9a1d.

Tsuboi S, Kobayashi M, Nanba M, Imaoka S, Ohmori S. S-(1,2-dicarboxyethyl)glutathione and activity for its synthesis in rat tissues. J Biochem. 1990a;107(4):539–45. https://doi.org/10.1093/oxfordjournals.jbchem.a123082.

Tsuboi S, Ohnaka M, Ohmori S, Sakaue T, Ogata K, Itano T, Hatase O. Inhibition of platelet aggregation by S-(1,2-dicarboxyethyl)glutathione, intrinsic tripeptide in liver, heart, and lens. Arch Biochem Biophys. 1990b;279(1):146–50.

United States Pharmacopeial Convention. Committee of Revision. The United States pharmacopeia. Rockville: United States Pharmacopeial Convention, Inc.; 1979.

United States Pharmacopeial Convention. USP. NF: the official compendia of drug standards information on disk. Rockville: USPC.

de Vlieger JSB, Crommelin DJA, Tyner K, Drummond DC, Jiang W, McNeil SE, Neervannan S, Crist RM, Shah VP. Report of the AAPS guidance forum on the FDA draft guidance for industry: "drug products, including biological products, that contain nanomaterials". AAPS J. 2019;21(4):56. https://doi.org/10.1208/s12248-019-0329-7.

Wang W, Sasaki H, Chien DS, Lee VH. Lipophilicity influence on conjunctival drug penetration in the pigmented rabbit: a comparison with corneal penetration. Curr Eye Res. 1991;10(6):571–9.

Wilhelmus KR. The Draize eye test. Surv Ophthalmol. 2001;45(6):493–515.

Yerxa B. Progress in inherited retinal disease drug discovery and development: a foundation's perspective. Pharm Res. 2018;35(11):239. https://doi.org/10.1007/s11095-018-2514-2.

Yoshida F, Topliss JG. Unified model for the corneal permeability of related and diverse compounds with respect to their physicochemical properties. J Pharm Sci. 1996;85(8):819–23. https://doi.org/10.1021/js960076m.

Young S, Larkin G, Branley M, Lightman S. Safety and efficacy of intravitreal triamcinolone for cystoid macular oedema in uveitis. Clin Exp Ophthalmol. 2001;29(1):2–6.

Younis HS, Shawer M, Palacio K, Gukasyan HJ, Stevens GJ, Evering W. An assessment of the ocular safety of inactive excipients following sub-tenon injection in rabbits. J Ocul Pharmacol Ther. 2008;24(2):206–16. https://doi.org/10.1089/jop.2007.0099.

Zhang Y, Ren K, He Z, Li H, Chen T, Lei Y, Xia S, He G, Xie Y, Zheng Y, Song X. Development of inclusion complex of brinzolamide with hydroxypropyl-beta-cyclodextrin. Carbohydr Polym. 2013;98(1):638–43. https://doi.org/10.1016/j.carbpol.2013.06.052.