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PRACTICAL ASPECTS OF OPHTHALMIC DRUG DEVELOPMENT

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CORNEAL DRUG ABSORPTION

Following the principle that generally holds for drugs at other absorption sites, the permeability of an ophthalmic drug into and through the cornea is a function of its lipoid and aqueous solubility. To help explain ophthalmic drug absorption, the cornea can be divided into three distinct layers; the outer epithelium, an inner stroma and the epithelium. The epithelium and endothelium have been chemically analyzed and shown to contain one hundred times as much lipoid material as the stroma[1]. Therefore, lipoid or fat soluble materials will predominately diffuse through the epithelium and endothelium whereas water-soluble materials would preferentially diffuse through the stroma. Consequently, an ophthalmic drug possessing dual or biphasic solubility will more easily traverse the cornea. This principle is referred to as the differential solubility concept[2] and is generally used to explain corneal penetration of ophthalmic drugs.

Weak Bases

For weak bases, such as tropicamide, epinephrine, pilocarpine, atropine, homatropine, or cyclopentolate, corneal penetration can be predicted from the fact that the unionized form of the drug is predominately lipid soluble; whereas, the ionized form is predominately water soluble. As commercial products, the above amine drugs are buffered at acidic pH's to prevent decomposition. In acidic media, amine drugs with relatively high pKa's will exist largely in the ionized form. As a result, the ophthalmic solutions are weakly buffered to permit the buffer capacity of the tears to rapidly readjust the pH back to 7.3-7.7. At physiological pH, the equilibrium between the ionized and unionized forms of the drug is rapidly shifted to the unionized drug which can then readily penetrate the outer layer of the epithelium. When the drug reaches the stromal surface, the ionized or charged form of the drug penetrates the stroma. As the drug enters the endothelium, the equilibrium again favors the unionized form. Finally, drug leaves the endothelium and penetrates the aqueous humor in the charged form, eventually reaching the target tissue within the eye.

Quaternary Ammonium Compounds

The differential solubility concept does not readily explain the corneal absorption of all ophthalmic drugs. For example, the quaternary ammonium compounds: carbachol, echothiophate iodide, and demecarium bromide, are charged at all pH's and consequently, are highly water soluble and poorly lipid soluble. However, they still penetrate the cornea sufficiently to be clinically useful.

All these drugs are highly potent anti-glaucoma agents and are applied to the eye in very small concentrations. It should be mentioned that due to the high potencies of these drugs, only small quantities are required to penetrate the cornea. Consequently, it is conceivable that a low lipid solubility, perhaps induced by a binding mechanism[3], would permit a small, but sufficient quantity of potent drug to reach the aqueous humor and evoke a therapeutic response.

Antibiotics and Fluorescein

The corneal permeability of antibiotics such as tetracycline and its analogs[4], gentamycin[5], carbenicillin and methicillin[6], is predictably low following topical administration. All show negligible liposolubility and possess no activity against internal eye infections unless dosed by the subconjunctival route. Chloramphenicol, on the other hand, exhibits good lipophilic properties and adequately penetrates the cornea[7]. The fact that poorly liposoluble substances are not absorbed, however, is used to advantage in the case of fluorescein. The intact corneal epithelium, having a high lipid content, resists penetration of predominantly water soluble fluorescein, which remains in the precorneal tear film coloring it yellow or orange. Any abrasion of the epithelial barrier permits rapid fluorescein penetration into the stroma and possibly the aqueous humor, if the endothelium barrier is also damaged. The slightly more alkaline pH of the stromal fluids and aqueous humor gives fluorescein a brilliant green color distinguishing it from its yellow or orange color in the precorneal tear film.

Physiological Factors Influencing Drug Absorption

In addition to the barrier properties of the cornea, physiological factors such as lacrimal drainage and blinking can profoundly influence the rate and extent of ophthalmic drug absorption. Lacrimal drainage of an instilled drug solution competes for drug along with corneal penetration and can account for a considerable loss of drug as far as ophthalmic therapy is concerned. When a drop of solution is applied to the eye, two processes occur simultaneously; the solution is diluted by reflex tearing and the added volume in excess of the normal lacrimal volume is drained from the eye. This is partly facilitated by reflex blinking. The lacrimal apparatus consists of the lacrimal glands which secrete tears via the excretory ducts. Tears flow over the cornea, and through the blinking process, enter the lacrimal puncta, the lacrimal sac, and continue down the nasolacrimal duct, potentially giving rise to side effects due to systemic absorption. Studies with rabbits[8] have demonstrated that the drainage rate of any sized drop decreases at a rate proportional to the volume of the drop remaining in the eye until the tear volume is back to the normal lacrimal volume; the smaller the drop, the slower the drainage rate and the more extensive the absorption of drug. The results of this animal research suggest that since the drainage of an instilled solution in humans is faster than in rabbits, administration of small volumes of ophthalmic solution to the human eye would provide for maximum bioavailability. An ideal dose of 1-5 µl accurately measured and

carefully administered has been recommended in order to optimize drug delivery[8]. Since the drainage rate is volume dependent and rapid, the drops should be 3-5 minutes apart[9]. Observations in humans have demonstrated that the administration of 25 µl of solution to the eye at 3 minute intervals will minimize volume build up, dilution, excessive drainage and overflow[10]. Shorter intervals would reduce ophthalmic bioavailability. The normal lacrimal volume in humans is approximately 7 µl and if blinking does not occur, the human eye can hold about 30 µl without spillage onto the cheek[11]. If blinking occurs, then the human eye can hold approximately 10 µl. Since, however, the size of a commercial ophthalmic drop is 50-75 µl, the loss of drug due to spillage out of the eye can be considered a significant factor in reducing the bioavailability of ophthalmic drugs.

In conclusion, several physico-chemical and physiological factors can influence ophthalmic drug absorption. The hydrophilic and lipophilic properties, and the ionic character of the drug molecule at physiological pH are the most important physico-chemical criteria. In addition, the size and the structure of the molecule, tonicity conditions, and the physiological condition of the barrier tissue which, for example, can be altered due to corneal abrasion, all may influence the rate and degree of therapeutic efficacy of an ophthalmic agent. The major physiological processes in the eye, potentially decreasing ophthalmic bioavailability, are summarized in Table I.

TABLE I: Major Physiological Processes in the Eye Which Can Potentially Decrease Ophthalmic Bioavailability

Process	Comment
Lacrimal Drainage Rate	Proportional to volume of drop, e.g., approximately 80% of a 50 µl drop is drained out of the conjunctival sac one minute after instillation.
Spillage Onto Cheek	Human conjunctival sac can hold 30 µl of fluid without blinking; therefore, a large drop (50-75 µl) is partially squeezed out of the eye.
Blinking	With blinking, the human eye can hold approximately 10 µl.
Reflex Tearing	Dilutes drug and promotes drainage.

OPHTHALMIC DISEASES

The eye and its components--the lids, lacrimal apparatus, conjunctiva, cornea, sclera, uvea, retina, optic nerve, lens, vitreous, and orbit--can suffer from approximately 250 different diseases, excluding blindness. Each year, I.M.S. America, Ltd.[12] publishes statistics based on the number of patient visits to practicing physicians in the United States. From October 1, 1974 to September 30, 1975, patient visits exceeded 60 million (Table 2). The major diseases of the eye which can be treated primarily with drugs will be briefly discussed. References 13 through 17 are recommended for detailed and specific study of the diseases of the eye.

Glaucoma

Glaucoma occurs in many forms and is characterized by an intraocular pressure higher than the eye can tolerate, without

the destruction of visual function. The degree of increased pressure-causing organic change is not the same in every eye. The major factors involved in the individual variation include the rate of production of the aqueous humor and the ease of excretion of the aqueous humor through the trabecular area. These two factors provide the homeostatic control of the level of the intraocular pressure. Another factor influencing individual variation is the adequacy of the blood supply to the intraocular portion of the optic nerve (papilla). This governs whether or not the optic nerve atrophies with accompanying visual changes. The healthy eye can indefinitely tolerate a pressure of 20 mm Hg, as measured with the Schiotz tonometer, without damage to the optic nerve.

The three major types of glaucoma are classified as primary, congenital and secondary. Primary glaucoma can take the form of open-angle glaucoma, narrow-angle or angle-closure glaucoma and hypersecretion glaucoma. Congenital glaucoma may be subclassified into infantile and juvenile glaucoma. Glaucoma leads to optic nerve degeneration, visual field loss and blindness if it remains untreated. The treatment of open-angle glaucoma and secondary glaucoma is primarily with drugs, whereas the treatment of narrow-angle and congenital glaucoma is primarily surgical. Three groups of drugs (miotics, epinephrine derivatives, and carbonic anhydrase inhibitors) may be employed singly or in combination for the medical control of open-angle glaucoma.

Conjunctivitis

Conjunctivitis is an inflammation of the conjunctiva, characterized by cellular infiltration and exudation. Classification is

TABLE 2

National Disease and Therapeutic Index[1] Data on Patient Visits to Privately Practicing Physicians in the United States

October 1, 1974 to September 30, 1975

——— in thousands, 000 ———

	Disease	Total Visits	Visits Treated With Drugs	Visits Treated Without Drugs	Most Mentioned Desired Action	Most Mentioned Drug Therapy
1.	Glaucoma	6,717	5,847	870	Decrease I.O.P.[2]	Pilocarpine, Diuretics
2.	Conjunctivitis	5,864	5,463	402	Anti-infective	Antibiotics
3.	Unspecified Disease	9,745	2,170	7,575	Anti-inflammatory	Corticosteroids
4.	Refractive Errors	20,952	1,248	19,705	Mydriatic	Miscellaneous
5.	Blepharitis	889	810	79	Anti-inflammatory	C/A Combination[3]
6.	Keratitis	926	749	177	Lubricant	Artificial Tears
7.	Cataracts	6,616	705	5,911	Pre-Operative Preparation	Miscellaneous
8.	Iritis	677	615	61	Anti-inflammatory	Corticosteroids
9.	Chalazion	1,269	612	657	Anti-infective	C/A Combination[3]
10.	Lacrimal Duct Gland Inflam.	760	506	254	Combat Infection	Miscellaneous
11.	Other Inflammatory Disease	584	489	94	Anti-inflammatory	Corticosteroids
12.	Hordedum	600	437	163	Anti-infective	Antibiotics
13.	Corneal Ulcer	490	382	108	Anti-infective	Antibiotics
14.	Uveal Tract Inflam.	502	362	140	Anti-inflammatory	Corticosteroids
15.	Strabismus	2,325	326	1,998	Cycloplegic	Miscellaneous

16.	Optic Nerve Inflam.	259	142	117	Anti-inflammatory	Corticosteroids
17.	Conjunctival Hemorrhage	336	140	196	Ophthal. Decongestants	Miscellaneous
18.	Retinal Vitreous Hemorrhage	363	91	272	Anti-inflammatory	Corticosteroids[3]
19.	Pterygium	267	74	193	Anti-inflammatory	C/A Combination[3]
20.	Eye Cysts	297	48	249	Prophylaxis	Miscellaneous
21.	Corneal Opacity	157	30	127	Symptomatic	Artificial Tears
22.	Dislocation of Lens	184	25	160	Mydriatic	Mydriatics
23.	Detachment of Retina	212	20	192	Mydriatic	Mydriatics
24.	Atrophy of Optic Nerve	120	16	105	Decrease I.O.P.[2]	Pilocarpine
25.	Blindness	173	12	161	Mydriatic	Miscellaneous

[1] A service of I.M.S. America, Ltd., Ambler, PA 19002.

[2] I.O.P. = Intraocular pressure

[3] C/A Combination = Corticosteroid/Anti-infective combination

based upon the cause (bacterial, viral, fungal, parasitic, toxic, chemical, mechanical, irritative, allergic, or lacrimal); the age occurrence; the type of exudate (purulent, mucopurulent, membranous, pseudomembranous, or catarrhal); or course (acute, subacute, or chronic). Clinically, the onset of conjunctivitis is usually insidious. The patient will notice a fullness of the lids and a diffuse, gritty, foreign body sensation. Within several hours of the onset, there is exudation. Special mention must be made of the leading eye disorder in the world, trachoma. Trachoma is an infectious keratoconjunctivitis that affects over 400 million people, mainly in the Near East and Asia. The disease occurs in regions of poor hygiene and the results are severe unless treated with sulfonamides and broad spectrum antibiotics.

Blepharitis

Blepharitis is an inflammation of the lid margin and it may be acute or chronic. Redness of the lid margins is the chief complaint. Blepharitis is frequently a mixture of seborrheic and staphylococcal forms, and treatment of which is often frustrating since the disease recurs. Antibiotics, sulfonamides, and steroids have been used, but in many cases, the condition can be arrested with treatment of the seborrheic dermatitis of the scalp.

Keratitis

Keratitis is a general name for all corneal inflammations. The inflammation may be exogenous or endogenous in nature. Keratitis is heralded by the appearance of edema, which is followed by infiltration and vascularization. The cornea will become opaque

and congested. Microbial causes include infections by bacteria (acute serpiginous ulcer), virus (dendritic keratitis), and fungi (keratomycosis). Congenital syphillis will cause interstitial keratitis. Other forms of keratitis result from hypersensitivity, vascular disease, nutritional deficiency, and decreased lacrimation.

Cataracts

Cataracts (lens opacity) result from various etiological factors among which are senility, genetic factors, endocrine disorders, immunological factors, local metabolic disturbances, and external physical changes. Any loss of lens transparency is called cataract. Cataracts essentially arise from protein denaturation and the accumulation of water.

Uveitis

The uveal tract is composed of the iris, ciliary body, and the choroid. The iris separates the anterior and posterior chambers; its aperture being the pupil. The ciliary body secretes aqueous humor, and the choroid provides the blood supply for the outer one-half of the retina. Inflammation of the uveal tract includes a variety of conditions ranging from minimal inflammation to abscess formation following introduction of pyrogenic bacteria.

Retina Abnormalities

The symptoms of retinal abnormalities mainly involve disturbances in vision. Interference with cone function causes diminished central visual acuity and decreased color vision. Opacities of the ocular media that interfere with image formation at the fovea cause depression of vision. Localized disturbance in the fovea centralis

area such as hemorrhage (diabetic retinopathy), edema, microaneurysms, deposits, or tumors may cause micropsia or macropsia. Interference with rod function causes defective dark adaptation. Retinal disease is characterized by a defect in the visual field that corresponds to the affected area.

Other Common Eye Diseases

Refractive Errors - Eye defects that prevent light rays from being brought to a single focus exactly on the retina. Such errors are treated with corrective lenses.

Iritis (Iridocyclitis) - Inflammation of the iris and ciliary body.

Chalazion - Inflammatory enlargement of a Meibomian (sebaceous) gland in the eyelid.

Hordeolum (Stye) - Infection of the glands of Moll or Zeis.

Strabismus - Failure of straightness of the eyes; one eye looks directly at the object of attention, whereas the other eye does not.

Pterygium - A triangular fold of tissue which extends from the conjunctiva over the cornea.

OCULAR PHARMACOLOGY [18-24]

Corticosteroids

These drugs have been employed in the treatment of inflammation for nearly 25 years. They have been widely used in ophthalmic medications to control the inflammation associated with wearing contact lenses, and as diagnostic agents in glaucoma testing. Corticoster-

oids are employed to treat a large number of eye diseases, including blepharitis, conjunctivitis, uveitis, keratitis, contact dermatitis, corneal ulcers and corneal chemical burns. They are also used in combination with specific antibiotics. Corticosteroids are contraindicated for the treatment of viral infections such as dendritic ulcer, small pox and chicken pox. In addition, they should never be used in the presence of fungal and bacterial infections not controlled by antibiotics.

Corticosteroids are administered topically, subconjunctivally and systemically depending upon the location and severity of the disease. A major side effect of corticosteroid therapy is an elevation of ocular pressure. To treat ocular inflammation, it is desirable, but sometimes difficult, to select an agent which will minimize the ocular pressure increase, while still producing sufficient antiinflammatory activity. Severe complications may result if both the dosage size and frequency of corticosteroid administration are not carefully controlled. The rise in ocular tension is most marked with dexamethasone and betamethasone.

Anti-infective Agents

These agents may be categorized into five main groups: antibacterials, antibiotics, sulfonamides, antifungals and antivirals. The major antibacterial drugs include silver nitrate, mild silver protein, boric acid and sodium propionate. They can be bacteriostatic or bactericidal and are used to treat minor irritations of the external eye, superficial eye infections, minor inflammation and chemical burns. Silver nitrate is required by law in some

states to be administered in the eyes of the newborn for the prophylaxis of ophthalmia neonatorum.

Similarly, antibiotics may exert bacteriostatic or bactericidal activity. Antibiotics exert their effect by disturbing cell wall synthesis, protein synthesis or altering membrane permeability, thereby disrupting the metabolic activities of the bacteria. The major ophthalmic agents in this class include the tetracyclines, bacitracin, neomycin, polymixin, chloramphenicol, erthyromycin and gentamicin.

The sulphonamides are bacteriostatic agents which are indicated in many external eye infections including conjunctivitis, blepharitis, keratitis, corneal ulcers and styes. They are also used prophylactically following the removal of foreign bodies, and to treat abrasive injuries to the eye. The major sulfonamide is sodium sulfacetamide. Two other important sulfonamides are sulfisoxazole and sulfamethizole.

Antifungal agents are employed to combat fungal keratitis and endophthalmitis. The drug of choice is amphotericin B. Other antifungals available include nystatin and flucytosine. Effective antiviral agents include idoxuridine and adenine arabinoside. These drugs are effective in treating dendritic keratitis and other corneal infections caused by herpes simplex virus.

Agents Acting on Autonomic Nervous System

Topical administration of cholinergic drugs in the eye produces constriction of the pupils, contraction of the ciliary muscles, dilation of blood vessels of the iris and conjunctiva,

and/or increase in aqueous outflow. Pilocarpine and carbachol are the most common cholinergic drugs in use and are employed for their miotic effects and to treat glaucoma. Pilocarpine is used in strengths of 0.25 to 10% and is the drug of choice for primary glaucoma. Carbachol is applied in strengths of 0.75% to 3%, to treat open-angle glaucoma. It is a more powerful miotic than pilocarpine and is used in patients where the glaucoma cannot be controlled with pilocarpine.

Anticholinesterase drugs produce similar effects to the cholinergics and are used to treat open-angle glaucoma. These drugs include echothiophate iodide, demecarium bromide and physostigmine, the latter being frequently combined with pilocarpine to treat glaucoma.

Adrenergic drugs are mainly used to dilate the pupil. In addition to this mydriatic effect, adrenergics are employed for their vasoconstrictive properties to treat congestion, for the relief of allergic reactions, for hyperemia of the conjunctiva, and for the treatment of glaucoma.

Epinephrine is used in strengths ranging from 0.5 to 2%. It is a poor mydriatic except in the treatment of Horner's syndrome, which is a lesion of the superior cervical sympathetic ganglion. The drug is often combined with pilocarpine to treat glaucoma. Phenylephrine is a very effective mydriatic agent at 10% concentration, however, at this concentration, it is less effective in lowering intraocular tension than a 2% solution of epinephrine. Phenylephrine is used primarily in ophthalmoscopic examinations.

Topical application of cholinergic blocking agents results in pupillary dilation and paralysis of accomodation, a condition called cycloplegia. These drugs are used for their mydriatic effects, particularly as postoperative agents in cataract and retinal detachment surgery. Atropine is the strongest cycloplegic agent available. Mydriasis from this drug persists for up to 2 weeks, while the cycloplegia may last up to 6 days. Scopolamine is used in patients sensitive to atropine. Other agents include homatropine, cyclopentolate, and tropicamide. Their cycloplegic activity is of shorter duration. Cycloplegia from tropicamide lasts from 0.5 to 4 hours and it is thus used in retinal photography and in refraction studies.

Anesthetics

Topical and local anesthetics permit the clinician to measure ocular tension, remove foreign bodies from the surface of the eye and to carry out lacrimal canalicular manipulation and irrigation. Cocaine is the proto-type and the only natural anesthetic compound. However, it is rarely used since it causes damage to the corneal epithelium and may influence intraocular pressure. The onset of action of topical anesthetics is within a minute and their duration of action is 10 to 20 minutes. The most commonly used topical anesthetics are tetracaine, proparacaine and benoxirate.

Local anesthetics have a more delayed onset of action (3-11 minutes). The duration of action may vary from 0.5 to 4 hours. Procaine and lidocaine are the two most frequently used local anesthetics in ocular surgery. To these are frequently added epinephr:

and hyaluronidase to decrease absorption and to increase diffusion of the anesthetic, respectively.

Miscellaneous Agents

Diagnostic agents are used to diagnose specific ocular abnormalities and to examine various parts of the eye for possible manifestations of systemic disease. Fluorescein and rose bengal are used to examine the conjunctiva, cornea and lacrimal apparatus. Fluorescein will turn bright green in ordinary light if defects exist in the corneal epithelium. Similar lesions of the conjunctiva will appear bright orange-yellow. Rose bengal will stain devitalized cells while normal cells will not stain. Other diagnostic agents include edrophonium chloride, used as a diagnostic agent in myasthenia gravis, and methacholine, used to differentiate the tonic pupil from the normal pupil. It will also diagnose weakness of ocular muscles.

Several products are available for self medication of ocular conditions such as artificial tears, eye washes, antiseptic drops, ointments and decongestants. Dry eye refers to a condition in which the eye may be deficient in either the aqueous or mucin components of the precorneal tear film. Mucin-deficient dry eyes may be seen in a variety of diseases including chemical burns and vitamin A deficiency. Artificial tear preparations contain either hydroxypropylmethylcellulose, methylcellulose, polyvinyl alcohol, and/or gelatin. Vasoconstrictors used as decongestant drugs available for O.T.C. use in ophthalmics are ephedrine, phenylephrine, naphazoline, and tetrahydrozoline. Vasoconstrictors "get the red out". Zinc salts are also used as decongestants.

In addition to the drugs discussed thus far, two other groups of agents have been used to treat glaucoma. Hyperosmotic agents, such as glycerol 50%, mannitol 20%, and urea 30% produce a fall in intraocular pressure by virtue of their ability to create an osmolar gradient between blood and the aqueous environment. These three materials are used in the treatment of narrow-angle glaucoma in preparation for surgery. The other group of compounds are the carbonic anhydrase inhibitors, and include acetazolamide, dichlorphenamide, ethoxozolamide, and methazolamide. These drugs are of great clinical value in both short and long-term treatment of glaucoma and act by suppressing the secretory formation of aqueous humor.

Ocular Complications of Drugs

Local and systemic administration of certain drugs has resulted in many forms of visual complications. These include blurred vision, disturbance in color vision, pigmentary degeneration of the retina, and damage to the cornea, retina and optic nerve. The drugs responsible for these adverse effects include those that are retinotoxic: the cardiac glycocides, the quinolines, and the phenothiazines, and those that produce toxic optic neuropathies: chlorpropamide, the corticosteroids, and chloramphenicol.

The incidence of ocular manifestations in patients with digitalis toxicity has been estimated to be as high as 25%. The most common ocular symptoms of digitalis toxicity are blurred vision and disturbed color vision. Color vision is affected so that objects may appear yellow or green. Objects may also seem to be

covered with snow or frost, i.e., "snowy vision". Several of the phenothiazines, e.g., thioridazine hydrochloride, have produced pigmentary degeneration of the retina and, occassionally blindness. The phenothiazines have been found to accumulate in the pigment cell, particularly within the melanin fraction. It appears that a certain dosage, usually 200 mg of thioridazine hydrochloride daily for many months, must be exceeded before ocular damage is observed. The quinoline drugs, e.g., chloroquine, may cause damage to the cornea, retina or optic nerve. The effects of some drugs can be predicted and occur shortly after drug administration. Other agents produce adverse ocular effects that occur only after long-term administration and which could not have been predicted from available information from experiments in animals or short-term clinical investigations.

OPHTHALMIC SOLUTIONS [25-29]

Ophthalmic dosage forms are unique since they are administered to very delicate membranes often traumatized by accident or surgery. Because of their method of use and the drugs employed, ophthalmic preparations may differ from parenterally-administered agents in the added substances used to enhance the activity and to maintain stability and sterility of the product. The industrial pharmacist faces several difficulties and challenges in formulating and preparing ophthalmic solutions and other ophthalmic dosage forms.

Ophthalmic dosage forms include solutions, ointments, suspensions, lyophilized powders, and oily solutions. Two newer types of dosage forms are new drug delivery systems involving

membrane inserts (Ocusert®) and spray devices (Mistura™). Some of the following formulation factors that must be considered in developing safe and effective ophthalmic dosage forms include stability, compatibility, tonicity, viscosity, packaging, and sterility.

Stability

The rate of degradation of ophthalmic drugs in solution depends on the nature of the active drug, the temperature and pH of the solution, and the amount of oxygen and ultraviolet light to which the drug is exposed. The relative stability of ophthalmic drugs has an important bearing on its formulation, method of preparation, and storage of the solution. A neutral pH is desired for comfort, yet most drugs are unstable at neutral pH. Autoclaving is the preferred method of sterilization, yet many compounds degrade at temperatures above ambient temperature. Drugs containing ester linkages, such as local anesthetics (procaine, tetracaine), cycloplegics (atropine), and many of the miotics (pilocarpine, carbachol, physostigmine) are all subject to hydrolytic degradation. Epinephrin and phenylephrine are prime examples of ophthalmic drugs which can be easily oxidized because of free hydroxyl (-OH) groups. Excessive exposure to light can degrade such ophthalmic drugs as atropine, prednisolone, and sodium sulfacetamide. Formulation additives, such as certain preservatives (chlorobutanol) and antioxidants (ascorbic acid, sodium bisulfite) are subject to degradation and, thus, must be protected to some extent by pH adjustment, light-resistant pack-

aging and chelating agents to exert their protective effects on the drug in solution.

Compatibility

Formulation additives may either interact directly with the drug, such as sodium bisulfite inactivating epinephrine, or may indirectly influence drug instability as a result of their function in the formulation. Buffers, which are employed for minimizing pain, insuring drug stability, or controlling drug therapeutic activity, may catalyze drug degradation or adversely affect product stability due to an incompatibility between the buffer ion and the drug. Salts, used to adjust the solution tonicity, may also accelerate the degredation rate of a drug sensitive to increases in ionic strength. Suspending agents have been known to alter product stability by the effects of increased solution viscosity. Antioxidants and preservatives, as already stated, self-degrade. They may also be incompatible with the drug or other formulation components, resulting in either decreased drug potency and/or physical stability problems, e.g., precipitation. Thus, the formulating pharmacist must carefully study and understand potential additive interactions with the drug and develop a formula which will minimize or eliminate these problems.

Tonicity

The importance of ophthalmic solutions being isotonic is well known. Considerable discomfort and less than optimal therapeutic effect may be avoided if ophthalmics are isotonic with lacrimal fluid. However, the eye can tolerate solutions having a tonicity value ranging from those equivalent to 0.5 to 1.6% sodium chloride

without great discomfort. Ophthalmic solutions do not need to be exactly isotonic with tears, especially if extemporaneous adjustment of tonicity could endanger the solution sterility. However, it has been discovered recently that solutions used as intraocular irrigating solutions in ocular surgery should be isotonic to minimize swelling of the sensitive corneal endothelial cells. Pain can be caused by factors other than nonisotonic solution administration. These factors include acidity, alkalinity, properties of the drug itself, and the volume of solution administered at one time. The eye will tolerate alkaline solutions better than acidic solutions Unbuffered solutions at low pH, due to stability requirements of the drug, will be easily neutralized by the tears if administered in small volumes. If a drug must be administered at high concentrations the solution should be buffered and isotonic, or discomfort most likely will occur. High concentrations of drugs such as local anesthetics, heavy metal salts, and quaternary compounds (carbachol, demecarium bromide, echothiophate iodide), will cause pain because these drugs are surface-active and, thus, will cause superficial corneal damage as a result of protein denaturation.

Viscosity

Additives used to increase viscosity are important because they increase the contact time of the instilled drug solution with the cornea. Without such additives, the tears will wash out the drug solution within five minutes. A very important use of viscosity inducing agents is their inclusion in artificial tear preparations and contact lens lubricant solutions. Artificial tear products are

designed for patients suffering from tear deficiencies such as keratoconjunctivitis sicca. Materials used to increase viscosity include cellulose derivatives, polyvinyl alcohol, polyvinyl pyrrolidone, and polyethylene glycol. The major disadvantage of artificial tear products is that excessive use will result in "stickiness" and irritation resulting from drying and granulating on the eyelids.

In addition, and/or in the place of viscosity-inducing agents, surface-active agents have been included in ophthalmic formulations to increase corneal drug penetration. Surface-acting agents are important additives in contact lens solutions as they improve wetting of the lens. Surface-active agents which have been used include benzalkonium chloride, polysorbate 80, polyoxy-40-sterate, and polyoxypropylene-polyoxyethenediol. The formulating pharmacist must employ careful judgment in avoiding indiscriminate use of these surface-active agents.

Packaging

The packaging of ophthalmic solutions can offer some perplexing problems since drugs and preservatives can potentially interact with certain components of plastic and rubber. Also, unless adequately controlled, containers and rubber stoppers can be sources of particulate matter. Containers must be able to be sterilized and maintain drug stability. Many factors can influence drug stability in plastics. These include plastic composition, processing and cleaning operation, absorption of drugs, permeability of preservatives, and effects of storage.

Sterility

Sterility is last, but certainly not least, of the factors to consider in formulating ophthalmic dosage forms. No one has ever lost an eye because the drug in solution was decomposed or the solution itself was irritating, but the instillation of contaminated solutions has too often resulted in serious infection and loss of the eye. The Food and Drug Administration, in 1953, declared that non-sterile ophthalmic products would be considered adulterated and misbranded. The most dangerous microorganism to the eye is Pseudomonas aeruginosa because it grows in the cornea better than in any other known medium. Various methods are available to sterilize ophthalmic solutions. Provided the drug will remain stable, autoclaving is the simplest method of sterilization. Chemical methods using ethylene oxide, formaldehyde, or beta-propiolactone gases, are widely used sterilization methods. Bacterial filtration, next to autoclaving, is the method of choice for sterilizing ophthalmic solutions. This method is best for drugs sensitive to heat and gas. However, filtration places greater emphasis on aseptic technique and does not remove viral contaminants.

Contamination of ophthalmic solutions during use is very probable. Thus, multiple-use solutions must contain a preservative. Benzalkonium chloride is the preservative of choice. Solutions prepared for single application, such as use in surgery or application to injured eyes, do not need a preservative. In fact, preservatives are irritating to the corneal endothelium, the iris, and the tissues lining the anterior chamber, and thus, are undesirable in solutions used in surgery and/or injury.

In summary, the most important factors to consider when preparing ophthalmic solutions are stability, pH, compatibility, tonicity, viscosity, packaging sterility, and preservation. The most important of these is sterility. The formulating pharmacist must confront and answer these challenging factors in the pursuit of producing safe, effective, and acceptable ophthalmic dosage forms.

OPHTHALMIC DRUG DELIVERY

In general, the term drug delivery is used to refer to controlled delivery systems that release drug at a rate which alters or controls the rate of the pharmacological or therapeutic effect. Appropriate systems achieve a relatively constant release rate which can be maintained generally over long periods without administering repeated doses or excessively large initial doses. The desired rate of release is one which is just sufficient to sustain a desired response and to replace drug which is lost by chemical degradation, metabolism or other mechanisms.

Slightly viscous commercial ophthalmic solutions when applied to the eye are uncontrolled with regard to drug release. The eye is initially flooded with drug of which only a small fraction is actually absorbed through the cornea. The remainder of drug either spills over the eyelid or enters the nasolacrimal duct to provide a potential for systemic drug toxicity. Drug which is absorbed does so at a rapid rate such that the peak response is often higher than therapeutically desirable, only to decline rapidly in a few hours

to drug levels below a minimum effective concentration. Consequently, two important concentration levels must be considered: the minimum effective concentration, which is the lowest concentration necessary to produce the desired effect, and the toxic concentration above which undesirable side effects occur. In order to minimize the "overdose-underdose" pattern of drop therapy, a controlled delivery system attempts to release drug within these limits. In addition, an ideal drug delivery system not only releases drug at a predetermined rate, but releases drug independent of small changes in the physiological environment. Under these conditions, normal biological variations in the physiological environment, do not effect therapy.

Although many types of drug delivery systems have been experimentally tested in the eye, only the diffusional, reservoir type insert, the Ocusert®, is commercially available. This insert is an elliptical device consisting of a drug-containing core surrounded by a flexible copolymer membrane through which pilocarpine diffuses. The ocular delivery system is in contact with the conjunctiva. After about 8-12 hours, it will release pilocarpine at 20 mcg/hr for the Pilo-20 system or 40 mcg/hr for the Pilo-40 system for the remainder of a seven day period.

During the first 8-12 hours after insertion, the release is relatively high due to drug migration to the surface of the device during storage. This initial burst is about equal to the amount of pilocarpine contained in one drop of a 2% solution. The insert contains a white border of titanium dioxide which prevents leakage at the edges and provides visibility in handling and inserting. The

insert is placed under the lower lid and removed by much the same technique as inserting and removing a soft contact lens. It is intended to remain within the conjunctival sac day and night. Since it is flexible and relatively insensitive to the eye, the insert can float to the sides or top of the eye unnoticed. This movement does not interfere with the proper functioning of the unit.

The inner core or reservoir contains 5 mg or 11 mg of pilocarpine for the Pilo-20 and Pilo-40 systems respectively. The rate controlling outer membrane is composed of ethylene/vinyl acetate copolymer. Diffusion through the outer membrane can be described by Fick's diffusional equation:

$$J = -DA \frac{dc}{dx} \qquad \text{Equation 1}$$

where J is the flux of drug in gm sec^{-1}, D is the diffusion coefficient for drug within the polymeric membrane in cm^2 sec^{-1}, A is the area of the membrane in cm^2, dc is the drug concentration gradient within the membrane along the direction of flow in gm cm^{-2} and dx represents the thickness of the membrane in cm. The minus sign indicates that diffusion occurs from the reservoir or higher concentration to the lower concentration at the outer surface of the membrane.

The 20 or 40 mcg/hr, released under steady state conditions, is predicted by equation 1 for each Ocusert® system as reported by Alza scientists[30]. Verification of the equation, through experimental work, indicates that drug diffusion is controlled by the equation parameters, namely, the type of polymer used (expressed as a function of D), its surface area (A) and its thickness (dx). The

quantity of drug in the reservoir determines the length of time a steady state could be maintained. It has been reported that in saline, the Ocusert® Pilo-20 and Pilo-40 systems released pilocarpine at steady state rates of 21.6 ± 0.3 mcg/hr and 44.7 ± 3.7 mcg/hr respectively over 168 hours. In humans, the Pilo-20 system released drug over seven days at an average rate of 17.9 ± 2.9 mcg/hr. The fact that steady state release rates are similar for in-vitro and in-vivo studies is an indication that pilocarpine release is controlled by the device and not by the immediate environment.

Since the Ocusert® is intended to remain in the eye for a seven day period, it provides greater convenience to the patient and better control of glaucoma by eliminating diurnal variations associated with drop therapy. The insert provides a reasonably constant and less marked myopia that can be treated with corrective lenses as compared to pilocarpine drop therapy which causes a variable change in visual acuity that is difficult to correct. On the other hand, it is approximately ten times more expensive than drop-therapy and may be less reliable for individuals in whom it can fall out unnoticed or become accidently perforated and leak its contents rapidly. In general, the therapeutic value of the Ocusert® Pilo-20 insert is equivalent to a pilocarpine eye drop concentration of less than 2%; whereas, the Pilo-40 is equivalent to 4% pilocarpine eye drops.

Historically, synthetic polymers have been widely used in aqueous solutions in the eye to prolong therapy. Methylcellulose, hydroxypropyl methylcellulose, and polyvinyl alcohol have been

used commercially most often to prolong therapy. These water soluble polymers impart a slight lowering of surface tension and an increase in viscosity to the solutions. The increase in viscosity prolongs contact time of the drug in the eye, thereby resisting drainage[31,32]; whereas, a lowering of the surface tension improves mixing with the precorneal tear film. In rabbits, a two to three-fold improvement in bioavailability has been found for the viscous aqueous solutions[31-33]. Although viscous aqueous solutions are purported to improve ophthalmic drug bioavailability, they cannot be considered controlled delivery systems.

One of first successes at prolonging ophthalmic therapy through membrane controlled releases was obtained by presoaking soft contact lenses in pilocarpine formulations and then placing the lenses on the cornea. In one study[34], the lenses were soaked for two months in 0.5% pilocarpine hydrochloride solutions and placed on the eye of glaucoma patients for 30 minutes to 2 hours. In all patients, intraocular pressure was controlled after 24 hours. This is in contrast to normal pilocarpine eyedrop therapy which requires dosing three to four times a day to achieve 24-hour control. It has been proposed[35] that the exceptionally long duration achieved from the relatively short corneal contact time of drug-saturated lens could occur from "loading" the cornea. The cornea, acting as a biological depot, would then accumulate drug and release it in concentrations above the minimum therapeutic level for a longer period of time. Direct evidence that this is occurring, at least for pilocarpine, has been recently reported by Sieg and Robinson[36] in rabbits.

Although the Mistura ophthalmic spray cannot be considered a controlled delivery system, it represents a new mode of drug delivery to the eye and, therefore, warrants mentioning. It is a hand operated, metered pump fitted with a detachable eyepiece. Depression of the spray head delivers a fine spray of an aqueous solution of eye medication devoid of viscolizer. It represents a fast and convenient way to instill medication, but a significant portion of the dose can be sprayed on the eyelid and run down the cheek. The cost to the patient is only slightly higher than drop therapy.

Current research interest is centered around drug-containing bioerodable polymeric membranes. With these devices, drug is dispersed throughout the polymer matrix resulting in drug release as the matrix erodes. Regardless of the shape of the device, its area decreases as it erodes. Since release rate is proportional to area, a constant release could only be achieved by using a higher concentration of drug in the interior of the device than in the surface layers. In terms of adequate therapy, however, a slowly declining but controlled release rate, e.g., low first order as opposed to zero order or constant release rate, would likely suffice for many ophthalmic drugs. Hydrocortisone[37] and tetracycline have been tested in the eye with some success with the use of a bioerodable insert.

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