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1. Opthalmic Preparations

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Key Points:

For the treatment of ocular disorders, topical, systemic (oral or injectable), intraocular, and periocular (injection or implant) medication delivery methods are available. Solutions, suspensions, ointments, gels, and submicrometer emulsions are the different categories of topical ophthalmic treatments. It is important to know what the eye can withstand before designing ocular medication delivery formulations. Volume, osmolality, pH, surface tension, and viscosity are crucial factors to take into account while creating topical ophthalmic solutions.

Topical ophthalmic medications are frequently an efficient means of treating the anterior segment of the eye. However, the primary drawback of the topical route is its inefficiency, with just 1% to 5% of the administered amount reaching the aqueous humor.

The primary causes for the low ocular medication bioavailability via the topical route are the very efficient lacrimal drainage system, the corneal barrier to drug permeation, and the fast absorption by conjunctiva blood vessels.

Compared to hydrophilic, ionized medicines, ophthalmic medications with mild lipophilicity and low molecular weight are absorbed more effectively via the ocular pathway. Ocular tissue is the site of phase I and phase II drug metabolic processes. Prodrugs have been designed to take advantage of these.

Diseases affecting the back of the eye are being treated with sustained-release intraocular implants. Implants assist in achieving constant drug concentrations and eliminate the need for recurrent, highly frequent injections into the eye. Biocompatibility and stability at the implant site are essential for intraocular implants. Bioerodible or nonbioerodible intraocular implants are available. Regulatory requirements state that preparations meant for ophthalmic use, such as eye wash solutions, must be sterile. Certain products are offered without preservatives because multidose formulations containing antimicrobial preservatives have the potential to irritate and harm tissue.

1.1 Introduction:

Ophthalmic preparations are those used for the eyes. Sterile suspensions, ointments, and solutions could be among them. The ophthalmic products can be applied topically as ointments, sprays, drops, or mists. They can be continuously injected into the eye.

a. Lotions for eyes
b. Ointments for eyes
c. Orthopaedic inserts
d. Contact Lens options

The human eye is an extremely delicate organ. Any alteration in the surroundings can have an immediate impact on it.

In order to ensure that ophthalmic products have the following qualities, many safety measures must be taken during the preparation process. All these features should make a product the perfect ophthalmic product.

a. To avoid the dangerous eye infections, they have to be sterile. (ii) Since foreign particles irritate and discomfort the eyes, they ought to be free of them.0.6 to 2.0% w/v NaCl solution.
b. With the lachrymal secretion, they ought to be iso-osmotic. An eye can withstand.
c. Their pH should be 7.4 (approximately), which is the same as tear fluid's pH. (v) They ought to have the ideal viscosity to lengthen the time that the readiness for the time. (vi) The right preservative should be present to stop the growth of microorganisms.
d. Sterile aqueous or oily solutions or suspensions are used as eye drops to be injected into the conjunctival sac. Anaesthetic, anti-inflammatory, antiseptic, diagnostic, miotic, and mydriatic agents are typically present in them. Their arrangement Therefore, the most crucial prerequisite for eye drops is sterility. Steam, gas, or filtration techniques can be used for sterilization, depending on the characteristics of the drugs and additives.

A. Foreign Particles:

a. Anguish and Distress
b. Athletics
c. Viscosity
d. Keepers
e. temperatures.
f. pH correction

To extend the time that eye drops are in contact with the eye and to enhance the therapeutic response, some thickening agents are added. Thickeners for eye drops should be compatible with other ingredients, simple to filter, and easy to sterilize. An appropriate thickening agent for eye drops is polyvinyl alcohol. Due to potential side effects on the inside of the eye, eye drops are not used during or after surgery.

Unfavorable eye conditions can also result from a variety of other factors, such as painotic pressure, pH, certain medications, and preservatives.

The pH of eye drops should be approximately 7.4. be free of particulates. It's a very sensual idea. Gants should be used to prevent pathogenic microorganisms from entering the partium and should tickle, which is uncomfortable. The ideal filtration medium for eliminating any foreign particles from the solution is the membrane epithelium fpore size of 0.8 mm.

If aqueous eye drops are provided in multiple application containers, they must be prepared in a bactericidal and fungicidal vehicle. It offers defense against harmful organisms unintentionally introduced during the removal of subsequent treatments. When stored normally, an eye drop preservative should be:

a. Quickly effective against a variety of bacteria and fungi warmth.
b. Does not irritate or cause pain to the eyes.
c. Harmonious with other ingredients and medications. similar to thickeners and stabilizers.
d. Consistent throughout storage and sterilization.
e. Adequately soluble to prevent precipitation or crystallization at low.

The most common are phenyl mercuric acetate, chlorhexidine acetate, and benzalkonium chloride.

Suggested preservative: in addition, thiomersal, phenyl ethyl alcohol, chlorocresol, propyl paraben, and chlorocresol are used. Since the majority of medications are broken down by basic or acidic hydrolysis, the prescription's pH is a crucial consideration. As a result, the pH is appropriately adjusted to prevent drug degradation and to fulfill additional purposes, such as minimizing irritability and preserving chemical stability, which may have been compromised by a slight pH shift due to a variety of factors, including temperature changes, the leaching of alkali groups from glass containers and rubber closures, and enhancing clinical response.

B. Reducing Agents:

If a medication is susceptible to oxidation, reducing agents, also known as antioxidants, are added to stabilize the medication. Sodium thiosulfate and sodium metabisulphite are two of them.

C. Sequestering Agents:

In order to stop some eye drops from breaking down, these extra stabilizing agents can be used either by themselves or in combination with reducing agents. Disodium edecate, the most widely used compound and the disodium salt of EDTA, forms complexes with di and tirivelent metals that may accelerate the oxidative drug degradation process. Typically, the concentration range between 0.01 and 0.3% w/v is safe and effective for the eyes. The state of being in equilibrium. The purpose of the eye drops is to prevent any discomfort or irritation. This is carried out in a manner akin to that of parentela's.

- **Getting Ready:**

There are four steps involved in making eye drops:

a. Getting a fungicidal and bactericidal vehicle ready
b. Medicine solution, and adjuncts if necessary
c. Explanation
d. Isolation

Making a Fungicidal and Bactericidal Vehicle Because there are issues with storing stock solutions of the majority of the advised bactericide, this solution is made fresh.

- **Among them are:**

a. The mercurial compounds are highly absorbed by rubber and incompatible with aluminum.
b. Phenylmercuric salt solutions become less effective when stored in polythene containers. metallic mercury depositing if the phenylmercuric nitrate solution is kept in storage for an extended period of time.
c. 3 kept for an extended period of time.
d. When autoclaved in solution, chlorohexidine acetate is slightly degraded and is weakened by the cork.
e. Polyvinyl chloride and its solutions absorb benzoalkonium chloride.
f. form a deposit when the rubber liner comes into contact with it.
g. All of the compounds listed above require light protection in order to dissolve.

D. Dissolution of Medications and Additives: Adjuncts and medications should be dissolved in the appropriate medium. The processes for preparing containers, equipment, and solutions, as well as storing the ingredients, are typically the same as those for parenterals.

E. Clarification: The best method for clarifying eye drops is to use a membrane filter with 0.8 mm pore size. Particles cannot pass through because of this. Check the filtering unit for any foreign particles and refilter the solution if required.

F. Sterilization: This completes the preparation of the eye drops. Sterilization with a filtered solution is required to make it microbiologically free. A number of techniques are suggested for this procedure, the principal ones being autoclave heating and filtration.

1.2 Anatomy and Physiology of The Eye:

Figure 1.1 illustrates the layers and chambers of the eye as well as the pathways and obstacles to ocular drug delivery. These are all covered in the sections that follow.

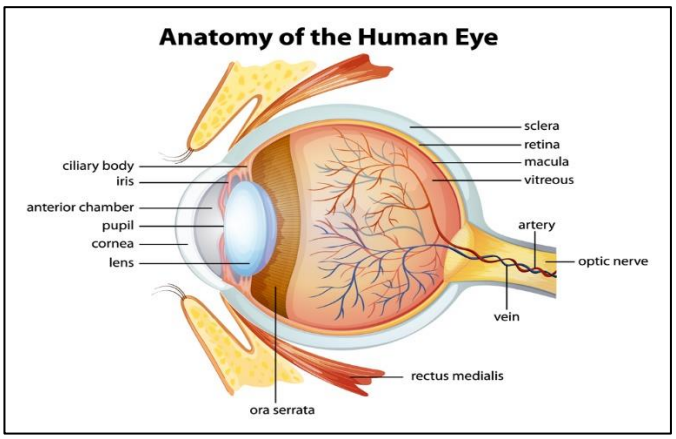

Figure 1.1: Anatomy of the Human Eye

A. Layers of the Eye:

The cornea and sclera, the two spheres that make up the outer layer of the eye, can be divided into segments. The front one-sixth of the globe is provided by the transparent cornea, and the remaining five-sixths are made up of the white opaque sclera. The sclera is a strong, fibrous tissue that keeps the eye's shape and shields it from external and internal forces. The term "white" of the eye refers to the area in front of the sclera. The outermost layer of the sclera, the episclera, has a plentiful blood supply. The visible portion of the sclera is covered by the thin, transparent conjunctiva, which also reaches the inside of the eyelids. It is a nonkeratinized, stratified columnar epithelium. In the back of the eye, the sclera is where the optic nerve exits.

The anterior portion of the eye, situated ahead of the iris and pupil, is called the cornea. Nerves, especially sensory nerves, innervate it densely. The anterior ciliary artery branches supply the corneoscleral limbus, whereas the central cornea lacks blood flow. Light is transmitted to the lens and retina through the cornea's refraction. Additionally, it shields the deeper portions of the eye from structural damage and infection. The limbus is where the cornea and sclera are joined. Tears, mostly secreted by the lacrimal gland, coat the surfaces of the cornea and conjunctiva. In addition to lubricating the surface of the eyes, it shields them from germs, chemicals, and solid particles in the air. It is composed of three layers: an aqueous layer produced by lacrimal glands, a superficial lipid layer produced by meibomian glands, and a mucous layer that adheres to the epithelium and is produced by goblet cells in the conjunctiva. The aqueous layer P is between 8 and 12 µm thick and contains electrolytes, proteins, glycoproteins, biopolymers, glucose, and urea. Fatty acids, wax esters, and sterol esters make up the lipid layer. Every blink of the eyelid permits the spread of the tear film across the surface of the eye due to interactions between the mucous layer and the cornea's epithelial cells. The precorneal tear film experiences a constant cycle of production, evaporation, and drainage, which results in a dynamic equilibrium.

The iris, ciliary li body, and choroid make up the middle layer of the eyeball. A ring of tissue called the ciliary body stretches from the choroid to the base of the iris. Its most noticeable structure, the ciliary muscle, is contracted to enable the lens to become convex. Aqueous and vitreous humour are also produced in the ciliary body. Aqueous humour production turnover rates range from 2.2 µL min^3 to 3.1 µL min^3.

The iris is a delicate diaphragm that divides the anterior and posterior chambers. It is positioned in front of the lens and ciliary body and contains radial dilator and circular constrictor muscles. It regulates the pupil's size, and consequently the quantity of light that reaches the retina. The amount of melanin expressed in the iris determines its color. The vascular layer of the eye that sits between the sclera and retina is known as the choroid. It gives the outer layers of the retina oxygen and nourishment, as well as creating a dark chamber where a higher-quality image can develop on the retina.

Light is processed by the retina, a sophisticated network of neurons that makes up the inner layer of the eye. The neural retina and the retinal pigment epithelium (RPE) are its two constituent layers. The RPE is the outer retinal wall that is encircled by the choroid and sclera, while the neural retina is the layer of the retina that surrounds the vitreous cavity.

The major classes of neural cells found in the retina are photoreceptors (the rods and cones that convert light into an electrical signal through a complex mechanism), bipolar cells, horizontal cells, amacrine cells, ganglion cells (which transmit and process light signals) with their long axon bodies that extend all the way to the brain, and Müller glia (which form the neural retina's organizational backbone). The neural cells of the retina are arranged in several parallel layers.

The RPE is made up of between 4.2 million and 6.1 million hexagon-shaped epithelial cells. Maintaining photoreceptor function, storing and metabolizing vitamin A, producing growth factors needed by surrounding tissue, and healing wounds following surgery or injury are just a few of their vital roles. Cone and rod cells are the two other types of photoreceptors. The primary cells involved in detecting contrast, brightness, and motion are rods, which number 115 million and are primarily found in the peripheral retina.

B. Chambers of the Eye:

The anterior chamber, posterior chamber, and vitreous cavity are the three main chambers of the eye. Both the anterior and posterior chambers are filled with aqueous humor. The fluid in question is transparent, colorless, and watery. It contains an extensive range of electrolytes, organic solutes, growth factors, and other proteins that support the nonvascularized tissue of the anterior chamber, specifically the corneal endothelium, lens, and trabecular meshwork. The ciliary body epithelium produces it, and it enters the anterior chamber.

The conventional pathway for aqueous humour to exit the anterior chamber is via the trabecular meshwork, which leads to Schlemm's canal and episcleral veins. The unconventional pathway involves the sclera and other tissues downstream. The primary mechanism for mass transfer from the eye is aqueous outflow. If the aqueous humor in the eye departs.

Increased intraocular pressure can result from an increase in the amount of fluid in the eye, which can harm the optic nerve and cause glaucoma. The extracellular matrix and specialized endothelial cells that make up the trabecular meshwork form a porous structure that allows aqueous humour to enter Schlemm's canal. Schlemm's canal has 25–35 collector channels that connect it to the venous system.

80% of the eye's volume is made up of the vitreous cavity. It has a weight of about 3.9 g and vitreous humour. This hydrogel is made up of about 98% water. The majority of the remaining 2% of vitreous components are made up of hyaluronic acid and collagen fibrils, or collagen type II. Moreover, there are proteins, organic salts, carbohydrates, and ascorbic acid. Vitreous humour has a viscosity two to four times that of water and a pH of about 7.5.

The viscosity of the vitreous humour is mainly caused by the presence of sodium hyaluronate. When compressed, it reverts to its original shape due to its viscous characteristics. The central and cortical vitreous bodies make up the vitreous body. The cortical vitreous humour has a slower turnover rate and a higher density, whereas the central vitreous humour has a greater turnover and is more liquid.

1.3 Ocular Drug Delivery Routes and Elimination Pathways:

With reference to Fig. 1.1 (see I, II, and III), the pathways and obstacles associated with ocular drug delivery can be summed up as follows: I. The primary pathway for ocular medications applied topically to reach the aqueous humour is the cornea.

a. into the systemic uveoscleral circulation from the aqueous humour
b. from the outflow of aqueous humour through the trabecular meshwork and Schlemm's canal.
c. from the vitreous humour into the anterior chamber via diffusion, and
d. through the blood-retinal barrier from the back.

1.3.1 Some Common Ocular Conditions and Pharmacological Interventions:

Ocular drug delivery is used to treat local disease at various sites in the eye, so a brief introduction to common eye conditions is appropriate.

A. Dry Eye Syndrome:

Dry eye is a common condition that occurs when either the tear volume is insufficient, or the tears are of poor quality (insufficiently lubricating). This frequently leads to unstable tears and, as a result, ocular surface disease, a term that is now frequently used instead of dry eye to reflect the complex nature of a poor tear film and abnormal ocular surface.

Depending on the underlying cause, dry eye and ocular surface disease can be difficult to control and can progress to chronic disease. The primary goal of management is to control symptoms and protect the ocular surface from damage. Initial treatments include the use of tear substitutes and mucolytic eye drops. In advanced cases, the use of anti-inflammatory eye drops, surgical intervention (e.g., to reduce lacrimal drainage by closing the lacrimal punctum) and contact lenses have been shown to be beneficial.

B. Cataract:

Cataract is the opacity of the lens caused by denaturation of the lens protein. Cataractes, which are typically age-related, are the most common cause of treatable blindness globally. Surgery is the only proven treatment and is widely regarded as the most successful surgical intervention in humans. The procedure entails removing the clouded lens, as well as the implantation of a synthetic intraocular lens.

C. Glaucoma:

Glaucoma is a group of diseases characterized by a specific type of optic nerve damage (optic disc cupping), resulting in a distinct pattern of visual field loss: first peripheral, then central vision loss. Glaucoma is the leading cause of irreversible blindness in the world and the second most common cause of blindness after cataract.

Raised intraocular pressure is the most important and only modifiable risk factor in this group of diseases. It has been demonstrated that lowering intraocular pressure through medical means (eye drops), laser therapy, or surgery can slow the progression of visual field loss.

D. Age Related Macular Degeneration:

AMD is a degenerative disorder that affects the macula, the most sensitive part of the retina, resulting in central vision loss. AMD is the leading cause of visual loss in developed countries, and it commonly affects people over the age of 50. AMD is classified into two types: wet and dry. Wet AMD develops when abnormal new blood vessels grow beneath the macula and leak, causing scar tissue to form in the macula and resulting in rapid loss of central vision. RPE cells degenerate in dry AMD, resulting in the loss of photoreceptors (due to the loss of RPE support). This results in atrophy and progressive blurring of central vision. Recent anti-VEGF treatments, such as pegaptanib (Macugen, Pfizer), ranibizumab (Lucentis, Genentech), and aflibercept (Eylea, Regeneron Pharmaceuticals), have shown to be effective in the majority of patients with wet AMD. However, these treatments necessitate multiple intra-ocular injections, with 8-12 injections required per year.

E. Endophthalmitis:

Endophthalmitis is an inflammation of the eye's internal layers. Infectious endophthalmitis is most common after ocular surgery and penetrating trauma, particularly with a retained foreign body. When injecting medications into the back of the eye, special precautions must be taken to ensure complete sterility. Gram-positive bacteria, such as Staphylococcus epidermidis, Staphylococcus aureus, and Streptococcus species, are the most commonly cultured bacteria in postoperative endophthalmitis (90%). Staphylococcus and Bacillus species are the most common bacteria found after trauma. Noninfectious endophthalmitis can be caused by a variety of factors, including impurities or aggregation in intraocular injections (for example, endotoxin or silicone oil precipitates). The main treatments are antibiotics and anti-inflammatory drugs administered via periorbital, intraocular, or parenteral routes, sometimes in conjunction with vitrectomy (removal of infected vitreous humour). Despite aggressive treatment, the visual outcome is frequently very poor.

1.4 Topical Ophthalmic Preparations:

Topical ophthalmic preparations include solution suspensions, ointments/gels, and the more recent dispersion systems. Traditionally, these have been used to treat pathological diseases of the front of the eye. Infection (conjunctivitis), inflammation, allergy, dry eye, glaucoma, and comeal ulceration are all conditions that affect the anterior eye segment.

Designing ocular drug delivery formulations necessitates an understanding of what the eye can tolerate. There are physical and biochemical mechanisms in place to protect the eye from harmful stimuli. Tears contain lysozymes and immunoglobulins, which have anti-infective properties. While these mechanisms are protective, they can sometimes interfere with drug absorption. The eye's lacrimal system is extremely dynamic. The tear volume in a normal eye range from 5 to 9 l. The lacrimal glands continuously secrete basal tears at an

average rate of 1.2 l. min, resulting in a tear turnover rate of approximately 17% per minute. Reflex tears are triggered by stimuli, and their secretion rate ranges from 3 l min to 400 l. min, with the goal of quickly eliminating the stimulus. The eyelid movements associated with blinking are another protective mechanism. Blinking transports tear fluids and foreign matter to the nasal corner of the lid surface, where the liquid exits through the puncta and is drained away by the nasolacrimal ducts into the inferior nasal passage (Figure. 1.2). Some of the drug may enter the systemic circulation quickly through absorption through the vascular nasal mucosa, inhalation as an aerosol, or absorption from the gastrointestinal tract after being swallowed.

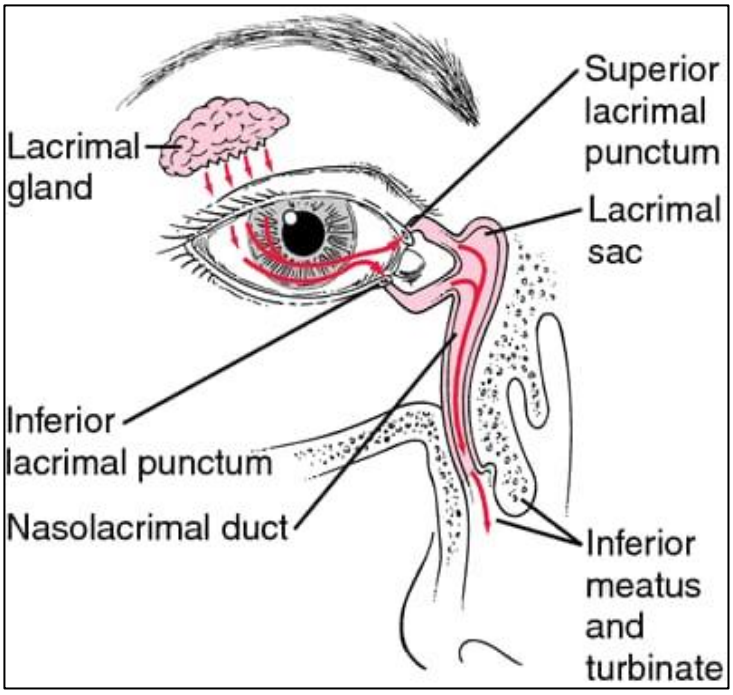

Figure 1.2: Topical Ophthalmic

Because of the combined mechanisms of lacrimal drainage and blinking, eye drops are rapidly cleared, with residence times ranging from 4 to 23 minutes. Furthermore, the rate of drainage from the eye has a positive, linear correlation with the volume instilled. The conjunctival sacs can only temporarily accommodate 20 l to 30 l of added fluid without spilling; however, the typical drop volume from eye drop bottles made by different manufacturers ranges from 34 l to 63 l. This variability is not only large, but it also exceeds the volume that the eye can accommodate if several drops are administered at once.

To minimize washout, eye drops should be administered at least 5 minutes apart. Punctal occlusion, which involves closing the eye and gently pressing the inside corner for at least one minute, increases local absorption while decreasing systemic exposure by up to 70%. It is critical that topical preparations do not cause irritation in order to reduce the elimination rate of administered eye drops. This can be accomplished by designing their properties to be as close to those of the lacrimal fluids that cover the surface of the eye as possible.

1.4.1 Formulating Ophthalmic Preparations:

A. Osmolarity:

The osmolality of lacrimal fluids is determined by the concentration of salts. Sodium, potassium, calcium, chloride, and bicarbonate ions are the most abundant inorganic ions in tears. These play an important role in controlling the osmotic pressure of the intercellular and extracellular fluids in the corneal and conjunctival epithelial spaces. During the day, the osmolality in healthy, non-dry eyes is 302 mmol kg on average. Patients with dry eye syndrome have been found to have tear film hyperosmolality, which contributes to the disease's symptoms. When the eye is exposed to a hypotonic ophthalmic solution, the corneal epithelium becomes more permeable, allowing water to enter the eye and cause oedema.The corneal epithelium is dehydrated by hypertonic solutions. Because hypotonic and hypertonic solutions irritate the eyes, they cause an increase in tear production. Through reflex tear secretion and reflex blinks, the rate of tear production increases to several hundred microlitres per minute. This faster tear turnover reduces the retention half-life of a solution applied to the eye. Hypertonic eye drops (5% sodium chloride solution) are occasionally used to treat eye conditions (for example, corneal oedema caused by a failing endothelial pump). The presence of hypertonic sodium chloride causes corneal osmotic dehydration, clearing some of the oedema and improving vision.

The osmotic pressure of normal tears is equivalent to 0.9% to 1.0% sodium chloride solution. The eye appears to tolerate solutions with osmotic pressures ranging from 0.6% to 1.3% sodium chloride. Tonicity agents such as sodium chloride, potassium chloride, buffering salts, dextrose, mannitol, and glycerol can be used to make ophthalmic solutions isotonic, as long as they are compatible with the other ingredients in the formulation.

B. Hydrogen Ion Concentration (PH):

The pH of tears is close to neutral and is regulated by a variety of substances dissolved in the aqueous layer of tears, including carbon dioxide, bicarbonate, proteins, enzymes, and fatty acids. The pH of tears varies throughout the day, rising gradually from 6.9 to 7.5 during the waking hours due to carbon dioxide evaporation. Tear fluids have a low but significant buffer capacity, which is primarily controlled by the balance of bicarbonate and carbon dioxide, as well as proteins. Because acidic or basic solutions instilled into the eye cannot be neutralized by the tears present, reflex tears are produced to dilute and eliminate the administered drop. Strongly acidic or basic solutions should not be used in the eye because they can cause damage to the ocular tissue. Topical ophthalmic preparations with pH values ranging from 3.5 to 9 are generally tolerated by the eye. However, it is preferable to formulate preparations that are as close to physiological tear pH as possible in order to minimize damage and discomfort, as well as the associated increased risk lacrimation.

The pH of a solution is critical for drug ionization and product shelf-life stability. Pilocarpine is a natural alkaloid that is used to treat glaucoma. It undergoes pH-dependent hydrolytic degradation, and one method for maintaining the pH of pilocarpine aqueous solution at 3.5-5.5 is to use a weak acidic buffer (e.g., boric acid and sodium citrate). Because the pH differs from the physiological pH of lacrimal fluids, the composing buffer

must be weak in order to reduce irritation and allow tear fluids to be restored to their normal pH in a short period of time without excessive lacrimation. Drug ionization also influences drug solubility and permeation across the corneal epithelium. The degree of ionization can be adjusted using lacrimation. The pH of a solution is critical for drug ionization and product shelf-life stability. Pilocarpine is a natural alkaloid that is used to treat glaucoma.

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C. Surface Tension:

In a healthy eye, the surface tension of tear fluid at physiological temperatures ranges from 43.6 mN m1 to 46.6 mmHg. The administration of solutions with surface tensions much lower than the surface tension of lacrimal fluid destabilizes the tear film and disperses the lipid layer into droplets that are solubilized by the drug or surfactants in the formulation. The oily film slows the evaporation of the underlying aqueous layer, and when it is lost, dry spots on the cornea form, which are painful and irritating. Surfactants are thought to be involved in the disruption of the oily layer.

Surfactants are commonly used in ophthalmic preparations to solubilize or disperse drugs, as well as to stabilize micro/ nanoemulsions. Polysorbates 20, 60, and 80, polyoxyl 40 stearate, and polyoxypropylene-polyoxyethylenediol are examples of nonionic surfactants that are the least irritating and thus the most commonly used. Polysorbates are the most commonly used nonionic surfactants in ocular preparations, and the European and American Pharmacopoeas have classified them as practically nonirritant.

Despite being the least irritating, some nonionic surfactants have been shown to remove the mucous layer and disrupt the cornea's tight junction complexes, increasing drug permeation. Surfactants in the preparation may also interact with polymeric substances, reducing the efficacy of preservatives. Surfactant concentration is important not only for drug solubility, safety, and patient tolerance, but also because high concentrations can cause foaming during product manufacturing or shaking.

D. Viscosity:

In ophthalmic solutions, viscosity-enhancing polymers are used to slow the drainage rate, extending drug retention in the precorneal tear film and improving drug absorption. Poly (vinyl alcohol) (PVA), polyvinylpyrrolidone, and various cellulose derivatives, particularly methylcellulose, hydroxypropyl methylcellulose, and carboxymethylcellulose (at concentrations ranging from 0.2% to 2.5%), and polyethylene glycol (at concentrations ranging from 0.2% to 1%), have all been used to increase solution viscosity. Tears are shear-dependent viscosity non-Newtonian fluids.

This is most common in linear, multiple-charged polymers like sodium hyaluronate and carbomers. Normal tears have been reported to have zero shear viscosity values of around 6.4 mPa s. Ophthalmic preparations have an acceptable viscosity of up to 15 mPa s; beyond that, increased lacrimation and drainage occur to restore the tear film to its physiological viscosity. Furthermore, very viscous solutions can cause blurred vision, potential puncta and canaliculi blockage, and pain when blinking.

1.4.2 Ophthalmic Liquid and Topical Preparations:

A. Solutions:

The most common topical ophthalmic preparation is ophthalmic solutions. They are usually the simplest to produce (have the lowest production costs) and are relatively simple for a patient or health care provider to administer. Ophthalmic solutions are also preferable when a quick onset of action is required because they do not require dissolution. This is true for local anaesthetics (such as lignocaine and proxymetacaine hydrochloride), ocular diagnostics (such as fluorescein sodium), and ocular preoperative drugs. Furthermore, because the solutions are homogeneous, the dose uniformity is improved. However, one limitation of solutions is that they are quickly drained from the eye. Furthermore, the rate of drainage is proportional to the size of the administered drop. The volume of eye drops administered from commercial eye dropper bottles has been reported to be between 34 and 63 l, depending on the physical shape and orifice of the dropper opening, the physicochemical properties of the liquid, and how the dropper is used.

B. Suspensions:

As suspensions, several ocular preparations are available. This method has been used to administer drugs that are only slightly soluble in water (e.g., steroids) or to extend drug release. Particles tend to be retained in the conjunctival sac (the pouch formed by the conjunctiva covering the inside of the lower eyelid and the sclera) and slowly dissolve, increasing the contact time. Particle size and shape must be carefully chosen because some particles can irritate sensory nerves in the epithelium. Furthermore, particle size influences drug dissolution rate (Chapter 20).

Because large particles cause irritation and increased tearing, the European Pharmacopoeia and the United States Pharmacopoeia set limits for the maximum particle size permitted in ocular suspensions.

The European Pharmacopoeia states that for a sample containing 10 g of solid active substance, "not more than 20 particles should have a maximum dimension greater than 25 m, and not more than two of these particles should have a maximum dimension greater than 50 m." The maximum dimension of any of the particles is 90 m'. To ensure uniform dose administration, the particles of a suspension must be easily dispersible when shaken by the patient. From the first to the last use of a multidose container, homogeneity and dose uniformity must be confirmed. A change in the crystal form of the drug (i.e. polymorphic changes during storage) can cause a problem with suspensions, this can alter drug solubility and dissolution behavior. Ostwald ripening may occur as a result of fluctuations in storage

temperature or prolonged storage if the drug particle size is polydisperse (see Chapter 26). Cake formation is another issue that cannot be solved by forming a flocculated suspension because large floccules can irritate the eye. The use of a polymer solution as a viscosity-increasing agent can prevent caking and allow particle resuspension through shaking. Suspensions of betaxolol and brinzolamide are available. The former's formulation includes carbomer 934P and ion-exchange resins. Nepafenac is a nonsteroidal anti-inflammatory prodrug used to treat the pain and inflammation caused by cataract surgery. Because it is practically insoluble in water, it is formulated as a suspension: Nevanac 0.1% (Novartis) three times daily and llevro 0.3% (Alcon) once daily. When compared to Nevanac, the Ilevro formulation has a higher active substance concentration, 2.5-fold smaller drug particle size, and higher viscosity (due to the use of carbomer-guar polymers). These formulation changes improved ocular bioavailability and allowed for once-daily administration, resulting in improved patient convenience and adherence.

C. Submicron emulsions:

Ciclosporin is an immunomodulator that also has anti-inflammatory properties. It is available as a submicrometre emulsion (Restasis, Allergan) at a concentration of 0.05% for topical application to the eye. Ciclosporin is hydrophobic (log P = 3.0) and has a very low aqueous solubility of 6.6 g mL, making it incompatible with conventional aqueous ophthalmic vehicles. It has been successfully dissolved in an oil-in-water submicrometre emulsion at a pH of 6.5-8.0. Restasis' oil phase is castor oil, and the emulsion is stabilized with the nonionic surfactant polysorbate 80 and glycerol, which acts as a cosurfactant here. When compared to suspensions, ocular submicrometre emulsions with droplet sizes of about 0.1 m have shown promise for prolonging drug release and achieving significantly higher drug concentrations in the cornea and aqueous humour. ophthalmic semisolid topical preparations

D. Ointments:

Ophthalmic ointments account for about 10% of ophthalmic products and are typically used to treat inflammation, infections, and ocular surface disease. They have the advantage of decreasing drug drainage through tear flow and thus increasing corneal residence time. Ointments can also become entrapped in the conjunctival sac, acting as a drug reservoir. Typically, sustained drug release occurs over 2-4 hours. Ointments also have the advantage of allowing drugs with low aqueous solubility to be included. Hydrophobic ointments, particularly peptides, can sometimes increase the stability of hydrolysable compounds. Soft and liquid paraffin are both common bases for ophthalmic ointments.

Antibiotics, antifungals, and steroids are the most common drug classes available as ointments. Drug bioavailability is typically higher in ointment vehicles than in solutions or suspensions. Ointments, on the other hand, are more difficult to administer than solutions and may result in a more variable dose. Furthermore, blurring of vision occurs, which reduces patient adherence, making ointments more useful for nighttime administration. Because of favourable partitioning towards the base, drug molecules may become entrapped within the ointment base, inhibiting drug release. The base is also sensitive to temperature changes.

E. Gels:

Gels are semisolid systems composed of water-soluble bases that are more advantageous than ointments for water-soluble drugs (see also Chapter 54). Polymers such as PVA, poloxamer, hydroxypropyl methylcellulose, and carbomers dispersed in a liquid are examples. Ganciclovir is an antiviral that is used to treat herpetic keratitis (eye ulcers caused by the herpes virus that primarily affects the cornea). It is available as a carbomer-based feed ingan, Bausch and Lomb. It is formulated at pH 74, which allows polymer interchain repulsion and swelling to form a transparent gel while also being well tolerated by the eye.

Ions, pH, and temperature-activated gels have also been developed. In the conjunctival sac, these go through a phase transition from liquid to solid to form a viscoelastic gel. The advantage of in situ forming gels over preformed gels is that the dose is more reproducible, and administration is easier, which improves patient adherence. Poloxamers (for example, poloxamer 407) are examples of temperature-activated polymers. Smart Hydrogel, a graft copolymer of poly (acrylic acid) and a poloxamer, has been developed and requires only 1% to 3% polymer concentration to gel at body temperature. Because of the presence of poly (acrylic acid), Smart Hydrogel has bioadhesive properties as well.

Timolol is a nonselective B-blocker that is approved for the treatment of glaucoma. The gel-forming solution of timolol maleate (Timoptic-XE, Merck) contains a purified anionic heteropolysaccharide derived from gellan gum. In the presence of cations in the precorneal tear film, the gellan gum forms a gel in aqueous solution.

The cations neutralize the polymer, reducing its solubility. They also connect the polymer chains, resulting in a structured polymer network. To achieve a similar reduction in intraocular pressure, Timoptic-XE is administered once daily, as opposed to twice daily for the regular Timoptic preparation. This gel is then washed away by the flow and drainage of tears. When exposed to the ionic strength of ocular fluids, alginates also undergo sol-to-gel phase transition.

Examples of gel and gel-forming ophthalmic preparations can be found in Table 41.1. Carbomers have pK values of 4-5, and these polymers' ophthalmic solutions are prepared in this pH range. When these systems are exposed to ocular fluids with near-neutral pH, the polymer solubility decreases and the system gels.

1.4.3 Systems for Mucoadhesive Adhesion:

Mucoadhesive polymers have also been used to increase the contact time of topical ophthalmic solutions with the ocular surface. These polymers have the ability to bind to the mucin coat that covers the conjunctiva and cornea. Mucin has a protein or polypeptide core with branching carbohydrate chains. The mucin coat protects, hydrates, and lubricates the eye's surface. Mucoadhesive polymers are typically macromolecular hydrocolloids with a high charge density and numerous hydrophilic functional groups. They should also have good ocular surface wetting to allow for maximum interaction with the mucin coat. The most common interactions between mucoadhesive polymers and mucin are electrostatic and hydrogen-bond interactions.

Natural, synthetic, or semisynthetic mucoadhesive polymers can be used. Poly (acrylic acid) and polycarbophil, as well as cellulose derivatives, are examples of synthetic polymers. Chitosan and various gums such as guar, xanthan, carrageenan, pectin, and alginate are among the (semi)natural mucoadhesive polymers. Chitosan is a cationic polymer that has shown promise in ophthalmic applications. It has good wetting properties, is biodegradable, biocompatible, and has good ocular tolerance in addition to being mucoadhesive. Because it is positively charged at neutral pH, electrostatic forces form between it and the negatively charged sialic acid residues of mucus glycoproteins, contributing to its mucoadhesion mechanism. Another polymer that has shown promise is hyaluronic acid.

It is a high molecular weight biological polymer composed of linear polysaccharides that is found in the extracellular matrix and is the primary component of vitreous humour. It has mucoadhesive and viscoelastic properties, as well as a high capacity for water binding. Some ocular surgical procedures use hyaluronic acid in the anterior chamber (e.g., cataract, glaucoma), subconjunctival space (e.g., glaucoma filtering surgery), or posterior chamber (retinal reattachment). Polycarbophil (poly (acrylic acid) cross-linked with divinyl glycol) was used in an azithromycin topical formulation (AzaSite/ DuraDite, Inspire Pharmaceuticals) that was shown to have higher bioavailability than conventional aqueous eye drops.

Therapeutic drug levels remain in the eyelids and conjunctiva for several days after the last dose is administered. Polycarbophil is water insoluble, and its swelling is pH dependent. The pH range of lacrimal fluids, pH 6-7, causes the most swelling. Polycarbophil swells and entangles with mucin on the ocular surface when exposed to tears. There is also hydrogen bonding between polycarbophil's unionized carboxylic acid and mucin.

A. Ion-Exchange Resins:

For more than 50 years, ion-exchange resins have been used and marketed in various dosage forms to control drug delivery. To form an insoluble complex, the drug (acidic or basic) is ionically bound to an ion-exchange resin. Only by exchanging bound drug ions with physiological ions in body fluids can the drug be released from the complex. The actual resin is an insoluble, ionic material made up of two parts: a structural portion made up of a polymer matrix, typically styrene cross-linked with divinylbenzene, and a functional portion containing the ion-active group.

The ion-active group can be negatively or positively charged, allowing it to function as a cation exchanger or an anion exchanger. These drug-resin complexes are typically spherical and porous, hydrating when exposed to aqueous fluids. They are insoluble, nonabsorbable, and are considered safe for use in human oral and ophthalmic preparations. They've been used in a variety of pharmaceutical applications, including taste masking, drug stabilization, and sustained-release solid dosage forms and liquid suspensions.

Betaxolol hydrochloride (a cardioselective B-blocker) is available in the form of an ion-exchange resin suspension. Alcon, Bet optic S). The positively charged drug is bound to an amberlite IRP69 cation-exchange resin. Amberlite IRP69 has a styrene-divinylbenzene polymer matrix and a sodium polystyrene sulfonate functional portion.

Sulfonic acid is a powerful cation exchanger. The mobile, or exchangeable, cation is sodium, which can be exchanged for a variety of cationic species (for example, potassium or calcium in lacrimal fluids). The sodium ions in the tear film displace betaxolol from the resin upon ocular instillation of the suspension. This exchange lasts several minutes. Because betaxolol's polar nature can cause ocular discomfort, it is best formulated as an ion-exchange resin to slow drug release and reduce discomfort.

One of the factors influencing drug release rate is resin particle size. To achieve a fine suspension, the resins in Betoptic S have been finely milled to a diameter of 5 m. A polymer, Carbomer 934P (a water-soluble acrylic polymer), is also included to improve the product's physical stability and ease of resuspension, as well as the ocular residence time.

1.4.4 Topical Ocular Drug Absorption Barriers:

The most common method of treating the anterior segment is through topical drug delivery, and more than 90% of ophthalmic medicines on the market are in the form of eye drops. The topical route offers selectivity with an improved therapeutic index, avoids first-pass metabolism, and allows drugs to be administered in a simple, noninvasive manner. However, its main shortcoming is inefficiency, as only 1% to 5% of the instilled dose reaches the aqueous humour. The mechanisms primarily responsible for this low ocular drug bioavailability are the highly efficient lacrimal drainage system, drug absorption by conjunctiva blood vessels into the systemic circulation, and the corneal barrier to drug permeation. Drug binding reduces absorption as well, and protein levels in lacrimal fluids are higher in inflamed or infected eyes.

A. The Corneal Layer:

The epithelium, stroma, and endothelium (froration the inner surface) are the layers that form significant barriers to drug outer surface (Fig. 41.4). The epithelium and endothelium are lipid-rich, whereas the stroma is water-rich. The meal epithelium is about 0.1 mm thick (six cells) and is thought to be the rate limiting barrier to transcorneal drug permeation. The barrier to hydrophilic drugs is contributed by epithelial cells, while the barrier to lipophilic drugs is contributed by a small percentage of the population. Drugs can enter this layer by passing through cells (via the transcellular route) or between cells (via the paracellular route). The epithelium, on the other hand, has tightly adherent cells with tight junctions and rejects macromolecules with diameters greater than 1 nm.Drugs can enter the cornea via passive diffusion, forced diffusion, or active transport. Transporter proteins expressed on the corneal epithelium facilitate diffusion and active transport. Passive diffusion does not require transporters, but it is determined by the drug's physicochemical properties. The cornea has five layers: epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium.

Only small drugs and ions with molecular weights less than 350 can pass through the paracellular route. The transcellular route allows most lipophilic compounds to pass through the corneal epithelium. Because the cornea is a tight tissue, tighter than the intestine, lung, and nasal mucosa, drug absorption via the paracellular route is more difficult than in these other organs.

However, drug permeation from ocular eye drops can be enhanced due to defects in the epithelial layer in certain ocular circumstances affecting the epithelial cells of the cornea (e.g. contact-lens-related infectious keratitis and multiple applications of eye drops, e.g. local anaesthetics).

The stroma is a cellular, aqueous environment containing glycosaminoglycans and collagen fibrils (collagen types I and III) organized in parallel lamellae. Because it is open knit, hydrophilic molecules can pass through relatively easily. However, it prevents highly lipophilic or high molecular weight compounds from penetrating. The endothelium of the cornea is a single cell layer with numerous intercellular junctions. It is in direct contact with the aqueous humour and partially resists the permeation of lipophilic but not hydrophilic compounds.

Ophthalmic drugs with low molecular weight and low lipophilicity are absorbed more efficiently through the cornea than hydrophilic, ionized drugs. The optimal lipophilicity for steroid and B-blocker permeation corresponds to log P of 2-3. Higher lipophilicity (log P > 3) compounds have been shown to have lower permeability because their permeation is rate limited by the slow transfer through the hydrophilic stroma. For good corneal permeation, drugs must have an appropriate balance of lipid and water solubility. Aqueous solubility is important because drugs must be in solution in order to permeate the cornea, particularly the stroma. It also produces a significant drug concentration gradient between the tear film and the corneal epithelium. Because the instilled drops are diluted by tear fluids and only have a brief contact with the corneal epithelium, high drug concentration is an important consideration for ophthalmic solutions when possible. The pH of an ionizable drug formulation can be adjusted to achieve the best balance of solubility and transepithelial permeation. A drug should have good aqueous solubility at the physiological pH of tears without losing lipophilicity for corneal permeation.

B. Noncorneal Routes of Absorption:

While the corneal route is the most common route for topically administered drugs to enter the eye, studies have shown that absorption can also occur through the conjunctival-scleral layer, particularly for large hydrophilic molecules such as timolol maleate and carbonic anhydrase inhibitors, as well as proteins and peptides that can be used as carriers. The conjunctiva is made up of 5-15 layers of squamous epithelial cells, each with tight junctions at the apex. It is more permeable or leaky than the cornea, allowing drugs to pass through both the paracellular and transcellular pathways.

Because the conjunctiva is highly vascularized, drug absorption frequently results in systemic drug distribution away from the eye. Because the cornea only covers about one-sixth of the surface area of the eye, conjunctival absorption is common. Drug efflux transporters on epithelial cells have also been identified. Blood vessels, nerves, and lymphatics connect to the sclera in the conjunctival stroma. The aqueous intercellular space between the collagen fibers allows drugs to permeate the sclera. Drug permeation through the sclera is not affected by lipophilicity or particle size. Drugs with molecular weights greater than 1000 are almost incapable of penetrating the cornea, whereas dextran (molecular weight 40000) and albumin (molecular weight 69000) penetrate the sclera well.

Despite this, the conjunctival-scleral route is considered ineffective because the instilled drug is rapidly absorbed by the blood vessels in the conjunctiva and dissipates into the systemic circulation rather than ending up in the aqueous humour.

As a result, significant drug interactions between ocular and orally administered medications can occur, and some topical ocular preparations are contraindicated in patients with certain medical conditions (for example, eye drops of B-blockers in patients with either asthma or overt cardiac failure). Despite the fact that topical ocular drug doses are much lower than oral doses, direct access via inhaled or nasal mucosal absorption bypasses losses such as intestinal absorption and liver first-pass effects.

1.4.5 Improving the Solubility and Absorption of Drugs in Topical Ophthalmic Preparations:

A. Ionization of drugs, salts, and esters:

The degree of ionization in solution is determined by the drug's pK (acid dissociation constant) and pH. While the PK can only be changed by structural changes in the molecule, the pH of the drug vehicle can be changed. Controlling the pH can improve drug solubility and thus the amount of drug that can be accommodated in the product.

Trans corneal permeation can be increased by a higher proportion of unionized species. Controlling drug ionization through the pH of the administered solution, on the other hand, has a short-term effect because lacrimation returns the pH of the administered solution to the physiological pH of tear fluids, which ultimately determines the ionization pattern. Carbonic anhydrase inhibitors, on the other hand, have a greater pharmacological effect (reduction in intraocular pressure) in the ionized form than in the unionized form.

Form that has not been ionized. This effect is observed not as a result of increased drug permeation, but rather as a result of these inhibitors' ability to be sequestered in the comea and form a depot. Drug solubility and lipophilicity are affected by chemical derivatization, which can be an important determinant of ocular bioavailability. When compared to its tablet form, prednisolone acetate suspension has higher corneal permeation and increased ocular bioavailability. Prednisolone sodium phosphate is the hydrophilic counterpart. When compared to the very water-soluble phosphate salt, dexamethasone acetate ester has the best balance of solubility and corneal permeability.

B. Cyclodextrins:

Cyclodextrins (CDs) have demonstrated significant potential in increasing the solubility of drugs that are poorly water soluble. CDs are lipophilic cyclical oligosaccharides with a hydrophilic outer surface. They have the ability to complex lipophilic drugs in their interior, resulting in water-soluble complexes. This preserves the structure and lipophilicity of the compounds, as well as their permeability. Noncovalently, the drug is linked to CD via hydrogen bonding, hydrophobic interactions, or van der Waals forces. The hydrophilic CD transports water-insoluble molecules to the corneal membrane, where they can separate from the CD complex.

The strength of the noncovalent interactions between the drug and CD determines the state of equilibrium between free and complexed drug. The relatively lipophilic membrane has a low affinity for the large hydrophilic CD molecules, and the biological membrane is not disrupted, as with penetration enhancers. Furthermore, because irritant drugs are not freely available and are entrapped in the complex, this provides an opportunity for them to be delivered. This formulation approach has been shown in studies to increase corneal penetration of dexamethasone, pilocarpine, and carbonic anhydrase inhibitors.

C. Prodrugs:

The use of prodrugs can result in increased corneal penetration. A prodrug is a drug with additional functions that, through enzymatic or chemical reactions, converts to the active parent drug. Prodrug-enhanced corneal penetration can be achieved by optimizing lipophilicity, increasing aqueous solubility, increasing affinity for uptake transporters, and evading efflux pumps. Drugs containing carboxylic acid groups, such as prosta- glandin analogues used to treat glaucoma, have low corneal permeation. This is due to carboxylic acid group ionization at the near-neutral pH of tears, which reduces permeation through the lipophilic epithelium. Esterification of the carboxylic acid group has been used to mitigate this. These derivatives can easily revert to their parent form due to the cornea's high esterase activity. One issue with ester prodrugs is their increased susceptibility to hydrolysis. Bulky isopropyl esters have been used to achieve aqueous solution stability. Latanoprost and travoprost are isopropyl esters of prostaglandins. When compared to their parent forms, these prodrugs have greater corneal permeability and lower intraocular pressure. (i.e free acids).

Dipivalyl adrenaline (dipivefrine) was the first marketed ophthalmic prodrug and is also used to treat glaucoma. It is metabolized to adrenaline, which was originally used as a drug but was later found to cause severe side effects in patients. Because adrenaline is a polar drug, it was rapidly cleared from the ocular surface via nasal lacrimal drainage. As a result, systemic absorption was significant, resulting in cardiac arrhythmias and blood pressure elevation. The prodrug, adrenaline dipivalyl ester, was designed to be more lipophilic than the parent drug in order to increase corneal permeation.

Other clinically used prodrugs include the B-blocker levobunolol (log P = 2.4). Levobunolol is converted to active dihydrolevobunolol in the cornea via metabolic reduction of its keto group. Dihydrolevobunolol is more lipophilic than its parent form and has a longer half-life. Active research is being conducted in the development of prodrugs for the antivirals aciclovir and ganciclovir. These prodrugs' amino acid and peptide derivatives target the cornea's amino acid and peptide transporters.

1.5 Sterility of Opthalmic Preparation:

Is a regulatory requirement that preparations intended for ophthalmic use, including those for cleansing the eyes, be sterile Ocular infections are extremely dangerous and can rapidly lead to the loss of vision. Eyebaths, droppers and all ether dispensers should also be sterile and regulated if packaged with the drug product. For ophthalmic preparations', terminal sterilization of products in their final containers should be adopted wherever possible.

If the product cannot withstand terminal sterilization, then filtration under aseptic conditions should be considered, usually performed using a filter pore size of 0.22 µm or less. Sterilization methods are discussed in detail in Chapters 16 and 17. The raw materials used for aseptic manufacture should be sterile, wherever possible, or should meet a low specified bioburden control limit. Ophthalmic preparations once must furthermore be labelled with the duration of use opened. Antimicrobial preservatives are included in multidose containers to destroy and inhibit the growth of microorganism that may have been accidentally introduced on opening the container (see Chapter 52).

They are not to be used in products for intraocular administration as they can lead to irritation. Ideally, a preservative should have a broad-spectrum antimicrobial activity, exhibit compatibility and stability with all the ingredients in the preparation and the container and be innocuous to the ocular tissue. Benzalkonium chloride is the most commonly used preservative, at concentrations ranging from 0.004% to 0.02%. It is a quaternary ammonium surfactant and causes epithelial inflammations and cell damage on repeated administration. Poor tolerance to treatment has been associated with Benzalkonium chloride, and chronic inflammation of the conjunctiva has been reported, Benzalkonium chloride is also found in other products, such as hand sanitizers and antiseptic. Never alternatives have been developed, SofZia and Purite, for which tolerances is better. Sofia is found in travoprost ophthalmic solution (Travatan, Alcon) and Purite is present in brimonidine tartrate (Alphagan P. Allegan).

These newer preservatives work in a different way from benzalkonium Sofia is an ionic buffered preservatives comprising boric chloride acid, propylene glycol, sorbitol zinc Purite is a stabilized oxychloro complex and break down into innocuous products on contact with air. Single dose units have been to the use of preservatives while maintaining the product stability. The manufacturing and packaging of however, expensive and so they have not been embraced for or all marketed ophthalmic solution. Several multidose containers have been developed that maintain sterility without the use of a preservative, one of these is the ABAK patented filter system, which uses a 0.2 um polyether sulphone membrane with both hydrophilic and hydrophobic properties to prevent bacteria from entering the bottle. The Airless Antibacterial Dispensing System (AADS, Pfizer) works by preventing air, and therefore bacteria, from entering the container as drops are dispensed. Furthermore, a silver coil is included in the bottle tip. Silver has anti- bacterial properties and therefore any bacteria contacting the tip do not contaminate the contents. This system guarantees 3 months of sterility in-use.

1.6 Ocular Drug Pharmacokinetics:

A. Drug half-life in the anterior chamber:

Peak drug levels in the anterior chamber are reached 20-30 minutes after eye drop administration for corneal permeable drugs. These concentrations in the aqueous humor are typically, however, at least twofold less than the administered concentration. From the aqueous humor the drug can diffuse to the iris and ciliary body, where it may bind to melanin and form a reservoir allowing gradual drug release to the surrounding cells. The drug is eliminated from the aqueous humor by two main routes aqueous turnover through the

trabecular meshwork and Schlemm's canal (Fig. 41.1. route 2) and by the venous blood flow of the anterior uvea across the blood aqueous barrier (Fig. 41.1, route 2). Aqueous humour turnover is at a rate of µl min to 3.1 pl. Min 2.2 For an individual with an average anterior chamber volume of 185 ul, the half-life of anterior chamber fluid is 43 minutes. Moreover, the directional flow of aqueous humor from the ciliary body towards the trabecular meshwork is often against the diffusion of the drug towards intraocular target tissues, The other mechanism of drug elimination by the weal and flow is dependent on drug permeation factors in the endothelial cells of the blood vessels and is therefore more favourable for lipophilic drugs. The clearance of lipophilic drugs can be in the range from 10 pl. min to 30 µl. min Drug half-lives in the anterior chamber are typically short, being approximately I hour. Drug distribution to the vitreous is extremely low as the lens prohibits diffusion.

B. Active Transporters of The Cornea:

Various uptake and efflux transporters have been shown to be present in the corneal epithelium. These transporters are also present in the epithelium of the intestine, blood-brain barrier and kidney tubuli. Efflux transporters protect cells from noxious stimuli and are also implicated in drug resistance. It is estimated that 25% of administered drugs are substrates for transporters. Because the cornea is in contact with the external environment, it is not surprising that it expresses efflux transporters as part of a protective mechanism.

Efflux transporters that have been identified on the corneal epithelium include P-glycoprotein (also known as multidrug resistance protein 1), breast cancer resistance protein (BCRP) and multidrug-resistance associated protein (MRP) 5. P-glycoprotein was found to be implicated in the transport of ciclosporin (immunomodulator for treating dry eyes) in the cornea. The prostaglandin agonists used in the treatment of glaucoma (bimatoprost latanoprost and travoprost) and their free acid forms are substrates of the MRPS efflux pump on the cornea. Bima toprost is also a substrate a substrate for P-glycoprotein. Coadministration of these prostaglandin agonists for the treatment of glaucoma has been proposed for overcoming efflux, as well as for achieving a synergistic pharmacological effect, since these molecules may act primarily at different receptors to reduce intraocular pressure. One of the main groups of uptake transporters in the corneal epithelium is the amino acid transporters. The corneal epithelium is a highly regenerative tissue with continuous synthesis, thus placing a on amino acid transport.

The aqueous humour is the main source of nutrient provision for the corneal epithelium. Oligopeptide transporters have also been identified and shown to be involved in the transport of valaciclovir (L-valyl ester of aciclovir) through the concha. They are also being utilized in prodrug delivery. The organic anion transporting polypeptide (OATP) family has substrates of a mainly anionic, amphipathic nature. Their presence in the cornea may be implicated in the transport of thyroid hormone, which has a role in the development and transparency of the cornea. Its involvement in drug transport has not been determined. The significance of the role of the secular transporters still requires investigation. With To topical solutions, the contact time is short and most of the drug absorption occurs in 2-3 minutes after instillation. Hence these transporters may become taut rated, and passive diffusion becomes the predominant mechanism.

C. Blood Retinal Barrier:

The blood-retinal barrier (Fig. 41.1, route II) restricts the entry of drugs from the systemic circulation into the posterior segment of the eye. It is composed of two parte an outer part formed by the RPE and an inner part, comprising endothelial cells of the retinal vessels. There two parts are connected to each other by tight junctions which pose a barrier to the perfusion of hydrophilic drugs from the highly vascular choroid into the retina and vitreous humour, and vice versa. The blood-retinal barrier has some structural similarities to the blood- brain barrier. Transporters that have been identified in the RPE include amino acid transporters, oligopeptide transporters, mono-Carboxylate transporters, folate transporters and vitamin C transporters, as well as glucose transporters, QATP, organic cation transporter (OCI) and organic anion transporter (OAT). The efflux transporters are P-glycoprotein, MRPT, MRP4, MRPS and breast cancer resistance protein. Drugs that have been found to have interactions with trans- porters in the blood-retinal barrier are predominantly substrates of OAT, OCT or OATP. Substrates of CIAT include various antibiotics (penicillin, erythromycin and tetracycline) and antivirals (aciclovir, zidovudine). The main substrates for OCT are the antiglaucoma drugs carbachol, dipivefrine, brimonidine and timolol. Peni cillin, erythromycin, steroidal anti-inflammatory agents (dexamethasone, hydrocortisone, prednisolone) and ciclosporin are OATP substrates Transporters seem to play an important role in drug delivery to the posterior segment of the eye. Moreover, drug concentrations are low at the blood-retinal barrier, which means that the trans porters are unlikely to be saturated and therefore their role is unlikely to be significant.

D. Ocular Metabolism:

Another ocular defense mechanism which protects the eye from the outside environment is the metabolism of xenobiotic. A xenobiotic is a chemical compound foreign to a given biological system. For humans, xeno- biotics include drugs, drug metabolites and environ mental compounds such as pollutants that are not produced by the body. In the environment, xenobiotics include synthetic pesticides, herbicides and industrial pollutants that are not found in nature. Both phase I and phase II metabolism reactions occur in ocular tissue Phase I is where a polar functional group is introduced into the molecule which makes it more susceptible to phase II conjugation reactions.

In some cases, however, the products of phase I reactions are eliminated from the body without further changes. Studies show that the most active metabolic sites in the eye are the ciliary body and pigmented epithelium of the retina. This may be attributable to the high perfusion of these sites by the blood circulation and consequently exposure to the xenobiotics circulating in the blood. Moreover, the main function of the ciliary body is to produce aqueous humour through ultrafiltration of plasma. It should therefore have an increased capacity to handle the exogenous to which it is exposed and convert them into harmless metabolites, which could otherwise have toxic effects on the lens and other internal organs of the eye. Alternatively, it is possible that these tissues may be more prone to long-term effects of xenobiotics (eg the products of cigarette smoke may have long-term effects on the RPE, which may become more susceptible to disease and may die more rapidly in people who smoke).

The enzymes involved in phase I reactions are the esterase, which have been identified in ocular tissue and include acetylcholinesterase, butyrylcholinesterase and catboxycholinesterases. This hydrolysis of compounds containing ester linkages has been exploited in prodrug design, including design of dipivalyl adrenaline and pilocarpine prodrugs. Various esterase has been iden tined in the cornea. Aldehyde and ketone reductases have also been in ocular tissue. Ketone reductase reduces levobunolol, a B-blocker indicated for the treatment of glaucoma.

Peptidase activity has also been determined. Cytochrome P450 (CYP) expression is considered marginal in the human cornea, iris-ciliary body and retina-choroid Several ocular drugs are substrates for CYPs and the expression levels of these enzymes in the liver have been implicated in the systemic response to these locally administred ophthalmic medicines. Timolol is a nonselective B-blocker used as an antiglaucoma medication. Although it is topically administered into the eye, it is partially absorbed into the systemic circulation, where it is metabolized by the CYP2D6. Individuals who are poor metabolizers of timolol can be more prone to its adverse systemic effects, such as reductions in heart rate and blood pressure. Moreover, CYPS aze inducible by several pharmacological agents, including phenobarbital, rifampicin and phenytoin, such induction can increase drug metabolism. One of the phase II enzymes identified in the eye is glutathione S-transferase. This binds to lipophilic compounds, such as bilirubin and haematin, which is a critical step in the detoxification process. Glutathione S-transferees has been identified in the lens, and deficiency of it has been associated with cataract.

1.7 Targeting the Posterior Segment of The Eye:

A. Intraocular Injections:

Intravitreal injections provide the most efficient means of reproducible drug delivery to the back of the eye. The drug bypasses the blood-ocular barriers, thus achieving higher intraocular levels, which improve treatment efficacy. Systemic side effects are also minimized Intravitreal injections have been shown to be effective in patients for a variety of low molecular weight drugs and antibody-based medicines.

The advent of antibody-based medicines since the early 2000s to treat blinding conditions has resulted in intravitreal injection becoming a routine clinical procedure, especially to treat the elderly population. The intravitreal route is approved for anti-VEGF indicated for the treatment of neovascular (or wet) AMD, which is the main cause of blindness in the elderly. Neovascular AMD can progress rapidly, leading to irreversible sight loss within days or weeks VEGF induces angiogenesis and augments vascular permeation and inflammation, which are thought to contribute to the progression of the wet form of AMD VEGF has also been implicated in blood-retinal barrier breakdown. The three approved treatments, pegaptanib sodium (Macugen, Pfizer), ranibizumab (Lucentis, Genentech) and aflibercept (Eylea, Regeneron Genentech), are all large antibody-based molecules that bind to and inhibit the activity of different isoforms of VEGF Pegaptanib is a PEGylated modified oligonucleotide, ranibizumab is a fragment of a monoclonal antibody (Fab fragment of humanized immunoglobulin (G1) and aflibercept is a recombinant fusion protein consisting of portions of VEGF receptors fused to the Fc portion of human

immunoglobulin G1. These antibody-based drugs need to be injected into vitreous humour approximately every 4-12 weeks Much research effort is ongoing to develop products that require intravitreal administration much less frequently.

Drug retention in the vitreous space depends on drug diffusion rates from the vitreous cavity and retinal permeability, which in turn determines the frequency of administration. The half-lives of most drugs for the treatment of posterior segment disease range from a few hours to a few days, which have been estimated with different animal models. Dexamethasone phosphate has a vitreal half-life of 5.5 hours. The half-life of pegaptanib in the vitreous Humour is 3-5 days, that of ranibizumab is 5-7 days and that of aflibercept is predicted to be at least 7 days because of its larger size. Triamcinolone acetonide is one of the few exceptions, with a long half-life of 18.6 days, the injections are therefore given only every 3-4 months. Triamcinolone aretonide is injected as a suspension, and its slow dissolution in the vitreous humour contributes to its longer half- life as a formulation.

Repeated intravitreal injections cause patient discomfort and associated complications include retinal detachment, endophthalmitis, vitreous hemorrhages and infection. The lens can also be affected, and cataracts may form. Elevation of intraocular pressure may also occur, especially with steroid injections: Small volumes of 0.05 ml. to 0.10 ml. are typically used for injection. Although these adverse events have a love incidence, they can be sight threatening Sustained-release implants are being developed to overcome these problems and to achieve steady concentrations of the drug while minimizing the peaks and troughs in drug levels. summarizes the different approaches for targeting the posterior segment of the eye. Intravitreal injections are a bunden om patients, and formulation strategies remain an active area of research to reduce dosing frequency as patient compliance in drop after the first year of treatment.

B. Intraocular Implants:

Implantable drug delivery systems can be classified into bio erodible and nonbioerodible systems. In both systems drug-release kinetics are determined by the polymer system used, the drug physicochemical properties and diffusion of the drug through the polymer. Biocompatibility in an essential property for all systems, the components should not interact with the surrounding tissue and should not elicit foreign body reactions through inflammatory or immune responses. Moreover, implants must not be affected by the host, and they need to be relatively stable at the implant site.

The inside of the eye is a viable location for implantation as evidenced by the use of intraocular lenses which are implanted to replace the clouded over natural lens during cataract surgery.

1.8 Nonbiodegradable Intraocular Implants:

Non-biodegradable systems are commonly reservoir Devices, whereby the drug core is coated by a semipermeable polymer through which the drug can pass, or the polymer coating may have an opening of a fixed area through which the drug can diffuse out. The other type of nonbiodegradable system is the ‘monolithic type, which is a homogeneous

mix of drug and polymer. It is easier, however, to achieve zero-order kinetics from a reservoir system. Vitrasert (ganciclovir 4.5 mg, Bausch and Lomb) the first implantable intravitreal device to be available in the clinic, was approved by the US Food and Drug Administration (FDA) in 1996. It is indicated for the local treatment of cytomegalovirus retinitis. Ganciclovir is embedded in a PVA and ethylene vinyl acetate polymer-based system. The drug is slowly released from this over 5-8 months PVA is a hydrophilic polymer acting as the scaffold for the implant, as well as controlling the rate of drug diffusion.

Ethylene vinyl acetate is hydrophobic polymer used to coat the implant to also control drug diffusion. Fluid is imbibed into the implant and dissolves the drug a saturated solution is formed within the core and drug molecules diffuse out of the system under a concentration gradient. The advantages of this system are that as long as a saturated drug solution remains in the core, the release rate will be constant. Moreover, no initial burst release of drug is observed Intraocular insertion of the implant requires surgery, a 4 mm to 5 mm sclerotomy at the pars plana is necessary for implantation. Further surgery is required to remove the implant depleted of drug. The risks associated with this invasive procedure include vitreous hemorrhage, cataract. retinal detachment and endophthalmitis. Retisert (fluocinolone acetonide 0.59 mg: Bausch and Lomb) was approved by the FDA in 2005 and is indicated for the treatment of chronic infectious uveitis affecting the posterior segment of the eye. The pure drug is compressed into a 1.5 mm tablet die and coated with a PVA membrane and silicone laminate which has a release orifice. The initial drug release rate is 0.6 µg per day, decreasing in the first month a steady state of 0.3 µg to 0.4 µg per day in approximately 30 months. With this course of treatment uveitis recurrence rates are reduced. However, studies have shown patients need cataract extraction and intraocular pressure-lowering surgery.

Iluvien (fluocinolone acetonide 0.19 mg Alimera Sciences) was approved by the FDA in 2014 and is indicated for the treatment of diabetic macular oedema. It takes the shape of a 3.5 mm x 0.37 mm cylinder, and the drug is in a PVA matrix which is encased in a polyimides tube (Fig. 41.5). One end of the tube is coated with silicon bio adhesive, and the other end is coated with PVA, which controls drug release.

A human pharmacokinetic study (the FAMOUS study) was conducted over 36 months and measured drug concentrations in the aqueous humour of patients receiving treatment with the Iluvien implant. The highest concentrations were observed at week 1 after administration and then the concentrations gradually declined, remaining stable between 12 and 36 months (Fig. 41.6), The Iluvien implant can be inserted into the vitreous humour through a 25-gauge needle, this contrasts with the other implants on the market, which need in be surgically inserted. Ongoing developments in this area include (1) a helical device, comprising a nonferrous metal scaffold coated with a polymer-drug matrix for the delivery of triamcinolone acetonide administered by transconjunctival injection for diabetic macular oedema and an implant containing genetically modified cells which produce growth factors includng ciliary neurotrophic factor.

The pore size of the implant allows the growth factors to diffuse outwards into the eye and nutritional molecules to enter but prevents the entry of antibodies or inflammatory cells that would attack the foreign genetically modified cells.

1.8.1 Biodegradable Intraocular Implants:

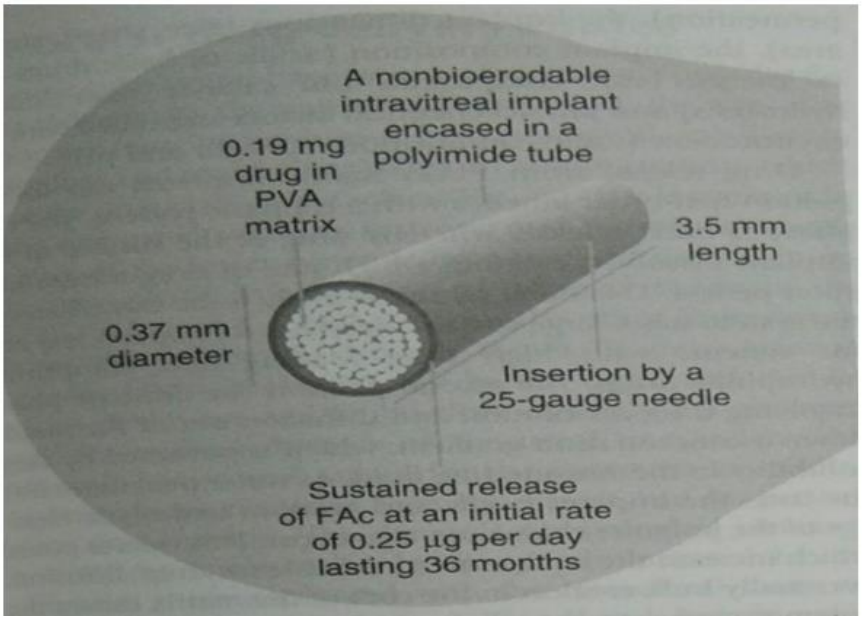

Figure 1.3: Nonbiodegradable Intraocular Implant

Biodegradable systems are composed of polymers that are metabolized by enzymatic or nonenzymatic (e.g., hydrolysis) reactions in vivo into more soluble forms that can be safely eliminated by the body. Their main advantage over nonbiodegradable systems is that they do not have to be removed from the body once the drug has been exhausted. Biodegradable polymers can be made into a variety of shapes and sizes, including pellets, sheets, discs and rods, through different processes. Hot melt extrusion has been used whereby the polymer and drug are subjected to elevated temperature and pressure, causing the polymer to undergo melting while being simultaneously propelled through a die to form uniform polymer strings or sheets. Solution casting has been used to produce polymer films. This involves the formation of a homogeneous solution or dispersion of the polymer and drug in a solvent which is spread onto a flat surface. The solvent is then allowed to evaporate and the dry film is peeled off.

Freeze-drying is another method employed, with the cake formed being subsequently shaped by heating and compression. Developing ocular biodegradable systems is, - however, more complicated as a multitude of factors need to be taken into consideration, including device stability, as well as erosion of the polymer and surface area changes which will affect in vivo kinetics. Ozurdex (Allergan) is a dexamethasone (0.7 mg) bioerodible ocular implant with a 6-month duration of action, it is approved in the USA for the treatment of macular oedema following retinal vein occlusion, diabetic macular oedema and uveitis. This implant is based on the copolymer poly (lactic co-glycolic acid) (PLGA) which has been used for more than 30 years in biodegradable sutures for ophthalmic surgery. To prolong the duration of action of corticosteroids in the vitreous cavity, intravitreal injection of a suspension of triamcinolone acetonide (Kenalog) has been used for many years off-

label. Since the introduction of Ozurdex, preservative free triamcinolone acetonide intravitreal injections, Trisesence (Alcon) and Tricaris (Allergan), have been registered for use. One advantage of Ozurdex is that it displays a similar pharmacokinetic profile between vitrecttomized and nonvitrectomined eyes whereas suspensions of triamcinolone acetonide clear more quickly in vitestomized eyes. Furthermore, the formulation of a corticosteroid in a PLGA matrix has the advantage that ocular pharmacokinetics can be better controlled compared with the dissolution of a free drug suspension.

PLGA is a copolymer of glycolic acid and tactic acid which are also degradable and biocompatible. Hydrolysis of the ester bond of these PLGAs generates acid, which can catalyse the degradation of the polymer. This is known as autocatalysis. Generation of the acid during PLGA degradation can cause a local decrease in pit, which has been associated with localized inflammation. Complete polymer degradation results in conversion to the original monomers, lactic acid and/or glycolic acid, which are metabolized to carbon dioxide and water by the Krebs cycle. PLGA is a versatile copolymer, the lactide to glycolide ratio and the stereoisomeric composition (the amount of lactide versus the amount of or lactide) ate the critical factors for PLGA degradation as they regulate polymer chain hydrophilicity and crystallinity. A 1:1 ratio of lactic acid to glycolic acid provides the fastest biodegradation rate, at increase or decrease of the proportion of either monomer often prolongs the degradation time.

Several other factors can modulate the degradation behaviour of PLGA and other polyester polymer implants, including the morphology of the copolymer (extent of crystallinity), the glass transition temperature (which determines if the polymer exists in the glassy or rubbery state), the molecular weight and molecular weight distribution (a large molecular weight distribution indicates a relatively large number of carboxylic end groups, which expedite autocatalytic degradation of the polymer), the porosity of the implant (which influences water permeation), the implant, dimension (size shape, surface area), the implant composition (acidic or basic drugs and excipients, basic compounds can catalyse ester linkage hydrolysis) and physicochemical factors associated with the environment (ionic composition, strength and pH) Drug release from PLGA matrix implants can follow pseudo first Order kinetics with a triphasic pattern.

The first phase is burning release, whereby drug at the surface of the implant dissolves, creating a high rate of drug release in a short period. This bursts release is likely to be exacerbated the system has a large surface area (eg microparticles) and for systems with high drug loading and comprising hydrophilic drugs. The second phase is the diffusive phase involving drug dissolution and diffusion out of the matrix down a concentration gradient, which is governed by drug solubility in the surrounding fluid. As water penetrates into the core, the implant swells and random hydrolytic cleavage of the polymer chains can also occur. This creates pores, which increase the surface area available for drug diffusion Eventually bulk erosion in the core of the matrix causes the polymer chains to lose their structural integrity and man loss occurs. This third phase results in rapid release of the remaining drug load when hydrolysis of the polymers reaches a threshold. The implant shape changes, and the implant finally fragments. This burst drug release is the main disadvantage of these PLGA biodegradable polymer implants over the nonbiodegradable ones.

A recent study combined two PLGA polymers of different molecular weight and in different ratios to achieve a pseudo first order release with a minimum burst effect. The polymer with the higher molecular wright provides the scaffold for the implant and the lower molecular weight polymer undergoes gradual hydrolysis and regulated drug dissolution and release.

In addition to PLGA, other aliphatic polyesters have abo been investigated for their use in ocular implants. Poly(e-caprolactone) is of particular interest as it has a slow rate of degradation and can therefore be used to achieve prolonged drug release for a year or more. It is a semi- crystalline polymer with a melting point between 59 C and 64°C. It is currently used for sutures, artificial skin support and cellular regeneration. In a recent study, triamcinolone acetonide loaded poly(e-caprolactone) implants were prepared by homogeneous mixing of the drug and polymer in solvent followed by solvent evaporation. The powder formed was then hot melt extruded into thin filaments using a syringe.

The filaments formed were 150 um in diameter and were cut into desired lengths of 2 mm. The rods were implanted into the subretinal space, and drug release was observed for at least 4 weeks. An initial phase of fast drug release followed by a pseudo-first order release was observed.

1.9 Periocular Drug Delivery Routes:

The periocular routes have become increasingly popular for drug delivery to the posterior segment of the eye. The periocular route encompasses subconjctival, sub-Tenon, pembubar and you the sclera It is superior in safety compared with the systemic and intravitreal routes because of the lower systemic exposure and risks of injection respectively.

With respect to efficacy, it lies at the middle to low end compared with the other (intravitreal, topical and systemic) delivery routes. It does achieve, however, better bioavailability in the outer and middle regions of the eye and is therefore currently the preferred route for treating diseases of the uveal tract, sclera and cornea. It is also well suited for the treatment of mild to moderate acute posterior segment disease and for preventative drug therapy. The dynamic physiological clearance mechanisms encountered by drugs administered by the periocular route compared with the intravitreal route are the subconjunctival-episcleral blood and lymph vessel flow and the choroidal vasculature.

The subconjunctival route bypasses the permeation hammer of the conjunctiva and cornea and can therefore achieve both anterior and posterior drug levels. It is a popular route for the administration of antibiotics (eg as prophylactic agents following cataract surgery). It is also used for the local delivery of cytotoxic injections of 5-fluormacil and occasionally mitomycin C in conjunction with glaucoma filtration surgery, in glaucoma filtration surgery sclera flap is created, forming a new channel for outflow of aqueous humour to reduce the intraocular pressure as is the case with all surgical procedures a wound healing response occurs, resulting in the formation of scar tissue. Here, scar tissue forms in the subconjunctival space, which can gradually reduce and block the aqueous drainage, resulting in a rise in intraocular pressure. This makes it necessary in some cases to administer cytotoxic agents repeatedly following surgery for the prevention of scarring.

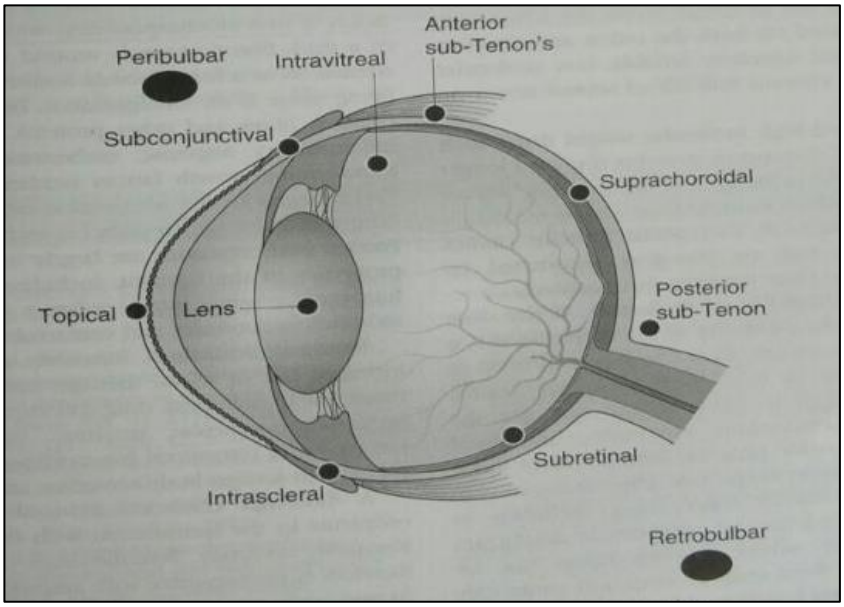

Figure 1.4: Different Routes of Ocular Drug Administration

Sub-Tenon injection is between the sclera and Tenon's capsule Tenon's capsule is a sheet of connective tissue between the eyeball (globe) and socket (orbit) which provides a smooth socket allowing free movement of the globe. This route allows prolonged contact of the drug with the sclera. The sclera has a relatively large surface area of 16.3 cm and high permeation relative to the cornea. Molecules of size up to 70000 Da have been shown to readily permeate through it. The ability of a drug to permeate through the sclera is inversely proportional to the molecular size. Although no dear correlation exists between drug lipophilicity and the steady-state permeation coefficient for the sclera, drugs with higher lipophilicities exhibit stronger binding to the sclera and longer transport lag times. injection via the sub-Tenon route is used to administer local anaesthetics, corticosteroids and anti-cancer agents.

1.9.1 Intravitreal Pharmacokinetics:

Drugs administered into the vitreous humour can be cleared by two router the anterior and posterior routes. The anterior route is where the drug diffuses into the anterior chamber and clean the eye by aqueous humour outflow, via the trabecular meshwork and Schlemm's canal.

The posterior route is across the retinal surface. The physicochemical properties that influence drug clearance are the molecular weight, compound lipophilicity (measured by log / or log D) and dose number (dose/solubility at pH 7.4).

The logarithm of the molecular weight has been found to correlate positively with the vitreal half-life of molecules. This can be explained by the slow diffusion of high molecular weight compounds in the vitreous gel, as well as the observation that high molecular weight

compounds are predominantly eliminated through the longer anterior pathway, log D and log p & correlate negatively with the vitreal half-life of the drug Lipophilic compounds have a shorter half-life than hydrophilic drugs. It has been proposed that hydrophilic molecules are predominantly eliminated by the anterior route.

The posterior route is the main elimination pathway for lipophilic drugs and offers a large surface area and active transporter mechanisms, thus providing a faster route of elimination than the anterior route: Molecules that can permeate across the retina (eg steroids) will be cleared via both the retina and aqueous outflow on intravitreal injection. Soluble, low molecular weight drugs have a vitreous half-life of several hours on intravitreal injection.

In contrast, charged high molecular weight drugs such as the antibody based therapeutic proteins display a longer vitreous half-life in the range of 1-7 days as they diffuse more slowly in the vitreous humour than do low molecular weight molecules.

Moreover, therapeutic proteins cannot permeate the retina and are therefore eliminated by aqueous outflow only. Dose number also positively correlates with the vitreal half-life of molecules. If the dose administered exceeds the solubility of the molecule and is administered as a suspension, then the drug will need to undergo dissolution before it is absorbed and/or cleated, thus prolonging its half-life. This is the case for the administration of triamcinolone acetonide. Traditional in vitro models of ocular pharmacokinetics have been relatively simple, including simple test tube release. In vivo models can provide pharmacokinetic data, including in humans, for dosing with topical or systemic antibiotics before cataract surgery, when aqueous levels can be sampled. However, for therapeutic proteins and antibodies which require intravitreal injection, this cannot be done in humans, and in experimental models an antibody response to the human or humanized antibody makes longer-term pharmacokinetics impossible to determine. New in vitro models being developed models which mimic the human eye and produce a much more clinically relevant longer-term result are currently being developed.

1.9.2 Problems with Traditional and New Ocular Drug Delivery Systems:

Deposits of triamcinolone acetonide particles and crystals have been identified in the vitreous humour and retina of patients who have been treated with intravitreal triamcinolone acetonide injections. These deposits have been observed in patient months and even a couple of years after the last administration of a triamcinolone injection. It is speculated that these insoluble deposits arise from aggregation or clamping of drug particles. It could even be that a polymorphic conversion of the drug occurs in the ocular fluids, resulting in an extremely stable, and therefore insoluble, form of triamcinolone which perists in the posterior segment of the eye.

Countless numbers of intraocular implants have been shown to perform successfully in Vitro during preclinical development, however, very few perform satisfactorily in vivo and make it to the clinic. One of the main reasons for this failure is non-biocompatibility, which triggers the formation of a thick fibrotic capsule around implants, which is often referred to as a foreign body response. The fibrotic encapsulating tissue is an amalgamation of cells, fibrinogen, fibrin, collagen fibers and other proteins. It is predominantly an inflammatory

response, orchestrated by interleukins and transforming growth factors synthesized by epithelial cell. This collagenous fibrotic tissue creates a diffusion barrier for drug molecules and retards biodegradation of the implant. Foreign body reactions are largely influenced by the surface properties of the implant, including contact angle, surface functional groups, water-polymer interactions, roughness, morphology, porosity and contact duration.

Repeated intravitreal injections are associated with an increased risk of scleral damage, toxic effects on the ocular tissue due to high peak drug concentrations, ocular infection increased intraocular pressure, incision-related subcon junctival and intravitreal hemorrhage and discomfort associated with foreign body sensation and pain in the patient A thorough characterization of the compatibility of excipients in the formulation with the active compound absolutely necessary.

Benzalkonium chloride is cationic and therefore is incompatible with anionic drugs. Its activity, andconsequently preservative efficacy, is reduced in the presence of multivalent metal ions and anionic and nonionic surfactant. Despite these interactions of benzalkonium chloride with drugs and other excipients, it may still be neccessary to use it in some cases. Example of these include sodium cromoglicate, and nedocromil sodium which form insoluble emulsion complexes with benealkonium chloride though ion pairing. These insoluble complexes are, however, removed by filtration during the manufacturing process.

1.9.3 Patient Adherence and Instillation of Eye Drops:

The short half-life of drugs in the anterior chamber means that eye drops must be instilled frequently. This leads to problems with patient adherence to treatment regimens Studies have shown that almost 50% of glaucoma patients were no adherent with respect to their medication use for more than 75% of the time. Eye drops are challenging to administer and require coordination, manual dexterity and vision, necessitating cleat instructions and patient counselling. Administration of eye drops requires relatively acceptable vision and the ability to open and squeeze the bottle

The self-application of drops is difficult for patients with limited vision. Elderly patients often suffer from joint disease such as arthritis and may also have poor coordination, which can result in missing the eye or the up of the bottle sit in the drop cornea. Most glaucoma patients are older individuals, a study has shown that 17% of glaucoma suffer rely on the other to administer their eye drops in den rely on patients have not had the necessary training for the appropriate method of drop administration, which often results in poor adherence. The easiest way to administer the drop efficiently is to pull the lower eyelid downwards and administer the drop into the lower ocular cul-de-sac The patient can do this while looking in a minor. Several devices are available for use in conjunction with different eye drop bottles to make this process easier. Dose timing and frequency have also been strongly associated with nonadherence to eye drop therapy.

Patients with a three times daily regimen were more likely to miss doses and also had irregular timing of doses compared to patients with twice daily regimens. This illustrates the importance of designing ophthalmic preparations that provide a sustained drug release and which require less frequent dosing.

A. Containers for eye drops:

Continers for eye drops should have following characteristics. They shoul Containerne sterility of the contents, not extract out any things to the content, not preserve the ett the chemical stability of medicaments and other adjuncts, no adversely affing from the content, provide protection from the light, if necessary, withstand sterilization by autoclaving, and be easy to handle etc. Eye drops are packaged in the following types of containers.

a. Single application packs, minim unit

b. multi-application containers:

i. Traditional eye dropper bottle

ii. Screw-capped bottle with separate dropper

iii. Plastic bottles.

B. Use of Eye Drops:

When using eye drops, person should take consideration of the following.

instructions, as firstly, wash hand and take the drug (container), pull lower eyelid down gently with one hand If the dropper is separate, squeeze rubber bulb while dropper is in bottle to bring the liquid into dropper or replace on bottle. Holding dropper above eye, drop medicine inside lower lid while looking up, do not touch dropper to eye or fingers. Release low lid and try to keep eye open and not blink for atleast 30 seconds.

1.10 Eye Lotions:

Eye lotions are sterile aqueous solutions intended for washing the eyes, with the help of eye bath (eye cup) to remove any irritant or foreign body from the eye. They are used first aid purpose or for intermittent domiciliary purposes and supplied in large 13lume bottles as large volume is required to wash the eyes. They are usually of 138 types:

- Preparations containing bactericide.
- Preparations containing no bactericide Firs.

pyepnich are sterile aqueous solutions employed only for once or a period o Firstly 24 hours, and secondly, which are aquous solutions, sterilized when used and employed for upto a week.

Eye lotions should be followed the ideal characters like:

- They should be sterile.
- They should not be toxic and irritant.

- They should be iso-tonic with lachrymal secretion.
- They should have neutral pli to avoid any irritation and discomfort of the eyes Preparation of eye lotions is classified into three stages just like eye drops.
- Dissolution of drug in proper vehicle
- Clarification
- Sterilization

Here we are not used the bactericide in all preparations (eye lotions). Containers must be properly sealed containing screw cap with either rubber, plastic or other impervious linear. It must not contain cork. They must be fluted to indicate that the preparation is not to be taken orally. They must be resistant to autoclavingto render them sterilized easily. Such containers can provide cleared, microb free solution for washing of the eyes.

A. Labellings the eye lotions:

The container of eye lotion must bear following requirements on the label:

a. Not to be taken orally.
b. Avoid contamination during use.
c. For external use only.
d. Discard any unused part 24 hrs. after opening or a week after first opening.

B. Labelling instruction for eye lotions:

To be used within 24 hrs. after first opening

1.10.1 Eye Ointments:

These are sterile oiniments meant for the application to the eyes. Ointment based used to formulate eye ointments must have following characteristics: Ointments should be sterilized by heating method.

- Eye ointments should be free from irritation.
- Eye ointments diffuse drug uniformly throughout the secretion of eye.
- Eye ointments melt close to the body temperature. The advantage of eye ointments over eye drops is the increased ocular contact time of the drug. IP recommends the following base for eye ointments.

Wool fat. 10g Liquid paraffin 10 g Yellow soft paraffin. 80 g the ingredients ar melted together on water bath and filtered through a course 139 fixed on a After sterilization, is then sterilized by keeping it at dered through a course one hour. After it should be stored to avoid any contamination. a sterilized co container immediately

Wool fatilie addups presenter satisfactory emulsification of the drug solution due to hydrophilic groups present in it. It also helps in the rapid absorption of the drugs Liquid paraffin is used to reduce the viscosity of the base and thus make the base having appropriate

viscosity so as to expel easily form the tube. The yellow soft paraffin is used to prepare this base since white soft paraffin, which is prepared by bleaching the yellow soft paraffin, may contain traces of bleaching ag…

The preparation of eve ointments must be carried out under the aseptic While preparing eye ointments.

For eye ointments, previously sterilized tin, aluminium, or plastic collapsible tubes for eye ointme used. The quantity filled in the tubes that they be more than 5 gm with nozzlespplied in small quantity due to the reason that they should not be used for long time. 5 gm ointment is sufficient to get finished after sufficient applicationised a duration of a week. Thus prevents the chances of contaminants.

A. Labelling of eye ointments:

Eye ointments must bear the following instructions on the label.

- Do not touch nozzle to the eye.
- For external use only
- Avoid contamination during application.

1.11 References:

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