INTERNATIONAL JOURNAL IN PHARMACEUTICAL SCIENCES

Journal Homepage: https://www.ijpsjournal.com

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Review Article

A Review On: Ophthalmic Drug Dosage Form

Shriram Gore*, Sonali Sonawane, Vaibhav Jadhav

Pratibhatai Pawar Collage of Pharmacy, Wadala Mahadev, Shrirampur

ARTICLE INFO

Received: 06 Dec 2023
Accepted: 09 Dec 2023
Published: 12 Dec 2023

Keywords:
Eye, Solution, Ophthalmic, Drug Delivery System, Dosage Form

DOI:
10.5281/zenodo.10352774

ABSTRACT

This paper discusses the drug forms that have been produced up to this point for topical ocular administration, including ophthalmic drug forms with bio adhesive characteristics, inserts, in situ gels, drops, and ointments. Previously, numerous studies have shown that novel and sophisticated ophthalmic drug forms are superior to conventional ones and can boost the bioavailability of the active ingredient through a variety of means, including lowering the susceptibility of drug forms to the human eye's defence mechanisms, prolonging the drug's contact time with the cornea, enhancing penetration through the intricate anatomical structure of the eye, and enabling controlled release of drugs into the eye tissues, which permits lowering the frequency of drug application. The remainder of the paper outlines suggested in vitro and in vivo investigations to be carried out for different forms of ophthalmic medications to determine whether the form is appropriate in terms of desired characteristics and patient compliance.

INTRODUCTION

Ophthalmic formulations have been one of the most important and growing areas of pharmaceutical technology for decades. The main reason why scientists are still so interested in these forms of drugs is the problem of low bioavailability of the drug after application to the eyeball. Caused, among others, by the complex anatomical structure of the eye, the small absorptive surface and low transparency of the cornea, lipophilicity of the corneal epithelium, metabolism, enzymatic decomposition, drug binding to proteins contained in tears. And defence mechanisms. that is, the formation of tears, blinking and flow of this substance into the nasolacrimal duct. (1) Ophthalmic drug delivery systems may be preferred over other delivery systems despite their potential risks and complications. Additionally, compared with oral drug delivery systems, ocular drug delivery systems may provide better equivalent bioavailability in the eye. Many methods have been tested to improve the rate and/or extent of ophthalmic drug bioavailability, controlled dose

***Corresponding Author:** Shriram Gore
Address: *Pratibhatai Pawar Collage of Pharmacy, Wadala Mahadev, Shrirampur.*
Email : shriramgore073@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

release and, thus, improve therapeutic efficacy and reduce drug side effects. (2) Ophthalmic preparations (eye preparations) mean sterile products intended for instillation into the eye in the space between the eyelid and the eyeball. These products must be sterile and prepared under the same conditions and using the same methods as other parenteral preparations. Ophthalmic preparations used topically to treat superficial or intraocular diseases of the eye are called ophthalmic products. Eye drops must be sterile, isotonic, properly buffered, and appropriately stored. These are the three most important dosage forms used clinically.

1. Solution
2. Suspension
3. Ointment. (3)

Ophthalmic drug delivery system may be superior to another delivery system, regardless of its risks and complications. (4,5) New drug formulations, researched in recent years, aim to achieve controlled release. From the drug to the tissues of the eyeball, including multicompartment delivery systems, inserts, collagen shields, contact lenses and so-called topical gels. (6,7,8) Despite their widespread use, conventional liquid eye drops come in a variety of -dosed containers that constitute a galenic formulation that is fraught with pitfalls. To maintain microbiological quality during use, preservatives must be added, which are known to cause damage to the cornea and conjunctiva. For active ingredients that undergo hydrolysis, the Ph is often adjusted to low non-physiological values for sufficient stability at the expense of optimal physiological tolerability. (3) Low viscosity eye drops will drain quickly, especially if the drops are large, and absorption of active ingredients through the nasolacrimal duct may lead to systemic side effects. (15) The medication is applied to the surface of the eye for two purposes. For external treatment of the eye for infections such as conjunctivitis, blepharitis, keratoconjunctivitis sicca or for intraocular treatment through the cornea for diseases such as glaucoma or uveitis. Most eye diseases are treated with topical application of solutions used as eye drops. These common dosage forms account for nearly 90% of the dosage formulas currently on the market. Eye drops used as soluble drugs need to be instilled regularly with a concentrated solution. The practical reasons for choosing the solutions are the overall cost advantage, greater simplicity in formulation development and manufacturing, and good patient acceptance despite some ambiguity (Fitzgerald and Wilson, 1994). One of the major problems encountered with the use of topical ophthalmic medications is the rapid and extensive loss of the anterior corneal area due to drainage and excessive tear flow. After instillation of eye drops, less than 5% of the topical dose penetrates the cornea and reaches the intraocular tissues, whereas a large portion of the drop dose is usually absorbed systemically through the conjunctiva and nasolacrimal duct (lang, 1995) (16).

2. Anatomy and physiology of the eye:

The eye is the organ of vision. It is located in the orbital cavity and is innervated by the optic nerve (second cranial nerve). It has an almost round shape and is about 2.5 cm in diameter. The space between the eye and the orbit is occupied by fatty tissue. The bony wall of the eye socket and fat help protect the eye from injury. The first is the anterior part, which includes the cornea, conjunctiva, aqueous humor, iris, ciliary body, and lens. The second is the posterior part which includes the retina, choroid, sclera and lens. The blood-eye barrier includes the blood/aqueous barrier and the blood-retinal barrier. They are visible barriers between the blood and the eye, playing a key role in penetration and destruction of ophthalmic drugs and maintaining homeostatic control. The blood-retinal barrier is a posterior barrier consisting of an innermost barrier in the endothelial membrane of retinal vessels and an outer barrier in the retinal

pigment epithelium. (3) The eyeball is made up of many layers with a specific structure and is divided into two segments. The first is the anterior part which includes the cornea, conjunctiva, aqueous humor, iris, ciliary body and lens. The second is the posterior part that involves the retina, choroid, sclera, and lens. (37) The eye is spherical, located in the eye socket and protected by the eyelids. With a diameter of 24 mm and a volume of 6.5 cm3, it weighs about 7.5 g. Several layers with a specific structure make up the eyeball and divide it into two segments. (38) The eye is surrounded by three different layers: outer layer, middle layer and inner layer. The outer layer is made up of the cornea and sclera. These are fibrous tissues that protect the eyeball. The sclera, continuous with the cornea, is a white, elastic, avascular tissue. It covers 80% of the eye tunic. The cornea, which connects to the sclera at the limbus, is a thin (0.5 mm), avascular, and transparent layer that allows light to pass through to the eyeball. The anterior and posterior parts of the eye are anatomically divided by the sclera and cornea. (36) The eye is one of the most complex organs in the human body. In the human eye, three layers can be distinguished. The outer region is made up of the cornea and sclera. The iris controls the size of the pupil and therefore the amount of light reaching the retina; the ciliary body controls the strength and shape of the lens and is where fluid is produced; and the choroid is a vascular layer that provides oxygen and nutrients to the outer layers of the retina. The inner layer of the eye is the retina, a complex structure composed of many layers of nerve cells that sense and process light. The three transparent structures surrounded by layers of the eye are called the aqueous layer, lens, and lens. (39) The eye is a spherical structure with a wall consisting of three layers; the outer part of the sclera, the middle part of the choroid layer, ciliary body and iris and the inner part of the neural tissue layer of the retina. The eye is made up of a transparent cornea, lens, and avascular vitreous body. Oxygen and nutrients are transported to this avascular tissue by aqueous humor, which has a high oxygen content and an osmotic pressure similar to blood. (fig:1)

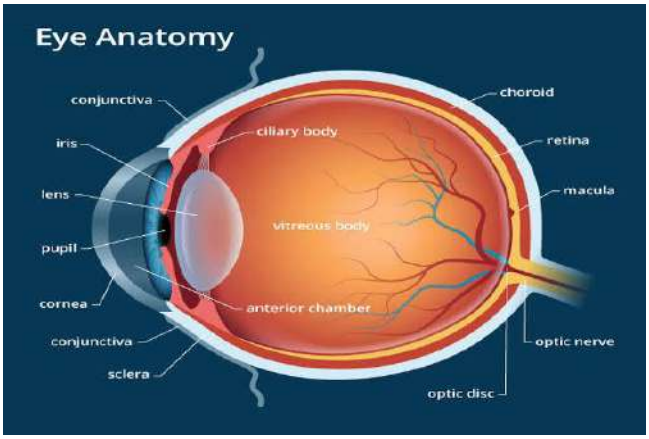
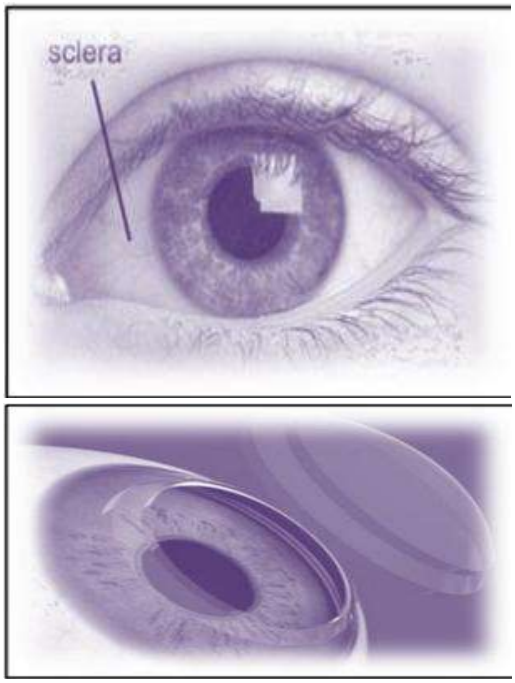


Fig no.1 Eye anatomy

1.Sclera (white part)

The sclera is hydrated and has large, randomly arranged collagen fibbers; therefore, it is opaque and white rather than clear. The sclera has three layers: episcleral, the outer layer; sclera; and the melanocyte layer, the inner lamina fusc. (19) The sclera is a hard white layer of skin (made of tissue) that covers the entire eyeball except the cornea. The whites of the eyes help the eyeball connect with the muscles. (3)



2. Cornea (clear lens in front of eye):

The cornea is the most anterior part of the eye, in front of the iris and pupil. This is the tissue with the most dense nerve distribution in the body and most corneal nerves are sensory nerves, originating from the ophthalmic branch of the trigeminal nerve. The cornea of the adult eye has an average horizontal diameter of about 11.5 mm and a vertical diameter of 10.5 mm and a fairly constant curvature throughout life. Five layers can be distinguished in the human cornea: epithelium, bowman's membrane, lamina propria, descemet membrane and endothelium. (39)

3. Retina:

The sensory retina covers the inner part of the posterior 2/3 of the earth's wall. It is a delicate structure; in its living state it is transparent and has a purple-red colour due to the rod's purple colour when seen. The retina is a multilayered sheet of neural tissue tightly attached to a layer of pigment epithelial cells. (40) The retina is the tissue that lines the inner surface of the eye, surrounding the vitreous cavity. During embryogenesis, the spinal retina develops from the optic cup. The latter is formed by the invagination of the optic vesicle, which is a natural development of the embryonic forebrain. The inner wall of the optic cup (surrounding the vitreous cavity) eventually becomes the neural retina; the outer wall (surrounded by the choroid and sclera) becomes the retinal pigment epithelium (rape). The retina is protected and held in its proper position by the surrounding sclera and cornea. The neural retina consists of six main types of neurons: photoreceptors, bipolar cells, horizontal cells, amacrine cells, and ganglion cells, which sense and process light signals, and muller glia, which act as the organizing backbone of the neural retina. The cells of the neural retina are arranged in several parallel layers. (fig:2) (39)

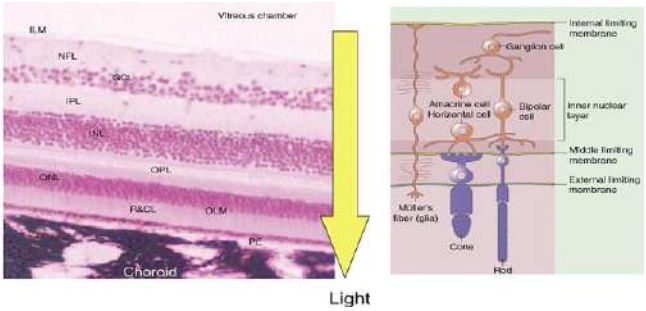


Fig no. 2 Retina

3.Topical ophthalmic drug forms:

3.1 Liquid ophthalmic drug forms:

Several studies and technological investigations have been carried out to modify liquid ophthalmic drug delivery systems. Furthermore, many methods have been proposed to prolong the contact period of the liquid dosage form with ocular tissue in order to increase the absorption of the active ingredient(s) and, thus, increase bioavailability in ocular tissue, glasses. These modifications include (but are not limited to) a variety of methods such as the addition of agents that increase viscosity, drug penetration, and the use of prodrugs or cyclodextrins. Mucosal ophthalmic drug delivery systems are characterized by higher bioavailability compared to conventional formulations. Candidate polymers tested for mucosal adhesion and enhanced drug bioavailability in ophthalmic liquid formulations include (but are not limited to) polyacrylic acid, hyaluronic acid, sodium carboxymethylcellulose, and chitosan. Other candidates which extend the time interval of contact with eye surface are lectins. Examples of such ophthalmic liquid formulations are novel produced by Novartis (timolol maleate) and piloted produced by Alcon laboratories (pilocarpine hydrochloride) are containing cross-linked polyacrylic acids carbomer and Carbopol, respectively, which exhibit mucoadhesive properties. (2)

3.1.1. Eye drops:

Eye drops are accessible in the forms of water and oil solutions, emulsions, or suspensions of one or more active ingredients, which may contain

preservatives if stored in multiuse packaging. These forms are sterile and isotonic. The optimum ph. For eye drops equals that of tear fluid and is about 7.4. In deciding whether to buffer the drug in this form, one should take into account the stability of active ingredient and the tissue tolerance to the preparation. (9) If the Ph value gets outside the range of 4–8 which is tolerated by eye, the patient may feel discomfort, there may be irritation, and the drug bioavailability can decrease because of increased tearing. (10) Eye drops are sterile and mainly isotonic solution containing drugs or only lubricating or tears replacing solution. This conventional dosage form for ocular administration represents 90% of the marketed formulations due to its simplicity of development and production. Eye drops are cheaper than the other forms and have a good acceptance by patient. Unfortunately, 95% of the drugs are eliminated with the lachrymal apparatus and the different barriers in 15 to 30 s after the instillation. Moreover, a secondary eye infection may be caused by a microbiological contamination with multidose packaging (36).

3.1.2. Ophthalmic solution:

Ocular solution is a sterile aqueous solution used to clean and rinse the eyeball. They may contain excipients that regulate, for example the osmotic pressure, Ph and viscosity of the composition. They may also contain preservatives if stored in reusable packaging. (9)

3.1.3 Microemulsion:

Microemulsion is a promising drug formulation, inexpensive to produce, easy to sterilize and stable, capable of introducing larger amounts of active ingredients. In vivo studies and clinical tests on healthy volunteers have demonstrated a prolonged effect and increased bioavailability of drugs applied in these forms. The mechanism of action involves the adsorption of nanoparticles forming a drug reservoir and an internal microemulsion phase on the corneal surface, helping to limit spillage. Active ingredients that have been developed for microemulsions include cyclosporin a difluorinated, flurbiprofen acetyl, and flurbiprofen prodrug. (11)

3.1.4. Prodrug:

Changing the properties of a drug by developing a prodrug also increases the drug's permeability through the cornea. This method involves modifying the chemical structure, giving the active ingredient new properties, specifically selectivity and site specificity. Examples of drug substances that have been developed as prodrugs include epinephrine, phenylephrine, timolol, and pilocarpine. (12.13) Dipivefrin, a diester of pivalic acid and epinephrine, has 17-fold greater corneal permeability than epinephrine, due to its 600-fold higher lipophilicity at Ph 7.2. Therefore, a small dose of dipivefrine applied to the eyeball has the same therapeutic effect as epinephrine. Compared with conventional eye drops containing 2% epinephrine, eye drops containing 0.1% dipivefrin have only slightly lower activity, reducing intraocular pressure and significantly reducing side effects. (1)

3.1.5. Modification of liquid dosage forms for eye use:

In the process of technological research on dosage forms, many methods have been proposed to prolong the contact time of liquid dosage forms with tissues. Eyes, as well as increasing the absorption of active substances by these tissues. These modifications include the addition of viscosity increasing agents, introduction of drug penetration improvers into the formulation, use of prodrugs or cyclodextrin. (8,13)

3.1.6. Cyclodextrin:

Cyclodextrins are cyclic oligosaccharides capable of forming complexes including active ingredients, thereby increasing the water solubility of hydrophobic compounds without changing their molecular structure. (7,27) As transporters, they retain hydrophobic drugs in solution and transport

them to the biofilm surface. In the case of eye drops, optimal bioavailability of the active ingredient is achieved at an appropriate concentration of cyclodextrin (<15%) in the eye drop solution (8). Cyclodextrin is commonly used in the developed form applied to the eyeball as 2-hydroxypropyl-β-cyclodextrin, which has no irritant effects. Eye drops containing a drug complex, specifically dexamethasone or pilocarpine with 2-hydroxypropyl-β-cyclodextrin, are well tolerated and provide higher bioavailability compared to conventional eye drops. (7)

3.2. Semi-solid ophthalmic drug formulations:

Semi-solid ophthalmic drug delivery systems include the following dosage forms:

3.2.1. Topical gel (or sol-gel system):

Topical gel is viscous liquid, demonstrating the ability to undergo a soul-gel transition when influenced by external factors, such as Ph, temperature, and the presence of suitable electrolytes. This property slows down the drainage of the drug from the ocular surface and increases the bioavailability of the active substance. Polymers used in the development of these formulations include gellant gum, poloxamer and cellulose acetate phthalate, while active ingredients used during topical gel research include ciprofloxacin. Hydrochloride, timolol maleate, fluconazole, ganciclovir and pilocarpine. (7,8)

3.2.2. Eye ointments:

Ointments are semisolid dosage forms for external use, usually consisting of solid or semisolid hydrocarbon base of melting or softening point close to human body temperature. After applying the ointment to the eye, it decomposes into small drops, which stay for a longer time period in conjunctival sac, thus increasing drug's bioavailability. Eye ointments have certain disadvantages although they are well tolerated and safe, they cause, among other things, blurring of vision and sometimes have irritating effects, because of which they are mainly applied night-time. (14) eye ointments are prepared in a semisolid base- e.g. Simple eye ointment bp, which incorporates yellow soft paraffin (eight parts), liquid paraffin (1 part), and wool fat (1 part). The base is filtered while molten to get rid of particles and sterilized at 160°c for 2 hours. The drug is integrated in advance than sterilization if heat-stable or added aseptically to the sterile base. Finally, the product is packaged aseptically in sterile aluminium or plastic tubes. Since the product contains virtually no water, the risk of microbial growth inside the ointment is negligible. (41)

3.3. Solid eye drops:

Solid ophthalmic drug delivery system includes the following dosage forms:

3.3.1. Coated contact lenses:

This form of medication can absorb water-soluble substances on its surface, releasing after application to the eyeball for a longer period of time. The first and most widely used polymer in lens manufacturing is poly (2-hydroxyethyl methacrylate) cross-linked with a small amount of ethylene glycol dimethyl acrylate (8,13). In recent years, research has been done on the use of lenses made of silicon. Interest in contact lenses continues to grow, which is confirmed by the increase in the number of articles about their use published in recent years. Examples of lens drugs that have been studied include timolol, ciprofloxacin, dexamethasone, and cyclosporine. (1)

3.3.2. Eye drops:

Eye drops are solid or semi-solid dosage forms that have no disadvantages compared to traditional ophthalmic formulations. They are less sensitive to protective mechanisms such as nasolacrimal duct flow, suggesting the ability to persist in the conjunctival sac for longer periods of time and more stably. Then conventional dosage forms.

Their undoubted advantages over conventional forms are also precise dosage, the ability to slowly release the substance at a constant rate and limit its systemic absorption. In addition, their use allows you to reduce the frequency of taking the drug, as well as side effects and blurred vision. (17) The main factors limiting the use of inserts in therapy remain the reluctance of patients to abandon traditional dosage forms, the feeling of foreign bodies in the eye and sporadic failures to use and insert the insert, such as unnoticed secretion from the eye. (18)

3.3.3. Soluble eye drops (soda):

This form of ophthalmic drug delivery system was originally developed so that astronauts could apply it in microgravity. Sodi is a soluble ocular insert in the form of small oval platelets produced from acrylamide, *N*vinylpyrrolidone and ethyl acrylate. After applying soda to the conjunctival sac, they become moist and end up with tear fluid, then soften and adhere to the ocular surface. This dosage form ensures prolonged effect since the release of the active ingredient(s)from soda is in pulsation and uncontrolled manner. Examples of drugs employed in soda involve sulphapyridine, neomycin, tetracaine, kanamycin, atropine and pilocarpine. (13,19,20)

3.3.4. Mini disc/eye therapy system (opts):

This is (opts) identical to contact lenses with a diameter of 4 to 5 mm. The candidate drugs used in opts are Sul isoxazole and gentamicin sulphate. Ots can be hydrophilic or hydrophobic, allowing for extended-release periods of poorly water-soluble and water-soluble active ingredients. Ots has a contoured, convex, concave appearance on the side in contact with the surface of the eye. (19,21)

3.3.5. Artificial tear insert:

Artificial tear insert developed from hydroxypropyl cellulose. It is commercially available under the name laciest. It is used to treat dry eye syndrome. It is a long, stick-shaped pill that contains no preservatives. After inserting the artificial tear pad into the conjunctival sac, the insert will absorb water from the conjunctiva and cornea, forming a hydrophilic layer that stabilizes the tear film and moistens the cornea. (8)

3.3.6. Collagen shield:

Collagen shield has been studied in animal and human models and can be used as a carrier for anti-inflammatory drugs such as dexamethasone, antibiotics such as gentamicin or antiviral drugs. The use of collagen shields resulted in higher drug concentrations in the cornea and aqueous humour compared with contact lenses and eye drops. (13,21) The collagen shield was developed from porcine sclera because this type of collagen shares similarities with collagen found in the human cornea. Collagen shields must be kept dry and hydrated before being inserted into the eye. The main limitation of collagen shields is that the standard dosage applied by ophthalmologists is not suitable for each patient's eyeball and may cause some discomfort by interfering with vision. Additionally, collagen shields may be unintentionally excreted from the eye immediately after insertion. A recent formulation has been made from collagen called collapses, which are small collagen fragments (1 mm × 2 mm × 0.1 mm) suspended in a 1% methylcellulose carrier. This dosage form (colla some) overcomes all the defects of the collagen shield. (8,13)

3.3.7. New eye drops delivery system "nods":

Compared with traditional eye drops, nods ensure delivery of the required dose of drug to the eyeball and improves its bioavailability even several times as in the case of pilocarpine combination, in which its bioavailability is increased eightfold. In addition, nods do not contain preservatives and can be sterilized by gamma rays. This ophthalmic drug delivery system has been patented by smith and nephew pharmaceuticals ltd. It consists of a cardboard handle and a polyvinyl alcohol flag (containing the drug) attached to the handle by a

dissolving film. A film containing the drug separates from the paper handle at the point of introduction of the drug into the conjunctival sac, which then dissolves in the tear fluid and thereby releases the drug from the film. (22.23)

3.3.8. Minitablets:

The candidate drugs which were formulated as minitablets ophthalmic delivery system involved gentamicin, acyclovir, piroxicam, timolol and ciprofloxacin. (23,24) There many advantages of minitablets dosage form involving. Resistance to defence mechanisms by tearing or outflow through nasolacrimal duct, easier for introducing to conjunctival sac, longer contact time with the cornea due to the presence of mucoadhesive polymers, and the gradual release of the drug from the preparation at the application site caused by swelling the outer carrier layers. (23,25) Minitablets are developed applying the method of direct compression or indirect method, the latter involving tableting the earlier obtained granules. The advantage of indirect method is the dry granulation stage, which increases flow properties of powders often containing bio adhesive polymers, which enables minitablets production on a larger than laboratory scale. Minitablets are biodegradable, solid drug forms, that, after application to conjunctival sac, transit into gels, which extends the time period of contact between active ingredient and the eyeball surface, which in turn increases the active ingredient's bioavailability. (26)

4.Methods of ophthalmic dosage forms:

4.1. Conventional ophthalmic dosage forms:

Solutions are extensively used dosage form for topical transport of therapeutics to the eye. Factors to be taken into consideration in formulating ophthalmic answers are solubility, ocular toxicity, pika, impact of Ph, tonicity, buffer capacity, viscosity, compatibility with different elements withinside the system, preservatives to be used, consolation while instilled into the eye, and the convenience of manufacturing. (3)

4.2. Viscosity enhancers:

Polymers are typically introduced to ophthalmic drug answers which will increase the viscosity on the basis and correspond to a slower removal from the preocular area, which cause stepped forward precorneal house time and consequently a greater trans corneal penetration of the drug into the anterior chamber. In terms of changing bioavailability, it has minimal effects in humans. The polymers used are methylcellulose, polyvinyl alcohol (pave), polyvinylpyrrolidone (pop), hydroxyethyl cellulose, hydroxypropyl methylcellulose (him), and hydroxypropyl cellulose. Natural polymers including ha, vee gum, alginate, xanthan gum, gelatine, acacia and tragacanth can also be used as viscosity improvers. However, they have the disadvantage of harbouring microorganisms and fungi. (3)

4.3. Permeation enhancers:

By increasing the permeability of the corneal epithelial membrane, transport through the cornea can be maximized. Cornea, in order to improve the bioavailability of ophthalmic drugs, one of the techniques used is to temporarily increase the permeability properties of the cornea with appropriate materials called penetration enhancers or enhancers. Absorb like eye infections and poisoning, these are some of the risks. On-line transport from the cornea to the receptor is a rate-limiting step, and permeation enhancers increase corneal absorption by altering the integrity of the corneal epithelium. (3)

4.4. Pre-medication:

The principle of pre-medication is to beautify the cornea. Permeability due to changes in the hydrophilic (or lipophilic) nature of the drug. In the cornea or after penetration into the cornea, the prodrug is converted chemically or enzymatically to form the active compound. Therefore, a suitable prodrug must not only have high lipophilicity and

high partition coefficient but also must have high enzyme sensitivity. The antiviral drugs ganciclovir and acyclovir are the correct prodrugs.

4.5. Chemical approaches to improve ocular bioavailability:

The goal of advanced ocular drug delivery is no longer simply to improve ocular drug absorption but also to reduce systemic absorption. Systemic drug absorption is not only ineffective absorption but also leads to drug-related systemic side effects. Therefore, it is essential to optimize drug delivery systems, which can deliver advanced biopharmaceutical properties and provide the necessary functionality to detect ocular tissues in a predictable manner. Changing the chemistry of drugs to improve therapeutic efficacy and decorate various physicochemical homes as well as solubility, stability, permeability and efflux drainage is an established technique in drug delivery. Medicine metabolic concerns in ocular tissues provide opportunities to use chemically modified capsules capable of predictable metabolic biotransformation in the eye. The maximum vital techniques in chemical procedures for ocular transport are designing pills that go through sequential metabolic conversion and eventually attain the target (retro metabolic design), and designing ocular drug which can be inactive at sites aside from the eye (prodrugs) chemical change of a recognised inactive metabolic or analogy to repair the healing interest that transforms lower back into the inactive metabolite in a predictable one- step biotransformation (Sb). (3)

5. Examinations of ophthalmic drug forms properties:

5.1. In vitro examinations:

5.1.1. Sterility examination:

The basic requirement for drug forms applied on the eyeball is their sterility. Examination of sterility involves inoculation in aseptic conditions of the sample examined on two microbiological media: Thioglycolate medium (fluid sodium decapacitate or sodium thioglycolate), which is used for growth of aerobic and anaerobic bacteria, and medium with hydrolysate of casein and soy (soya-bean casein digest media) used for growth of aerobic bacteria and fungi. A thioglycolate medium with an applied sample is incubated at the temperature of 30–35c, whereas a medium with hydrolysate of casein and soy with an applied sample is incubated at the temperature of 20–25c for the time not shorter than 14 days. Two methods are distinguished for inoculation of examined material: Direct inoculation and a method involving use of membrane filters. (28,29,30) The direct inoculation method, as described in pharmacopoeia, involves transferring the suitable amount of examined preparation to the medium. If the product has antibacterial properties, this effect of the substance must be neutralized before testing. Before introduction into the medium, the ointment must be diluted with an appropriate sterile solvent containing the selected surfactant. During incubation, the medium containing the sample must be observed for a specified period of time. (28,30) Indirect methods (membrane filtration methods) are used when the nature of the product allows. For water and oil solutions, cellulose nitrate filters with a pore size of no more than 0.45 μm are used. For certain products, for example antibiotics, specially adapted filters are used. In the case of testing a product with an antibacterial effect, the membrane must be washed with the selected sterile solvent at least 3 times, not exceeding 5 filter wash cycles per 100 ml of solvent. The entire membrane is transferred to the appropriate medium or aseptically cut into two identical parts, which are then transferred to two different media. In the case of a water-soluble solid, the substance must be dissolved in a suitable solvent and the subsequent procedure must be the same as for an aqueous solution. The indirect method can also be used for ointments. Fat-based

ointments may be diluted with isopropyl myristate if necessary, at a temperature not exceeding 40∘C. In special cases, the upper temperature limit may be 44∘C. The product is then filtered as quickly as possible. For each drug formulation, after filtration and washing the membrane is transferred to the medium or the medium is introduced into the filtration system located on the membrane. (28,29)

5.1.2. Determination of Ph:

The Ph of topical solutions, drops, suspensions and gels are usually determined by potentiometric methods. In this method, the Ph value is determined by measuring the potential difference between electrodes placed in the solution under test and a reference solution of known Ph or between the measuring electrode (glass) and reference electrode (calomel or silver chloride), both of which are placed in the composition being tested. (28, 31,32)

5.1.3. Clarity test:

Clarity test includes include visual evaluation of the formula under appropriate lighting on a white and black background. It is taken in liquid form, except for suspensions. This review applies to topical eye drops and gels before and after gelation. (29,30) Another method to test clarity is to measure transmittance with a is spectrophotometer. This method can be used in research on active substance-filled contact lenses. The lens was hydrated in physiological serum and placed on the surface of a quartz basin. Transmission was then measured at wavelengths from 200 to 1000 nm. (34)

5.1.4. Check particle size and morphology:

The cornea is the most anterior part of the eye, in front of the iris and pupil. It is the densest tissue in the body and most corneal nerves are sensory nerves. Originating from the ophthalmic branch of the trigeminal nerve. Five layers can be distinguished in the human cornea: epithelium, bowman's membrane, lamina propria, Descemet membrane, and filtering endothelium with a pore diameter of 1 μm. This inspection allows them to calculate the number of particles $\geq$ 10 μm in size in the products tested. Testing starts from low magnification, for example ×10 or ×50, where particles larger than 25 micrometres can be found. (35)

5.1.5. Stability assessment:

The purpose of stability assessment is to provide information about changes in the quality of the active ingredient or drug over time due to the influence of environmental factors, i.e., temperature, humidity and light. Of the substance/product tested, as well as setting the date for further testing of the drug substance or the expiration date of the medicinal product and recommended storage conditions. (43) General stability requirements for ophthalmic products, such as drops and ointments, are similar to those for other pharmaceutical products. They are harmonized through the ich (international conference on harmonization) process in the United States, Europe and Japan, recognizing the contributions of the European organization EMEA (European medicines evaluation agency) and the special pharmaceutical committee (camp), its twp. (quality working group), and the us fad (food and drug administration) as well as the Japanese ministry of health. (44) In general, active ingredients should be stored under conditions that allow them to be thermally stable and, where possible, also to assess their moisture trends. Storage conditions and inspection times should be correlated with the conditions of storage, transport and subsequent use. (43) There are many guidance documents on stability assessment. However, they are general and often do not recognize the unique characteristics of ophthalmic products. Matthews and wall, in their article, referenced (with brief descriptions) documents that could form a supporting point for planning stability testing of ophthalmic products, especially products other than conventional drops and ointments. (44)

5.2. Other tests performed for some dosage forms:

5.2.1. In situ gel test:

Test for gel forming ability. This test is performed to evaluate the ability of the formulation to form gel on the ocular surface. A sample of examined formulation is introduced to a vial containing a solution whose components simulate a tear fluid and visual technique is employed to assess the sol-gel phase transition. (1)

5.2.2. Examinations for inserts:

Swelling index. Hydrophilic polymers of different structures exhibit different swelling degree, depending on relative resistance of matrix network structure to water particles' movement. Polymer chains exhibiting low ability to form hydrogen bonds may not be able to form strong network structure, resistant to fast water penetration. The bigger the strength and number of hydrogen bonds between polymer chains are, the slower the water particles diffuse into the hydrated matrix. Swelling of the polymer is vital to activation of bio adhesive abilities, which activate just after swelling begins. With increasing hydration of the polymer, adhesion increases until over-hydration causes a sudden decrease in adhesion strength, which is the effect of peeling off the outer polymer layer. The degree and rate of hydration of the insert as well as swelling influence the release of the drug from the dosage form.. Therefore, this parameter is extremely important for predicting drug release and bio adhesive matrix potential. The swelling test is performed to measure the overall hydrophilicity and hydration of the polymer. (42)

5.3. In vivo testing:

5.3.1. Eye irritation test (Draize eye test):

There are many modifications to the eye irritation/toxicity test (Draize eye test Draize) is made for dosage forms, i.e. Solutions, emulsions, ointments, solids, e.g. Inserts, etc. Testing is typically performed on rabbits, whose anatomy and physiology of the visual organs are well described in the literature. Additionally, rabbit eyes are often more sensitive to irritating compounds than human eyes. For testing, 3 to 6 rabbits are usually used, which, on the one hand, allows to obtain reliable results, and on the other hand, meets the requirement to use toxic substances in as few animals as possible. The most commonly used animal subspecies are albino rabbits (From New Zealand), which are inspected and weighed before testing, then placed in specially adapted, designed cages. To avoid accidental injury. The tested preparations are introduced into the conjunctival sac or applied directly to the cornea. Initially, approximately 0.1 ml of the drug analysed was applied to the eyeball, but multiple subsequent tests showed that the amount of drug was reduced, for example to 0.01 ml, which better reflects real-life situations. In the test, one eyeball, usually the left eyeball, is used as a control. After introducing the medicinal form into the eyeball, the eyelids usually close for a few seconds, although this is not required. Sometimes a sterile solution is also used to wash the ocular surface. Evaluation of the condition of the eyeball before and after application of the formulation is performed by observing the eyeball under appropriate lighting, often using a magnifying glass or slit lamp to ensure a more accurate assessment. Ancillary procedures that make it easier to observe changes include fluorescein staining and photography of the eyeball. In addition, the degree of discomfort after application can be expressed by the number of times you blink or rub your eyes. Evaluation usually takes place 1 h,24h, 48h and 72h after intraocular administration of the formulation and, if necessary, also after 7 or 21 days. The test time, as well as its scheme, is individually adapted to the formulation being analysed. Ocular changes were evaluated using a scoring system in which each change in the eyelid, conjunctiva, cornea, and iris regions was noted. Although many scoring

systems have been proposed in the literature, the modified methods of Frieden Wald and Draize are still widely used. (42,33,30,46,)

5.3.2. Corneal permeation studies:

For corneal permeation studies, as in the Draize eye test, healthy albino rabbits are selected in allowed numbers obtain reliable results. The amount of active ingredient in the aqueous humor after introduction of the formulation into the conjunctival sac was marked at defined time intervals. Using a syringe fitted with a needle, after an intramuscular or intravenous injection of an aesthetic that may contain, depending on the application, ketamine hydrochloride, xylazine hydrochloride or sodium pentobarbital, an aqueous solution of the mood sample is taken at a rate of approximately 150 to 200 µl and store at negative temperature. Temperature, for example −20 °c, before plc analysis. (45)

5.3.4. Evaluation of in vivo release of the insert:

To evaluate in vivo release, the formulas that yielded the desired results in the in vitro release assessment was selected. Inserts were placed into the conjunctival sacs of healthy rabbits selected for study. At specified intervals, the inserts were carefully removed and examined to determine the amount of drug remaining using appropriate analytical techniques. (47)

ADVANTAGES

1) Their benefits encompass convenient management and acknowledge reliability.

2) Eye emulsions offer the advantage of effectively delivering hydrophilic medications, while

Oil-in-water (O/W) emulsions are less likely to cause irritation to the eye.

3) Inserts, on the other hand, provide advantage such as prolonged duration of action sustained drug release, consistent dosage, and minimized adverse effects. (48)

4) The ocular route has faster drug absorption and less systemic and visual side effects.

By avoiding the pulsed doses of conventional systems, it offers accuracy and uniformity in dose rate.

It offers better housing of delivery systems. (49)

DISADVANTAGE:

1) The major disadvantage of the ocular route of drug administration is that the rapid and extensive elimination of traditional eye drops which can cause extensive loss of drug resulting in poor retention of the drug at the site of action.

2) The quick elimination of the medication through tear flow and eye blink results in a short period of therapeutic effect, which can lead to frequent dosing.

3) After application of the ointment, drops, and other medication may be a temporary blurring of vision.

4) Limited drugs are suitable to formulate for the ocular route.

5) It has limited permeability to the cornea resulting in reduced absorption of ophthalmic drugs.

6) The pharmaceutical industries need special processes, equipment, and requirements (sterile) to manufacture ophthalmic dosage forms, which make them more costly than oral dosage forms. (49)

8. Case Study of Ophthalmic Drug Dosage Forms:

8.1. Case Study 1

Acute R Eye Pain:

Diagnosis:

Suspected acute angle closure glaucoma R eye.

Narrow angle L eye.

Differential Diagnosis:

The affected person described is imparting with acute angle closure glaucoma because of shallow anterior chamber angles. Other causes of boom intraocular pressure consist of open angle glaucoma or different pathology of the trabecular meshwork (pigmentary dispersion, pseudo exfoliation, trauma, neovascularization, etc.) That

obstructs aqueous outflow. Ahead displacement of intraocular structures (posterior tumour, choroidal swelling, and so forth). Also, can block the outflow of aqueous and multiplied the intraocular stress.

Definition:

Acute attitude closure glaucoma happens when there's a particularly sudden blockage of the trabecular meshwork causing elevation of the intraocular strain.

Examination:

Acute perspective closure normally offers with intense ocular pain, headache, blurred imaginative and prescient, halos round lights, nausea, and vomiting. some of the obvious non-ocular manifestations (nausea/vomiting) will be deceptive to the green doctor. however, the activate popularity and next treatment of an acute attitude closure disaster is paramount within the protection of the patient's imaginative and prescient. common eye examination findings, as in this affected person, consist of moderate conjunctival injection, hazy cornea, mid dilated pupil, shallow attitude and accelerated intraocular pressure. angle closure is high-quality determined the use of a gonioscopy contact lens that permits the viewer to see into the perspective of the attention. even supposing the acute episode is recognized and treated speedy and correctly, there can still be optic nerve damage and resultant visual loss. every other viable alternate consists of iris ischemia which could cause sloughing of iris pigment. Pigment may be cited inside the anterior chamber and on the corneal endothelium. Iris damage may additionally motive the pupil to remain in a dilated function. The intraocular strain may additionally upward push sufficient to cause retinal vascular occlusion and retinal ischemia. Anterior subcapsular lens opacities may additionally arise due to ischemia (this is termed glaukomflecken).

Treatment:

Treatment of acute attitude closure glaucoma is either laser or surgical peripheral iridectomy (putting a hole in the peripheral iris). This procedure restores aqueous flow from the posterior to anterior chamber through developing an additional starting within the iris, relieving the pathologic strain gradient. This in the end lets in the iris to regress and shrink back from the trabecular meshwork and then regular aqueous humor drainage is restored. This system is frequently curative of the affected eye. A prophylactic peripheral iridectomy of the non-affected eye is important to save you an episode from happening within the fellow eye. Individuals with one episode of acute perspective closure glaucoma have a excessive probability of an attack inside the fellow eye over the next five-10 years. Even when the intraocular strain has decreased, subsequent follow up is essential to be sure that the perspective remains open. Iop might also lower soon after the assault because of ciliary frame ischemia and decreased aqueous humor production and no longer because the attitude has reopened. (50)

8.2. Case Study 2: Red, Itchy Eyes:

Diagnosis:

Acute conjunctivitis of both eyes.

Differential Diagnosis:

He above presentation is steady with viral conjunctivitis. Other possible diagnoses encompass allergic conjunctivitis (normally with pruritus), atopic conjunctivitis (commonly with a records of eczema), bacterial conjunctivitis (typically with purulent discharge and excessive redness), remedy toxicity (ex. Affected person on continual drops), publicity toxicity (ex. Exposed to fireplace fumes or different toxic fumes/chemicals) and pediculosis (eyelash lice infestation with chronic follicular conjunctivitis).

Definition:

Viral conjunctivitis is an inflammatory response to contamination of the conjunctival tissues surrounding the globe and lids by a virulent disease.

Examination:

Ocular findings include conjunctival hyperaemia, chemosis and haemorrhages, follicular conjunctival reaction, epiphora, preauricular adenopathy, corneal subepithelial infiltrates, oedematous eyelids, conjunctival membranes or pseudo membranes and/or corneal epithelial defects. Visual acuity is minimally affected in viral conjunctivitis. Analysis of viral conjunctivitis is usually based totally on history and examination findings. Fluorescein can help stumble on corneal epithelial defects. Cultures (to stumble on bacterial conjunctivitis) should be executed in cases of excessive purulent discharge, persistent symptoms and symptoms or excessive corneal findings.

Treatment:

Remedy of viral conjunctivitis is supportive with synthetic tears and funky compresses. Topical antibiotics are not wanted unless a bacterial etiology is suspected. Corticosteroid drops are usually averted however can be beneficial inside the convalescent duration inside the maximum extreme instances (proof of membranes/pseudo membranes). Topical anaesthetics have to know not be used as those can hinder recuperation. Patients that use contact lenses need to keep away from lens wear until signs and symptoms have resolved. Prognosis of viral conjunctivitis is very good as most sufferers could have spontaneous decision in two weeks. Membranes/pseudo membranes may purpose everlasting conjunctival scarring and continual subepithelial corneal infiltrates within the visible axis which can impair imaginative and prescient. Reassessment by way of an eye care issuer could be crucial in this example. Hand washing and different disinfectant techniques (changing pillowcases and towels) are critical to save you transmission. (51)

8.3. Case Study 3: Eye irritation and dryness:

Diagnosis:

Graves ophthalmopathy.

Differential Diagnosis:

This patient affords with viable Grave's ophthalmopathy, additionally know as thyroid ophthalmopathy. Different illnesses inside the differential diagnoses consist of conditions that reason orbital congestion (orbital tumours, orbital infections like orbital cellulitis), other causes of orbital inflammation (orbital pseudotumor - now known as idiopathic orbital irritation, Granulomatosis with polyangiitis, orbital myositis).

Definition:

Grave's ophthalmopathy takes place secondary to an autoimmune system which leads to modifications in orbital content (especially extraocular muscle mass and orbital fats).

Examination:

Signs and symptoms may additionally consist of upper and decrease eyelid retraction, dry eyes, double imaginative and prescient, limit of extraocular actions, excessive tearing, and eye inflammation. Examination findings may additionally show exophthalmos or proptosis (ahead motion of the globe), lagophthalmos (inability to close eyes), strabismus (misalignment of eyes), swelling of the eyelids, corneal dryness, chemosis of the conjunctiva, accelerated intraocular stress, and, in severe instances, congestion of the optic nerve via the swollen orbital systems and vision loss. Work up of grave's ophthalmopathy consists of a non-comparison orbital cut for you to often show bilateral extraocular muscle (eom) growth with sparing of tendons. Other paintings-up can include tosh, and free t3, t4 stages.

Treatment:

Treatment of Grave's ophthalmopathy is unbiased of systemic sickness. Remedy relies upon on signs and symptoms and severity of sickness. Artificial tears may be used for corneal publicity. Eyelid surgical treatment may be considered for excessive lid retraction. High dose glucocorticoids are used for intense orbital congestion and optic neuropathy. Steroid-sparring sellers and extra immunomodulators also are used (cyclosporine, azathioprine). Now and again, surgical decompression of the orbit is needed to save you extreme exophthalmos and optic nerve compression. If patients expand diplopia secondary to muscle growth and fibrosis, prisms and then strabismus surgery are presented after the inflammatory response is controlled. Eyelid surgical treatment is offered in sufferers which have extreme publicity due to a fibrotic elevator muscle. Most instances of grave's ophthalmopathy stabilize inside 8-36 months. (52)

CONCLUSION:

Despite many achievements in the discipline of ophthalmic dosage paperwork, nevertheless substantial majority of active materials for use in ocular problems are inside the form of eye drops. In connection with the improvement of latest ophthalmic dosage paperwork, a hassle regarding the evaluation in their physicochemical houses and in vitro-in vivo correlation appears. In the treatment of eye disease, the ocular inserts represent a widespread advancement. This device of ousters presents many benefits includes with; enhance affected person complicance thru manner of method of decreasing the frequency of dosing, offer sustained and controlled drug delivery and decrease the dose and thereby lessen the adverse effects of the drug. This paper is a evaluate of the available literature which allows planning research to be conducted on standard and contemporary ophthalmic drug forms..

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HOW TO CITE: Shriram Gore*, Sonali Sonawane, Vaibhav Jadhav, A review on: Ophthalmic Drug Dosage Form, Int. J. in Pharm. Sci., 2023, Vol 1, Issue 12, 202-219. https://doi.org/10.5281/zenodo.10352774