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A REVIEW ON: OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

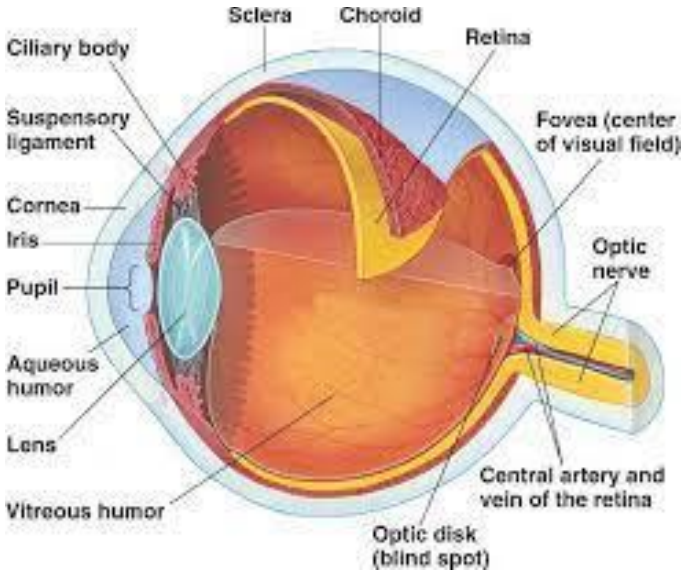
Due to the anatomical and barrier complexity of the eye, ocular medication administration is a tremendously tough subject for ophthalmologists and drug delivery experts. Drug transport to the anterior region of the eye is limited by barriers such as distinct layers of cornea, sclera, conjunctival blood flow, and tear dilution as well as additional obstacles to the posterior region of the eye As a result of this, scientists have created and researched different delivery technologies in order to improve medicine delivery and treatment efficacy the pupil Ophthalmic solution or eye drop is the most common traditional ocular medicine delivery technique.Consumers prefered and commonly utilised Marketed conventional dosage formulations are emulsion, solution, ointment, and polymeric gels Several ocular preparations, such as nanoformulations, liposomes, and ocular formulations, liposomes, ocular inserts, and ocular mini-tablets are also being widely studied as future treatments to improve ocular drug delivery and as an alternative to conventional drug delivery. This review intends to summarise several conventional and novel topical formulations for Ocular drug delivery system
Keywords: ocular drug delivery systems, novel approaches, ocular formulations, nanotechnology

1. INTRODUCTION

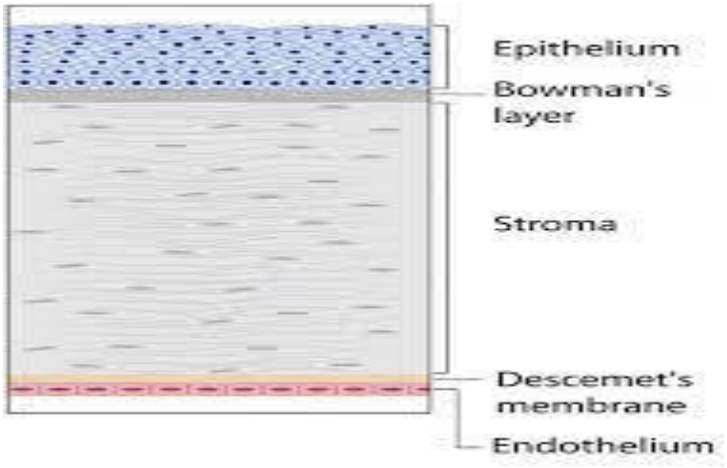
The eye is one of the most important organs in the human body. As a sensory organ, it allows humans to observe and interact with their surroundings. Generally, the eyeball is divided into two parts, the anterior part and the posterior part. The anterior part of the eyeball contains the cornea, iris, lens, conjunctiva, ciliary body, and water-like body, and the posterior part contains the sclera, choroid, retinal pigment epithelium, neural retina, optic nerve, and vitreous fluid (monk). House, 2007), as shown in Figure 1, the eyeball has many structures, but only the anterior part is exposed. The rest of the structure is covered and protected by the orbit that houses the eyeball. Although there are multiple protective mechanisms such as eyelashes, eyelids, and tears, small exposed areas of the eye are susceptible to various infections (Tortora & Derrickson, 2015). However, eye diseases are not limited to infections. Other illnesses such as glaucoma, cataracts and allergic conjunctivitis can also affect the eyes. Therefore, whenever there is an infection or illness in the eye, treatment is needed. Local infusion of the active ingredient is the preferred approach for treatment because it is simple, convenient and non-invasive. Eye drops are the most commonly used conventional topical ophthalmic dosage forms due to their ease of administration and high patient compliance (Patel, Cholkar, Agrahari & Mitra, 2013). However, as a result of lacrimal turnover, nasolacrimal duct drainage, and blinking, the bioavailability of the eye is very low and the drug penetrates less into the eye tissue, making it less effective in certain situations and treatments. These barriers have been considered in enhancing the effectiveness of topical ophthalmic dosage forms. (Souza, Dias, Pereira, Bernardi & Lopez, 2014). As a result, a variety of conventional and novel drug delivery systems have been developed and researched, including systems that utilize technological developments in emulsions, suspensions, ointments, lipid-based systems and polymer systems.

MECHANISMS OF OCULAR DRUG ABSORPTION

Topical delivery to dead ends is the most common route of drug delivery in the eye. Adsorption from this site can be corneal or non-corneal. A schematic diagram of the human eye is shown in. The so-called non-corneal absorption pathway involves penetration into intraocular tissue through the sclera and conjunctiva. This mechanism of absorption is usually not productive, as drugs that penetrate the surface of the eye beyond the corneal limbus are taken up by the local capillary bed and removed into the systemic circulation. This extracorneal absorption generally prevents entry into the aqueous humor. However, recent studies suggest that extracorneal absorption pathways may be important for drug molecules with low corneal permeability. Studies with inulin, timolol maleate, gentamicin, and the prostaglandin PGF2_ have shown that these agents gain intraocular access by spreading across the conjunctiva and sclera. Ahmed and Patton studied the non-corneal absorption of inulin and timolol maleate. Penetration of these agents into the intraocular tissue appears to be through diffusion across the conjunctiva and sclera, rather than re-entry from the systemic circulation or absorption into the local vasculature. Both connections were able to access the iris ciliary body without entering the anterior chamber. It has been found that up to 40% of inulin absorbed by the eye is the result of non-corneal absorption. Non-corneal absorption pathways may be important for drugs with low corneal permeability. However, corneal absorption is the primary absorption mechanism of most therapeutic entities, and local absorption of these agents is considered to be the rate-determining factor of the cornea. The anatomy of the cornea presents uniquely different solubility requirements for drug candidates. A cross-sectional view of the cornea is shown. With respect to the flow of drug through the cornea, the cornea can be thought of as a three-layer structure consisting of three major diffusion barriers: epithelium, stromal, and endothelium. The epithelium and endothelium contain about 100 times the amount of lipid material per unit mass of stroma. Depending on the physicochemical properties of the drug entity, the diffusion resistance provided by these tissues will vary widely



Anatomical structure of human eye



Cross-sectional view of the corneal membrane depicting various barriers to drug absorption

The outermost epithelium provides a rate-determining barrier to the spread of most hydrophilic drugs through the cornea. The epithelium is composed of 5-7 layers of cells. Basal cells are columnar in nature and minimize paracellular transport. However, the epithelial cells narrow distal to Bowman's membrane, and the zonules at the junction form flat epithelial cells that occlude the complex. This cell sequence interferes with paracellular transport of most ophthalmic drugs and limits lateral movement within the anterior epithelium. The intracellular pore size of the corneal surface epithelium is estimated to be about 60 Å. Small ionic and hydrophilic molecules appear to be able to access the anterior chamber through these pores. However, for most drugs, paracellular transport is impeded by the interjection complex. In a recent review, Lee discusses attempts to temporarily alter the epithelial integrity of these junction complexes to improve the bioavailability of the eye. However, this approach has been moderately successful and can significantly impair corneal integrity. The stroma (parenchymal propia) lies between the corneal epithelium and the endothelium. The stroma occupies 85-90% of the entire cornea and is mainly composed of hydrated collagen. Due to its hydrophilicity, stroma acts as a diffusion barrier against highly lipophilic drugs. There is no tight junction complex in the stroma, and paracellular transport through this tissue is possible.

2. CONVENTIONAL TOPICAL OCULAR DRUG DELIVERY SYSTEM:

There are several types of ophthalmic drug delivery systems currently on the market, including eye drops commonly used by patients. Others are emulsions, suspensions, ointments and polymer gel formulations.

EYE DROPS:

Among topical eye therapies, topical eye drops are the most convenient, non-invasive, and patient-friendly. However, ocular drops face a few challenges in therapy, according to Pahuja, Arora, and Pawar (2012). According to the research, a high proportion of patients had difficulty administering the drops. Furthermore, tear outflow that rises with the volume of eye drops might result in solution loss and dilution. Aside from that,

the amount of medicine absorbed into the ocular tissue cannot be approximated due to the eye pocket's low holding capacity. Benzalkonium chloride, a popular preservative, may also cause various difficulties, including the peeling of the corneal epithelial cells at their borders, which limits cell development and enlarges the intercellular gaps in the cornea's surface cells (Pahuja et al., 2012). Despite the fact that Ghate and Edelhauser (2006) claimed that benzalkonium chloride might increase the ocular permeability of certain medications, the unfavourable side effects should not be overlooked. Due to these constraints, Patel et al. (2013) proposed the use of viscosity enhancers to improve contact duration ,permeation enhancers to boost active ingredient absorption, and cyclodextrin as a carrier for hydrophobic compounds to promote topical eye drop

BIOAVAILABILITY EMULSION:

Interest in the use of emulsions in the past was revived by submicron emulsions (range 0.1 μm to 0.3 μm) containing nonionic surfactants to enhance stability (Ghate & Edelhauser, 2006). Pate et al. (2013) It was noted that emulsion-based formulations may improve both the solubility and bioavailability of ophthalmic drugs. In general, there are two types of emulsions already on the market as a medium for active pharmaceutical ingredients: oil-in-water (o / w) and water-in-oil (w / o) (Vandamme, 2002). Of these two emulsions, the (O / W) type is preferred. This is because it is less irritating to the eye and has better eye receptivity. According to Liang et al. (2008), Emulsion-based formulations may provide several benefits to eye formulations, including improved pre-corneal residence time, improved drug corneal permeability, increased bioavailability, and sustained release. There is sex. The use of an emulsion containing chitosan as a surface coating can also improve precorneal residence time. This is based on a pharmacokinetic study by Yamaguchi et al. (2009) Chitosan coated emulsion compared to uncoated emulsion in male albino rabbit eyes. The results showed improvements in the average residence time (1.5-fold) and drug half-life (1.8-fold) of the emulsion compared to the uncoated emulsion. However, eye emulsions have their own limitations. They are less stable and prone to various types of instability such as aggregation, coalescence, and creaming (Aldrich et al., 2013). Aggregation occurs when the dispersed phase exits the suspension to form flocs. Coalescence is another instability process in which droplets dispersed in a suspension combine continuously to form larger droplets. Apart from that, the phase of the emulsion moves up and down according to its specific gravity, forming another layer between the two phases called creaming. Therefore, this study suggested the use of surfactants to improve the dynamic stability of emulsion products.

SUSPENSION:

Suspension can be defined as a dispersion of the finely insoluble pharmaceutical active ingredient in a solvent (Patel et al., 2013). In other words, it is a concentrated solution of the active ingredient of the drug. This type of eye drug delivery system has several advantages over eye drops. The main advantage is that instead of being washed away or diluted with tears, an insoluble suspension remains in the precorneal pocket, which can improve drug contact time and duration of action. The improved duration of action of the drug is also due to the different particle sizes of the suspended particles. Small particles complement the absorbed drug, while large particles remain in the precorneal pocket and dissolve slowly (Remington, 2011). According to Ghate & Edelhauser (2006), prednisolone acetate suspension is most effective in crossing the cornea and suppressing inflammation of the cornea compared to prednisolone phosphate solution. There was also a 4-week randomized, double-blind, multicenter, phase II clinical trial conducted using 1% and 2% rerabmid suspensions for placebo. This study found that both suspensions were well tolerated and effective in treating dry eye when compared to placebo (Kinoshita et al., 2012). In addition, higher concentrations of suspension were found to be more effective than those of lower concentrations.

OINTMENTS:

Ophthalmic ointment is a vehicle system for topical application that has demonstrated improved bioavailability and sustained drug release. They are composed of solid and semi-solid hydrocarbon molecules (paraffin) and have a melting point of 34 ° C, which is the physiological eye temperature. Fukuda et al. Study the intraocular kinetics of vancomycin-based ophthalmic ointment (an antibiotic with high activity against methicillin-resistant and cephem-resistant Staphylococcus aureus and anaerobic and aerobic Gram-positive bacteria) in rabbits and induced by Bacillus subtilis. Higher corneal concentrations in eyes with corneal infections, a more normal control group than eyes, and higher growth inhibitory concentrations than methicillin and cephem-resistant Staphylococcus aureus (MRSA) troughs up to 240 minutes after topical administration It lasted. The rationale for the observed effect is a violation within the eye barrier that appears to increase drug penetration in the unhealthy eye, as improved results based on increased permeability of healthy eye tissue have not yet been predicted. It is derived from. Eguchi et al. We concluded that 0.3% was an appropriate and effective vancomycin concentration for the elimination of MRSA keratitis after topical application of liquid paraffin-petrolatum-based ointment to the eyes of a rabbit model..

POLYMERIC GEL:

Eigel is another dosage form for the topical delivery of the drug to the eye. Gels are composed of various materials such as mucosal adhesive polymers that are important for the topical delivery of drugs. Mucosal adhesive polymers have been used in eye gels to enhance their effectiveness (Shaikh, Raj Singh, Garland, Woolfson & Donnelly, 2011). This polymer provides the attachment of drug carriers to living tissues, prolongs contact time and improves eye bioavailability (Ali & Lehmussaari, 2006). There are two types of eye gels: preform gels and in situ forming gels. According to Lunch et al. (2017) Preformed eye gel is a gel substance at room temperature, so it is not very preferable as a dosage form. This property has limited use in ophthalmic drug delivery due to the low accuracy and reproducibility of drug delivery that commonly causes visual impairment, eyelid crust formation, and lacrimation. For this reason, in situ gels are becoming the focus of gelling systems as they offer the benefits of both solutions and gels. A in situ forming gel is a viscous liquid preparation that transforms into a gel phase using one of three mechanisms: pH control, temperature control, or ion activation. It is preferred over preformed gels because it is more comfortable, easier to administer as drops, and has less or no vision problems (Rathore, 2010). Kaur, Singh & Kanwar (2000) stated that criteria for good in situ gelation should include low viscosity, fluidity for administration as droplets, and strong gelation to withstand the shear forces of the conjunctiva. Said. According to Gurtler & Gurny (1995), it is difficult to deliver the correct dose in a preformed gel due to the varying amount of drug released during administration. However, it is possible to provide accurate and reproducible doses with in situ gelling formulations. In addition, the relatively long duration of action of the gel formed in situ reduces the frequency of administration and thus enhances patient compliance.

3. NOVEL TOPICAL OCULAR DRUG DELIVERY SYSTEM

Although traditional topical ophthalmic treatments are now commonly used, their use, efficacy, and safety remain severely limited. As a result, numerous routes have been developed and studied. One method is the use of nanotechnology in ophthalmic drug delivery systems using nanoparticles and nanocells. Liposomes and eye implants are two other techniques for enhancing the eye delivery system.

NANOPARTICLES:

Sahoo, Dilnawaz & Krishnakumar (2008) define nanoparticles as all particles less than 1 micron in diameter composed of a variety of natural or synthetic polymers, lipids, phospholipids, or metals. There are two types of nanoparticles: nanocapsules and nanospheres. In nanocapsules, the drug is encapsulated in polymer capsules, whereas in nanospheres, the drug is evenly distributed in the polymer matrix (Patel et al., 2013). One of the advantages of nanoparticles is that their size-dependent uptake and distribution of nanoparticles can prolong drug delivery to tissues (Gaudana, Jwala, Boddu & Mitra, 2009). This is evidenced by a study by Sakurai, Ozeki, King, and Ogura (2001) on the importance of particle size in tissue distribution. In this study, we conclude that smaller particle sizes can be further dispersed in tissue areas where large particles are absent. Many other approaches have been developed using nanoparticle technology. One of them is solid lipid nanoparticles. Solid lipid nanoparticles improve corneal absorption, increase bioavailability of the corneum in both hydrophilic and lipophilic drugs, allow autoclave sterilization, and use physiological lipids during the manufacturing process. It has several advantages, including no biotoxicity (Seyfoddin, Shaw, and Al-Kassas, 2010). Apart from that, solid lipid nanoparticles also exhibit sustained drug release properties based on in vivo studies by Cavalli, Gasco, Chetoni, Burgalassi, and Saettone (2002). Tobramycin solid lipid nanoparticles showed sustained drug release for up to 6 hours compared to the same dose of short-acting tobramycin eye drops. De Campos, Diebold, Carvalho, Sánchez & Alonso (2004) conducted a study on fluorescent chitosan nanoparticles and found that the nanoparticles were stable when incubated with lysozyme and did not affect the viscosity of the mucin dispersion. discovered. This study found that the amount of fluorescent chitosan in the cornea and conjunctiva was higher for nanoparticles than for controlled fluorescent chitosan solutions and remained constant for up to 24 hours. After 24 hours of incubation with chitosan nanoparticles, cell survival was remarkable and the survival rate of recovered cells was almost 100 percent. Apart from that, there is also a study by Motwani et al. (2008) Ultramicroscopic reservoir using nanoparticles. In this study, mucosal adherent chitosan-sodium alginate nanoparticles were used to deliver gatifloxacin to the eye. As a result, the system was determined to have a fast release for the first hour and a slow release for the remaining 24 hours of investigation. As a result, dosing is less frequent and patient compliance is improved.

NANOMICELLES:

According to Patel et al. (2013), Nanocell is the most commonly used carrier system for turning therapeutic agents into clear aqueous solutions. Nanomicelles are composed of amphipathic molecules, which are essentially surfactants or polymers that self-assemble into micelles. There are three types of micelles: regular micelles, inverted micelles, and single molecule micelles (Trivedi & Kompella, 2010). Normal micelles are amphipathic copolymers that self-assemble in aqueous media, and reverse micelles are amphipathic copolymers that self-assemble in non-aqueous media. Monomolecular micelles, on the other hand, are composed of copolymer blocks with multiple hydrophobic and hydrophilic regions within a single molecule. This allows the molecule to be assembled into a micelle. Of these three types, inverted micelles are excellent candidates for encapsulating and delivering hydrophilic drugs because the polar part of the inner shell forms micelles facing hydrophilic substances. In addition, Qiu, Zhang, Yan, Jin, and Zhu (2007) state that polymer particles can also be encapsulated using inverted micelles. The nanocell offers several advantages as a drug delivery system. Nishiyama & Kataoka (2006) have shown that they are easy to prepare and have the ability to improve drug solubility, reduce toxicity, increase circulation time, and increase tissue penetration with targeted delivery properties. rice field. In vivo studies in rabbits performed by Civiale, Licciardi, Cavallaro, Giammona, and Mazzone (2009) suggest that nanomicelle formulations are a better option for topical administration of small molecules compared to suspensions. Did. In another study, Cholkar, Patel, Dutt Vadlapudi, and K. Mitra (2012) concluded that nanomicelles can efficiently pass through the ocular tissue and deliver the drug to the posterior part of the ocular tissue. However, traditional micelles have minor drawbacks. It is not stable for long periods of time, has short sustained release, is poorly compatible with hydrophilic drugs, and requires system optimization for each drug (Torchilin, 2006). Therefore, these need to be taken into account for improvement

LIPOSOMES:

Liposomes have an aqueous core containing the drug encapsulated by one or more phospholipid bilayers. According to Patel et al. (2013), liposomes capable of encapsulating both hydrophobic and hydrophilic drugs can be divided into three types. That is, small single-layer vesicles (10-100 nm), large single-layer vesicles (100-300 nm), and multi-layer vesicles (double layers). These liposomes are a promising tool for ophthalmic drug delivery due to their natural phospholipids, cell-like membranes, and the presence of excellent biocompatibility (Gan et al., 2013). Apart from that, liposomes attach to the hydrophobic corneal epithelium and continuously release the bound drug content, thereby improving pharmacokinetics and reducing toxic side effects (Chetoni, Burgalassi, Monti, Najarro). , And Boldrini, 2007). Also, cloth bags and others. (2007) It was noted that sustained release of the drug could be produced by the use of multi-layered vesicles, depending on the nature of the selected lipid composition. A study using the rabbit model was performed by Shen & Tu (2007) to measure the concentration-time profile of ganciclovir in the aqueous humor after instillation of ganciclovir-containing liposomes and ganciclovir solution. The results showed that the area under the curve of the liposome containing ganciclovir was 1.7 times larger than that of the ganciclovir solution. The drug distribution of the liposome preparation was higher in the sclera, cornea and vitreous. Another study was conducted by Habib, Fouad & Fathala (2008), comparing fluconazole solution with fluconazole-loaded liposomes in a rabbit keratitis model. After 21 days, the liposome formulation was found to successfully eliminate the infection and outperform the solution. These two studies clearly show that liposomal formulations are a better delivery system than solutions. However, liposomes also have some drawbacks. This formulation is unstable, prone to decomposition and aggregation, but its fuse leaks trapped drug during storage and after administration (Zhang & Wang, 2009). Therefore, Mehanna, Elmaradny, and Samaha (2010) proposed to perform surface modification and polymerization to improve the performance of liposomes.

NIOSOMES:

Niosomes are bilayer biodegradable, non-immunogenic vesicles from 10 nm to 01 μm and are composed of nonionic surfactants capable of transporting both hydrophilic and lipophilic compounds in an aqueous compartment. I am. They have long shelf life, improved therapeutic effect, and reduced side effects due to their low systemic absorption. Niosomes are available as eye drops for topical eye drops used to treat ocular hypertension, dry eye, glaucoma, and eye infections. Increased preocular residence time and drug absorption provide sustained and long-term clearance at the site of action, as inhibition of ocular metabolism by tears and reduced systemic drainage prolong the duration of action. Allam et al. Demonstrated improved antibacterial activity of vancomycin-niosomes gel against MRSA in rabbits. Nabarawi et al. Developed natamycin (NAT) loaded niosomes in ketrolactromethamine (KT) gels to increase permeability after topical administration and improve efficacy against fungal keratitis. Corneal ulcers are resistant to antibacterial and antifungal therapies.

OCULAR INSERTS:

Ophthalmic inserts are sterile formulations of thin, multi-layered drug-impregnated solid or semi-rigid devices that are placed in the conjunctival sac and have a special size and shape for ophthalmology (Kumari, Sharma, Garg & Garg, 2010). The main purpose of the eye insert is to improve the contact time between the delivery system and the conjunctival tissue to ensure long-term release suitable for topical or systemic treatment. According to Kumar, Bhowmik, Harish, Duraivel & Kumar (2013), there are two types of eye inserts, soluble and insoluble. Soluble ophthalmic inserts are generally defined as erosive monolithic polymers that slowly dissolve while releasing the drug and do not need to be removed from the eye. Insoluble type eye inserts are composed of insoluble polymers that can deliver the drug at a given rate in a variety of ways, but must be removed from the eye when empty. Sultana, Jain, Aqil, & Ali (2006) considered the delivery of eye inserts to be more controlled, sustained and continuous. By doing so, the effective drug concentration in the target tissue is maintained and the number of applications is minimized. However, based on reviews, they found that the use of this delivery system was due to physiological factors such as the patient not wishing to abandon conventional liquid and semi-solid medicines, and occasional treatments such as unintended clearance. Due to the failure, it was found to be less popular among users. Eye and membrane rupture. Eye inserts increase contact time, prolong release, reduce systemic side effects, reduce frequency of dosing, provide accurate dosing, extend shelf life compared to aqueous solution, eliminate preservatives, and sensitize reactions It offers several benefits, such as less (Kumarietal., 2010). However, eyepiece inserts also have their own drawbacks. Foreign body sensation in the eye can cause discomfort and can lead to decreased patient compliance, stimulating heavy tearing, drug dilution, and decreased concentration (Friedrich, Saville, Cheng, and Rootman, 1996). .. Kumari et al. (2010) also noted some other disadvantages of eye inserts such as unwanted migration to the conjunctival sac, accidental loss and difficulty in placement or removal, and impaired vision.

DENDRIMERS:

Dendrimers are branched nanoscale, star-shaped polymer drug delivery systems available in a wide range of molecular weights with a variety of functional end groups that can contain both hydrophobic and hydrophilic drugs. Van Dam et al. PAMAM Dendrimer Long-term ocular retention time of poly (amidoamine) (PAMAM) dendrimer as an ophthalmic vehicle for drug delivery due to higher miosis and muscle tone activity in albino rabbits after co-administration of pilocarpine. , Improved ocular bioavailability, and nitrates and tropicamides with better treatment results were observed. Subconjunctival administration of glucosamine and glucosamine-6-sulfate-loaded dendritic processes in the eyes of rabbit models from glaucoma filtration surgery promotes angiogenesis and significantly inhibits pro-inflammatory responses with reduced scar tissue formation showed that

MICRONEEDLES:

Sclera or choroid using microneedling because diffusion into deeper ocular tissues such as the choroid and retina can have therapeutic effects on diseases such as AMD, diabetic retinopathy, and posterior uveitis. The drug can be delivered to the upper cavity. This minimally invasive technique reduces the risks and complications associated with intravitreal injection. This is because the microneedles penetrate only the superficial sclera and avoid damage to the retina, vitreous, or choroid [1,193]. Jason et al. It showed high drug deposition of sulforhodamine-coated microneedles after scleral injection into the cadaver's eye [1,194]. E et al. [195] and Patel et al. [196] Attempts to inject drug solutions, microparticles, and nanoparticles into the scleral and suprachoroidal space of the human corpse eye. The results showed strategic safety and sustained drug release, but the drug may not reach the tissues within the retina.

4. CONCLUSION

There are many types of ophthalmic drug delivery systems in the literature and on the market. Nevertheless, due to the complexity of the anatomical structure of the eye, drug delivery remains a mystery and is a major concern for ophthalmologists and pharmaceutical scientists. Due to the convenience of administration, topical eye drops have so far remained the most popular strategy for eye treatment. However, there are some important limitations to prescribing eye drops that can affect their effectiveness. B. Loss of active ingredient due to tear drainage, limited corneal permeability, and decreased patient compliance after frequent doses. As a result, many traditional ophthalmic drug delivery devices have been developed as therapeutic options. Examples include eye emulsions, suspensions, ointments and polymer gels. Apart from these traditional delivery systems, scientists are developing other eye delivery systems such as nanocells, nanoparticles, liposomes, and eye inserts. These new systems have been developed to further enhance the effectiveness and safety of eye drug delivery applications. Nevertheless, there were still some drawbacks. It is hoped that future new systems will be able to overcome all the disadvantages.

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