JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON ENHANCEMENT OF OCULAR DRUG DELIVERY SYSTEMS

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Abstract : The major challenge faced by today's pharmacologist and formulation scientist is ocular drug delivery. Topical eye drop is the most convenient and patient compliant route of drug administration, especially for the treatment of anterior segment diseases. Delivery of drugs to the targeted ocular tissues is restricted by various precorneal, dynamic and static ocular barriers. Also, therapeutic drug levels are not maintained for longer duration in target tissues. In the past two decades, ocular drug delivery research acceleratedly advanced towards developing a novel, safe and patient compliant formulation and drug delivery devices/techniques, which may surpass these barriers and maintain drug levels in tissues. Anterior segment drug delivery advances are witnessed by modulation of conventional topical solutions with permeation and viscosity enhancers. Also, it includes development of conventional topical formulations such as suspensions, emulsions and ointments. Various nanoformulations have also been introduced for anterior segment ocular drug delivery. On the other hand, for posterior ocular delivery, research has been immensely focused towards development of drug releasing devices and nanoformulations for treating chronic vitreoretinal diseases. These novel devices and/or formulations may help to surpass ocular barriers and associated side effects with conventional topical drops. Also, these novel devices and/or formulations are easy to formulate, no/negligibly irritating, possess high precorneal residence time, sustain the drug release, and enhance ocular bioavailability of therapeutics. An update of current research advancement in ocular drug delivery necessitates and helps drug delivery scientists to modulate their think process and develop novel and safe drug delivery strategies. Current review intends to summarize the existing conventional formulations for ocular delivery and their advancements followed by current nanotechnology based formulation developments. Also, recent developments with other ocular drug delivery strategies employing in situ gels, implants, contact lens and microneedles have been discussed.

Keywords*:* Anatomy and physiology; Cornea; Contact lens; Drug delivery; Eye; Emulsions; Formulations; Implants; Liposomes; Nanomicelles; Ointments; Retina; Suspensions

INTRODUCTION

The eye is a highly complex organ with distinct anatomy and physiology. The structure of the eye can be separated into two primary parts: the anterior and posterior segments (Figure). The anterior section of the eye takes up roughly one-third of the space, with the posterior segment taking up the remainder. The anterior includes tissues such the cornea, conjunctiva, aqueous fluid, iris ,ciliary body, andlens.
Because of unique anatomical and physiological features, eyes are vulnerable to a variety of diseases such as keratitis, cataract, glaucoma, and retinopathy, which harm patients' health and lower their quality of life. Currently, vision impairment related to ocular illnesses is the leading cause of disability worldwide. By 2015, there were 34.3 million blind persons, 24.3 million with severe vision impairment, and 214 million with moderate visual impairment globally (Stevens et al., 2013). Therefore, active prevention and treatment of ocular illnesses is critical.portion. The sclera, choroid, retinal pigment epithelium, neural retina, optic nerve, and vitreous humor are all located in the back of the eye. Anterior and posterior. Glaucoma, allergic conjunctivitis, anterior uveitis, and cataract are examples of disorders that affect the anterior portion of the eye. The most common illnesses affecting the posterior portion of the eye are age-related macular degeneration (AMD) and diabetic retinopathy.
Network topology is widely recognized as a key tool for network design and applications, particularly in large-area networks where network stability and dependability are critical to network performance. The employment of such technologies is also applicable to increasingly complicated systems, particularly when network devices and components are shrunk to nanoscale levels. Nanoscale devices and networks can serve as molecular networks for a variety of applications, including biomedical engineering[1], health care, pharmaceuticals[2,3], and Nanomedicine[4,5] The use of the medical information bus (MIB) standard[6,7] for the bidirectional interconnection of medical devices and computers was first proposed in 1984 and approved by the Institute of Electrical and Electronics

Engineers and the American National Standards Institute in 2000-2001 for digital communication networks. Extensive research has enhanced and supported the MIB standard[8-10] Recently, the application of molecular buffer and bus networks for the detection of Alzheimer's disease has been proposed4, and the stability of a multi-access drug delivery network has been investigated[5] The necessary molecular volumes for a medication or protein can be captured and dynamically transported inside the molecular bus network. The system has the advantage of being able to perform the diagnostic procedure within a compact system that is available as a human-embedded diagnostic device.

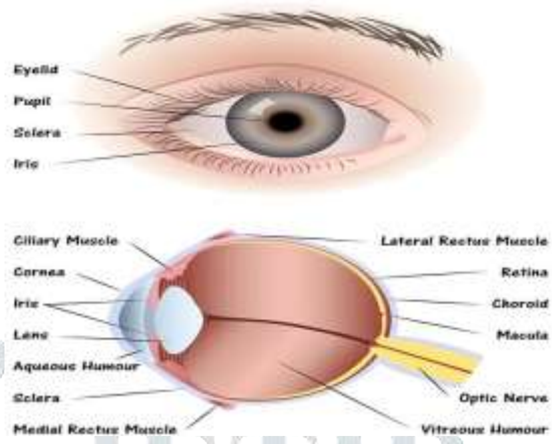

Fig1: Structure of Eye [3]

TYPES

Topical drops

Topical drops are the most convenient, safe, immediate-acting, patient-compliant, and noninvasive method of ocular medication delivery. An eye drop solution offers a pulse of drug penetration during topical drop instillation, after which its concentration rapidly decreases. The kinetics of drug concentration drop may be approximately first order. To improve medication contact duration, penetration, and ocular bioavailability, topical eye drops may contain various additives such as viscosity enhancers, permeation enhancers, and cyclodextrins. Viscosity enhancers improve precorneal residence duration and bioavailability after topical drop delivery by increasing formulation viscosity. Viscosity enhancers include hydroxymethyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose, hydroxypropyl methyl cellulose, and polyalcohol [14-16].

Emulsions

An emulsion-based formulation technique improves medication solubility and bioavailability. There are two types of emulsions that are commercially used as carriers for active pharmaceuticals: oil in water (o/w) and water in oil (w/o) emulsion systems[26]. For ocular medication delivery, o/w emulsion is commonly used and recommended over w/o systems. The explanations include less discomfort and improved ocular tolerance to o/w emulsion. Current commercial ocular emulsions in the US include Restasise™, Refresh Endura® (a non-medicated emulsion for eye lubrication), and AzaSite®. Several investigations have shown that emulsions can improve precorneal residence duration, drug corneal penetration, and provide sustained drug release, hence increasing ocular bioavailability [27].

Gene therapy

The use of viral vectors to modify the genome is being researched as a potential treatment for inherited retinal disease. These treatments would be implanted in the subretina, allowing the vectors to target the photoreceptors or RPE cells while reducing the immune response and dosage needed[1]Animal studies have already shown that the adeno-associated virus (AAV) is a viable technique for longer-term gene expression in the retina; further development of this vector will allow it to be used to treat more disorders and enhance efficiency [6]. It is the most prevalent technique of introducing genetic material into the retina [1]. It has been used successfully to treat a variety of degenerative disorders in animal models by targeting both RPE and photoreceptor cells [1]. Other vectors, such as helper-dependent adenoviral vectors, have been utilized to enhance AAV performance [1]. Lentiviral vectors have also been used in gene therapy for the retina [1]. While most research has focused on hereditary and degenerative disorders, some has been done on treating autoimmune uveoretinitis in animals [1]. AAV-based treatments for humans are currently in clinical studies; these tests have proven that AAV medicines are not systemically toxic, have no significant side events related with their use, and show encouraging improvements in patients' vision [1]. It is worth noting that these treatments are delivered using subretinal injections [1]

Cell therapy

Cell therapy is the injection of cells into the subretina to treat retinal degenerative disorders [1, 7]. These systems primarily involve the injection of stem cells intended to integrate into the retinal layers and aid restore function or support cell regeneration; however, alternative photoreceptive or RPE cells have occasionally been employed [1, 5]. While animal studies indicate that this approach is safe and nontoxic, there is concern about the increased risk of consequences. Currently, some phase 1 and 2 research are underway [1]. Gandhi et al. at the Mayo Clinic recently established the safety and efficacy of degradable fibrin hydrogels for subretinal implantation, allowing for precise and continuous implantation of an RPE monolayer [8]. These promising hydrogels dissolved effectively in the space within 8 weeks of delivery, making them the first totally degradable scaffold created to treat macular degeneration and retinal degenerative illnesses [8].

Novel Delivery Methods

Because of the segregated structure of the subretina, there is a lot of interest in researching how to successfully deliver medications using minimally invasive methods. While many different ways of medication delivery are being investigated, this review will focus on the most prevalent. One of the options examined is the use of nanoparticles to aid with drug distribution. Nanoparticles could be employed to preserve the medicine, transport it over the blood-retina barrier, or allow for long-term release. Cerium oxide nanoparticles were employed to scavenge reactive oxygen species in mice's eyes, avoiding oxidative stress and demonstrating their ability to halt disease development [2]. Nanoparticles can also be utilized to encapsulate DNA or RNA, facilitating their reception into retinal cells in the absence of a viral vector [5]. This would allow for a novel method of gene therapy for the cells of the eye. In terms of boosting drug dosage and extending drug delivery time, nanoparticle encapsulation has been found to deliver hydrophobic chemicals to RPE cells over time [5].

Liposomes, which are hydrophobic, could also be used to deliver medications to the subretina via diffusion over the blood-retina barrier. PEG molecules have been utilized to encapsulate medications for transport to the brain via the blood-brain barrier, which is a comparable anatomical barrier [4]. Given the parallels between the blood-brain and blood- retina barriers, such a device is likely to be successful for medication delivery to the subretinal area[4].
Injectable hydrogels have the potential to deliver drugs in the subretinal region for an extended period. Previous studies have employed hyaluronic acid hydrogels to transplant retinal progenitor cells into the subretinal area [2]. After three weeks, the transplanted cells were equally distributed across the subretinal region and displayed features consistent with photoreceptor maturation [2]. Hydrogels could be used to deliver medicines and biologics into the subretinal region over an extended period of time [3]. Their usage would eliminate the need for recurrent subretinal injections, but it would still result in the production of a bleb and stress to the eye.

Systems Challenges for Commercial Development of New Ophthalmic Drug Delivery

Despite the large number of articles reporting innovative ophthalmic DDS, only a few items are ultimately commercialized. From bench to batch to market, various phases must be completed, including preclinical and clinical research, as well as pharmacovigilance. Regulations for the commercialization of new ophthalmic DDS differ by nation. We shall outline the regulatory issues of the three regions where the majority of eye drops are currently available.

Regulatory Affairs

Eye drops are classified as medicinal items in the United States, Europe, and Japan if they work via pharmacological, immunological, or metabolic mechanisms, or as medical devices if they are used for cleaning, washing, or hydrating [67]. Eye drops comprising polymers (HA, cellulose derivatives, and others), such as artificial tears, are classified as medical devices because their activity is limited to hydrating the ocular surface. DDS-based eye drops are classified as medicinal items since they contain active pharmaceutical medicines in their formulation. Pharmaceutical companies must conduct preclinical and clinical studies to demonstrate the efficacy and safety of a new eye drop formulation before commercializing it. Following these steps, they can request marketing authorization from the relevant competent authority in the country where they want to sell the product, specifically the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, United States), and the Ministry of Health, Labour, and Welfare (Japan).

Process and Quality Prontrduction cools

These batches must adhere to Good Manufacturing Practices (GMPs), which are principles that ensure quality and consistency from batch to batch. Modifying the manufacturing process between academic laboratories and industry can have a major impact on product qualities, as well as efficacy and safety [68]. The Pharmacopeia is a regulatory publication that describes Day T.P., Byrne L.C., Schaffer D.V., and Flannery J.G. Retinal Degenerative PMC free article all of the criteria required for the manufacturing of One of the most difficult steps in the commercialization of new DDS is the production of large-medicinal products and the methods of analysis to ensure quality controls. A thorough description of the product must be provided in accordance with the applicable country's Pharmacopeia, including biological and chemical characterizations, production processes, and quality controls. Biological and chemical criteria encompass product composition as well as physicochemical qualities. More specific criteria for NP-based systems include particle size/distribution, surface characterization (zeta potential, functionality, and surface chemistry), morphology, drug loading, and drug encapsulation [69].

Particle size

Particles larger than 10 µm are not absorbed by ocular tissues or removed through nasolacrimal channels, leading to ocular irritation [70]. The US Pharmacopeia demands less than 50 particles with a diameter of 10 µm per mL solution.

Stability

Stability tests are necessary to ensure that the formulation retains the same traits and characteristics within prescribed limitations and over the course of storage and use as it did at the time of manufacture. Natural materials, such as chitosan or gelatin, are known to be less stable and more degradable than synthetic polymers [71], which explains their minimal utilization in ophthalmic formulations. Maintaining the stability of nanoemulsions and nanosuspensions can be especially difficult due to the danger of NP aggregation and degradation [72].

Purity

Endotoxin levels in ocular solutions should not exceed 0.5 EU/mL, according to several Pharmacopeia. As previously stated, natural polymers such as chitosan or alginate have particularly appealing qualities for usage in ophthalmic DDS. However, because they are taken from natural sources, contaminants such as endotoxins may be present, causing immunogenic reactions [75]. These contaminants may explain why chitosan is seldom employed in commercial formulations, despite its obvious benefits for ocular medication delivery.

Preclinical and clinical trials

Larger animal models offer the advantage of being closer anatomically and in size to human eyes, but they are more expensive, and some species (e.g., rabbits, dogs) require fewer reagents, such as particular antibodies for pharmacodynamic investigations. Pharmacokinetic studies for eye drops are typically carried out by quantifying the medication in plasma, tears, and other ocular tissues at various time points following instillation. Preclinical research have constraints, such as a small number of animals and a short observation period. Furthermore, the differences in ocular tissue size and shape, metabolic activity, and blinking rate between animal models and humans may limit the applicability of such data to humans.

Contact lenses

Low medication adherence is one of the most common difficulties linked with glaucoma. The topical drugs must be administered two or three times per day. This condition can also be addressed by using contact lenses, which can deliver a regulated or sustained release of medication.[9]Thus, medicated contact lenses can address the drug carrier system's low ocular availability and short residence period. Both conventional and silicone hydrogel contact lenses quickly release ophthalmic medicines.[10] However, nanoparticle-laden lenses, biomimetic and imprinted contact lenses with multilayer architectures may allow for longer drug administration along.Contact lenses have been shown to be as effective as other therapy regimens in glaucomatous patients.[11,12] According to Peng et al, contact lenses with only 20% medication loading can provide the same efficacy as eye drops. The continued use of it results in a significant reduction in IOP.[13] Hsu et al developed contact lenses loaded with dorzolamide and timolol, and the method was found to prolong the release of the loaded moieties for two days while causing a significant decrease in IOP when compared to eye drops. Furthermore, the system has been shown to be more useful when used with Vitamin E due to its antioxidant properties.[14]

Table1: Carriers with its advantages and disadvantages

Carrier	Advantages	Limitations
Eye solution	• Easy to instilled • Convenient • Economic	• Drainage • Drug loss by tear fluid • Low bioavailability • Regular instillation
Suspension	• Prolonged contact time • Patient compliance	• Irritation (particle size) • Loss of drug solution
Ointments	• Prolonged contact time • No tear dilution • Improved stability • Improved bioavailability	• Blurring vision • Poor patient compliance
Ocular inserts	• Comfortable • Prolonged delivery • Reduced dose frequency	• Difficult to insert & remove • Requires skill for insertion
Liposomes	• Stable • Control drug release • Reduced dosing frequency • Improved bioavailability	• Stability problems • Not reproducible • Rapid clearance • Uptake by conjunctival cells
Niosomes	• Stable • Controlled drug release • Reduced dosing frequency • High entrapment efficiency	• Less bioavailability when uptake by conjunctival cells
Nanoparticles	• Small size • Long shelf life, • Highly stable • Improved bioavailability • Reduced dosing frequency	• Particle contamination
Microparticles	• Stable • Improved bioavailability • Reduced dosing frequency	• Irritation occurs • Large particle size
Implants	• Biodegradable • Non-toxic	• Surgical application
Penetration enhancers	• Promote penetration of drugs • Improved bioavailability	• Toxicity & irritation • Large concentration
Prodrugs	• Prolonged residence time • Reduced dosing	• Metabolism problems
Hydrogels	• Prolonged residence time • Increase bioavailability	• Triggered by temperature, pH and Ionic strength
Dendrimers	• Small size • Decreased dosing frequency • Prolonged residence time • Improved bioavailability	• Blurring vision
Micro-emulsions	• Stable • Improved solubility • Improved bioavailability • Reduced dosing frequency	• Toxicity (higher concentration), • Selection of surfactant/co-surfactant and aqueous/organic phase affects its stability
Nano-suspensions	• Stable • Prolonged contact time • Improved bioavailability • Enhance solubility	• Used for poorly soluble drugs

STRATEGY ENHANCEMENTS.

Nanoparticles

Nanoparticles are colloidal carriers whose sizes range from 10 to 1000 nm. Nanoparticles used in ocular administration are often made up of lipids, proteins, and natural or synthetic polymers such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA), and polycaprolactone. Drug-loaded nanoparticles might be either nanocapsules or nanospheres. In nanocapsules, the drug is confined within the polymeric shell, but in nanospheres, the drug is uniformly dispersed throughout the matrix. Nanoparticles have received increased attention in recent decades for ocular drug delivery, and various researchers have attempted to produce drug-loaded nanoparticles for delivery to both anterior and posterior ocular tissues[24-25].

Gold nanoparticles

Gold nanoparticles are highly appealing for use as drug carriers due to their unique physical and chemical properties, including the ability to be synthesized in various sizes and shapes and easily functionalized with a variety of molecules, allowing for targeted drug delivery [76,77,78,79,80,81]. These properties enable gold nanoparticles to target specific cells and tissues and deliver medications in a regulated manner. One of the primary obstacles in employing gold nanoparticles as therapeutic carriers is optimizing drug loading. The amount of drug that can be loaded onto nanoparticles is determined by various parameters, including the nanoparticles' size and shape, surface functionalization, and the drug's physicochemical properties. To obtain the intended therapeutic impact, gold nanoparticles' drug loading and release properties must be carefully optimized. Many papers in the literature have indicated the potential of gold nanoparticles as carriers for various medications [82,83,84,85,86,87], but additional research is needed to optimize the control of drug loading and to compare widely used coatings such as polyethylene glycole.

Silver nanoparticles

Silver nanoparticles (Ag NPs) are used as medication delivery methods in the pharmaceutical industry. The current study aims to create drug-loaded Ag NPs utilizing a previously documented 3-methyl-1-phenylbutan-2-amine as a mebeverine precursor (MP). Methods: A green, galactose-assisted technique for rapidly synthesizing and stabilizing Ag NPs as a drug- delivery system is described. Galactose was utilized as a reducing and capping agent, creating a thin coating around the nanoparticles. The structure, size distribution, zeta potential, surface charge, and role of the capping agent of drug-loaded Ag NPs were investigated. The drug release from MP-loaded Ag NPs was also examined. The Ag NPs showed a very good medication release of 80 to 85%. Based on preliminary findings, Ag NPs may be a potential medicine delivery mechanism for MP and a therapy option for inflammatory bowel disease. As a result, further investigation into the possible medical applications of the created Ag NPs is required.[88]

Quantum dots (QDs)

Quantum dots (QDs) bridge nanotechnology and drug testing. Their distinct photoluminescence and electronic features, which include broad and continuous absorption spectra, narrow emission spectra from visible to near-infrared wavelengths, long light duration, and high brightness, make them attractive probe materials for (bio)sensing or immunosensing platforms. . Quantum Quantum dots (QDs), nano-sized semiconductors, are one of the most essential materials. Because of their unique physicochemical properties, QDs are regarded excellent fluorescent labels used in a drug delivery system to monitor drug metabolism in the body. They can also be used in a range of biological applications, including illness detection and fluorescence tests for drug development. This study discusses QDs' physical and chemical properties, production methods, surface modification, and bioconjugation, as well as some fascinating current uses in analytical chemistry, drug administration, biosensing, and immunoassays.Natural polymers such as arginine, chitosan, dextrin, polysaccharides, poly (glycolic acid), poly (lactic acid), and hyaluronic acid have been processed to create polymeric drug delivery systems.[89] Synthetic polymers such as poly (2-hydroxyethyl methacrylate), poly(N-isopropyl acrylamide), poly(ethylenimine), dendritic polymers, biodegradable, and bio-absorbable polymers have also been considered for polymeric drug delivery. Biomimetic and bio-related polymeric systems, as well as drug-free macromolecular therapies, have been studied for polymeric drug delivery purposes. In polymeric gene delivery systems, virial and non-virial vectors for gene delivery have been briefly examined. Non-virial vector systems for gene delivery include polyethylenimine derivatives, polyethylenimine copolymers, and polyethylenimine conjugated bio-reducible polymers, whereas virial vector systems include DNA conjugates and RNA conjugates for gene delivery.[90]

POLYMERS

Polymers that may change their characteristics in response to an external or internal stimuli have emerged as a promising platform for medication delivery. Polymeric nanoparticles can be employed to reduce drug toxicity, improve the circulation of hydrophobic medicines, and increase treatment efficacy. Furthermore, polymers that respond to certain stimuli can be utilized to deliver medications to specific parts of the body in a regulated manner. This review examines the various stimuli that can be utilized for regulated medication delivery, including internal and exterior stimuli. Internal stimuli have been defined as events that cause changes in several properties within the body, such as pH, redox potential, and temperature.

External stimuli are described as the use of an external source, such as light or ultrasound, to effect such changes. Special emphasis has been made to the specific chemical structures that must be introduced into polymers to generate the appropriate stimulus response. A contemporary trend in this field is the combination of many stimuli into a single polymer to obtain greater specificity. To gain access to the most current breakthroughs in stimulus- responsive polymers, the focus of this review is on combining several stimuli. The combination of various stimuli is examined, as well as the molecular structures capable of producing it.[90]

Nanosuspensions

Nanosuspensions are colloidal dispersions of submicron drug particles that are stabilized with polymer(s) or surfactants. It has emerged as a potential method for the delivery of hydrophobic medicines. For ocular distribution, it offers various benefits, including sterilization, ease of eye drop formulation, decreased discomfort, increased precorneal residence time, and increased ocular bioavailability of medications that are insoluble in tear fluid[34]. Several investigations have shown that nanosuspensions improve ocular bioavailability of glucocorticoids. Glucocorticoids such as prednisolone, dexamethasone, and hydrocortisone are extensively used to treat inflammatory diseases affecting the anterior portion of the eye. The present treatment with these medications involves regular administration at larger doses, which causes cataract formation, glaucoma, and optic nerve damage.

Efforts have been undertaken to improve the ocular bioavailability of glucocorticoids by forming nanosuspensions. For example, Kassem et al[35] investigated the ocular bioavailability of several glucocorticoids (prednisolone, dexamethasone, and hydrocortisone) in nanosuspensions, solutions, and microcrystalline suspensions. The formulations were administered into the rabbit eye's lower cul-de-sac, and intraocular pressure (IOP) was monitored at regular intervals lasting up to 12 hours. The area under the percentage increase in IOP vs time curve (AUC) values for all suspensions were greater than those for the corresponding drug solutions. Furthermore, all steroids in nanosuspensions showed better drug absorption and more powerful pharmacological effects than solutions.Another study evaluated the ocular bioavailability of hydrocortisone (Hc) nanosuspensions generated using the precipitation and milling process to HC solution in rabbits after topical instillation. Nanosuspensions made through precipitation and milling had considerably higher AUC (0-9 h) values of 28.06 ± 4.08 and 30.95 ± 2.2 μg/mL compared to HC solution (15.86 ± 2.7 μg/mL). The nanosuspensions maintained a prolonged pharmacological activity, as measured by changes in intraocular pressure, for up to 9 hours, but the drug solution only lasted five. The results of the preceding research experiments suggest that nanosuspensions could be an effective ocular medication delivery strategy for poorly soluble medicines. In Patel et al., page 12, World Journal of Pharmacology. The author's manuscript is available in PMC on January 12, 2015. NIH-PA: Author Manuscript Author Manuscript, NIH-PA In addition, nanosuspension can be integrated into hydrogels or ocular implants to achieve sustained medication release over a specific time period.[35]

Liposomes

Liposomes are lipid vesicles with one or more phospholipid bilayers enclosing an aqueous core. They range in size from 0.08 to 10.00 μm and can be classified as small unilamellar vesicles (10-100 nm), large unilamellar vesicles (100-300 nm), or multilamellar vesicles (contains more than one bilayer)[31]. Liposomes are suited for ocular applications because of their high biocompatibility, cell membrane-like shape, and ability to encapsulate both hydrophilic and hydrophobic medicines. Several investigations have shown that liposomes are effective for ocular distribution to both the anterior and posterior segments. summarizes recent advances in liposome-based ocular medication delivery [32-33]. Natarajan et al. produced a liposomal formulation in a recent study to deliver latanoprost to anterior segment ocular tissues[32]. A single subconjunctival injection of latanoprost/liposomal formulation in rabbit eyes resulted in a persistent IOP lowering effect over 50 days, with IOP reduction comparable to daily eye drop dosing. . For drug delivery to anterior segment of the eye, efforts are mainly put toward improving precorneal residence time by incorporating positively charged lipids or mucoadhesive polymer in liposomes. The positively charged liposomes i.e., cationic liposomes have exhibited better efficacy in ocular delivery than negatively charged and neutral liposomes due to binding with negatively charges of corneal surface. Didodecyldimethylammonium bromide, stearylamine, and N-[1-(2,3- dioleoyloxy)propyl]- N,N,N-trimethylammonium chloride are commonly employed for fabricating cationic liposomes.

Dendrimers

Dendrimers are nanoscale, highly branching, star-shaped polymeric structures. These branching polymeric systems are available in a variety of molecular weights and include terminal end amine, hydroxyl, or carboxyl functional groups. The terminal functional group can be used to conjugate targeted moieties [26]. Dendrimers are used as carrier systems in medication delivery. To distribute medications, it is crucial to select the appropriate molecular weight, size, surface charge, molecule shape, and functional group. Dendrimers' highly branching structure enables for the inclusion of a wide variety of medicines, both hydrophobic and hydrophilic. Few promising outcomes have been reported for ocular medication delivery using these branched polymeric systems[30,27,29]. Poly(amidoamine) (PAMAM) dendrimers are commonly used for ocular medication delivery[27]. Vandamme et al. [94] PAMAM dendrimers have been shown to be effective ocular carriers for the administration of pilocarpine nitrate and tropicamide for miotic and mydriatic activity. In this study, the mean ocular residence duration for fluorescein in saline and PAMAM solutions was investigated in the rabbit eye. Fluorescein in 0.2% w/v Carbopol solution served as a reference bioadhesive polymer. In comparison to saline, PAMAM solutions and 0.2% w/v Carbopol solution had considerably longer mean ocular residence times. As a result, dendrimers may be another alternative for prolonging ocular residence time and therapy, hence improving ocular bioavailability and achieving improved therapeutic effects. For example, when PAMAM dendrimers were combined with pilocarpine nitrate and tropicamide, albino rabbits demonstrated increased miotic and mydriatic activity[29].

Targeted medication delivery

Targeted medication delivery is a strategy for selecting and preferentially delivering therapeutic drugs to the target location while preventing access to the nontarget region. One appealing strategy for this goal is the employment of a "ligand" to aid in the homing of therapeutic compounds to specific tissues. Ligand-targeted chemotherapeutics rely on the use of antigens or receptors that are either inherently expressed or overexpressed on tumor cells in comparison to normal tissues in order to protect normal tissues from anticancer drugs while selectively delivering the anticancer drug to tumor tissue. These ligands may be tiny molecules (e.g., carbohydrates, folate), low-density lipoproteins (LDL), or peptides and proteins (e.g., transferrin or antibodies). The selection of the ligand used to target the therapeutic molecule is governed by several significant considerations. [29]

Strategies for Targeted Antibiotic Delivery

Resistant bacteria can deactivate medicines by either preventing drug entry at the site of action or by modifying drugs [47]. Successful antibiotic delivery is extremely difficult, especially for Gram-negative bacteria, whose cell walls are made up of a cytoplasmic membrane, peptidoglycan layer, and lipid bilayer [48, 49]. The lipid bilayer contributes to Gram-negative bacteria's resistance to many drugs [50]. Because of such defense.

limitations of targeted antibiotic delivery strategies and potential solutions while antibiotic-siderophore

conjugation is a promising technique for targeted antibiotic delivery, it does have limits. Non- β-lactam antibiotic-siderophore conjugates may struggle to penetrate the inner bacterial membrane due to the difficulty of finding a suitable linker for siderophore-antibiotic conjugates. A non-cleavable linker can cause loss of antibiotic action if medication targets are precisely positioned in

Aptamers

Aptamers use attached nanoparticles to enter cells. As a result, aptamers can be used as effective targeting ligands for drug delivery. Because of their superior features, various aptamer-mediated drug delivery methods have been investigated[7]

Passive targeting

Passive targeting was created for cancer treatment. This article provides a concise overview of current improvements in drug delivery systems based on aptamers. The advantages, problems, and future prospects are likewise distinct. In passive targeting, macromolecules, including nanoparticles, concentrate preferentially in neoplastic tissues due to the increased permeability and retention (EPR) phenomenon, which was first observed by Maeda and Matsumura [7, 8]. The EPR is based on the nanoscale size range of the nanoparticles and two key properties of the neoplastic tissues, which are leaky vasculature and poor lymphatic drainage. Our current understanding of EPR effectiveness is constrained by a lack of data gathered from pre-clinical tumor models that effectively mimic solid tumors in patients.

In reality, the most often utilized subcutaneous tumor xenografts are rapidly developing, resulting in very high-EPR tumors that may give an incorrect impression of the therapeutic efficacy of NCs in therapies that rely on passive EPR-based targeting. There is also a lack of patient-based experimental evidence on the EPR phenomenon and its impact on drug accumulation in the tumor site, which translates into therapeutic efficacy. Further research into the EPR in various human cancers, as well as the creation of better preclinical models, are required for the design of NCs with improved tumor penetration and therapeutic outcomes[9,10]. Recently, Theek et al. studied the relationship between tumor vascularization and EPR-based passive targeting in a subcutaneous tumor model37. Miller et al. demonstrated that an FDA-approved 30-nm carboxymethyl dextran-coated magnetic nanoparticle (MNP) (ferumoxytol) could be used as a surrogate or companion particle to predict intratumoral transport, pharmacokinetics (PK), and distribution of a therapeutic NC based on poly(d,l-lactic-co-glycolic acid)-b-poly(ethylene glycol) (PLGA-PEG). Lee et al. used 64Cu-labeled HER2-targeted liposomes and PET/CT to measure medication accumulation in 19 patients with HER2 positive metastatic breast cancer40. Patients were classified based on 64Cu-liposomal lesion deposition, with a cut-point comparable to a response threshold reported in preclinical research. Peak liposome accumulation was observed at 24-48 hours. Patients with increased 64Cu-liposomal lesion deposition had better treatment results. These investigations show that using imaging techniques to evaluate and characterize EPR may someday allow clinicians to pre-select patients with high-EPR tumors who are likely to respond to passively targeted NCs, significantly enhancing therapy outcomes.

Size impacts delivery efficiency

Size, as one of the most essential features of nanoparticles, has a significant impact on the efficiency of tumor-targeted drug delivery in a variety of ways, including circulation, biodistribution, tumor accumulation and penetration, cellular uptake, and subcellular distribution. A full grasp of size will be introduced initially to help explain the significance of size-tunable techniques. After entering the body, the circulation duration of nanodrugs largely impacts the efficacy of tumor targeting, as the bulk of nanodrugs are swiftly cleared by the mononuclear phagocytic system (MPS) or filtered by the liver and spleen. There is a link between circulation and particle size. MPS clearance has a size-dependent tendency, meaning that nanoparticles with small diameters are less likely to be taken up by macrophages than larger ones.[15,16] Because organ cutoff sizes vary, the size of nanodrugs has a significant impact on biodistribution. The renal filtration cutoff size is 5.5 nm17, while vascular fenestrations in the liver range from 50 to 100 nm. Particles smaller than 5.5 nm are expelled more easily through urine, whereas those smaller than 50 nm can easily pierce the endothelium and become stuck in the liver.[18,19]

EPR

One of these helpful properties is the distorted tumor vasculature, also known as the increased permeability and retention (EPR) effect. Nanocarriers with small diameters (~100- 400 nm) [6] can seep through tumor vasculature and accumulate inside tumor tissues due to poor lymphatic drainage. This is known as "passive tumor targeting." Although the EPR effect can be used for the accumulation of nanodrugs in the tumor, this effect alone is not sufficient; typically, the EPR effect yields less than a 2-fold increase in drug delivery to the tumor compared to normal tissues[7]. As a result, biomarkers can be attached to the nanocarrier's surface to match specific receptors overexpressed on cancer cells, enhancing the target ability. This is known as active tumor targeting. These smart nanocarriers can be programmed to respond to internal or external stimuli, resulting in the controlled release of the encapsulated medicine once they have accumulated inside the targeted tumor. Nanocarriers that respond to internal stimuli benefit from several tumor properties such as acidic pH, elevated temperature, and enzymatic and redox activities. However, internal stimuli are typically sluggish and difficult to manage [8]. External triggers, such as ultrasound, magnetic fields, and light, are more adjustable for long-term drug release in both space and time . analyzes the benefits and challenges of the aforementioned triggering techniques.

Triggering Mechanism

Implantable localized drug delivery systems (LDDSs) with cognitive capabilities have developed as an effective chemotherapeutic platform for cancer treatment. Developing LDDSs with rationally regulated drug release and real-time monitoring functions holds promise for tailored therapy procedures, but it presents significant obstacles. To address these issues, a set of porous Yb^{3+}/Er^{3+} cooped $CaTiO_3$ (CTO:Yb,Er) nanofibers with carefully optimized surface functionalization were developed for doxorubicin (DOX) delivery. The release of DOX could be optically monitored by increasing the intensity ratio of green to red emission (I_{550}/I_{660}) of up conversion photo luminescent nanofibers under 980 nm near- infrared (NIR) excitation due to the fluorescence resonance energy transfer (FRET) effect between DOX molecules and nanofibers. More crucially, 808 nm NIR irradiation resulted in significantly faster DOX release, confirming typical NIR-triggered drug release features. As a result, CTO:Yb,Er nanofibers shown dramatically increased in vitro anticancer activity under NIR irradiation. This discovery has inspired another potential fibrous LDDS technology for customized tumor chemotherapy that releases DOX triggered by NIR and monitored by optics. [8]

RISK FACTORS

Distinguishing the glaucomatous population is difficult because the sickness is only detected after a significant percentage of RGCs have been lost. Evidence demonstrated that a geriatric community, Africans, Americans, a family history of glaucoma, elevated IOP, lower diastolic perfusion pressure, and myopia are the primary risk factors for glaucoma. [15]

Age

Age-related susceptibility might be seen as a major factor in the growth of the glaucomatous population. Patients over 40 are more likely to develop glaucoma[15,16].

Gender

According to reports, the female population is more likely to develop glaucoma, namely angle-closure glaucoma.[17]

Familial History

According to research, people who have a first-degree relative with glaucoma are four times more likely to forget about the disease than those who do not have such a relative.[15]

Genetics

GLC1A is a gene that codes for a molecule found in the aqueous outflow channels. Mutation in these channels causes an obstruction in the outflow, resulting in an increased IOP.Both the trabecular meshwork and the ciliary bodies regulate IOP and include moiling fractions. The MYOC locus in the GLC1A gene encodes moiling, and mutations in this locus are thought to contribute to 3%-5% of adult-onset primary open-angle glaucoma.[26]

Ethnicity

Glaucoma is regarded one of the leading causes of blindness among African Americans, Caucasians, and others.[15]

Cataract

Cataract is the leading cause of eyesight loss worldwide. Cataract complications account for around 40-60% of blindness worldwide [36]. According to the National Programme for Control of Blindness and Visual Impairment, cataracts account for the majority of avoidable blindness in India (62.6%) [37]. Cataract can be characterized as the development of cloudiness or opacification in the eye lens. The risk factors include UV radiation exposure, diabetes, poor diet, genetic predisposition, and smoking. Cataract can be classified into three types: cortical, nuclear, and posterior subcapsular. The crystallin protein regulates the clarity and transparency of the lens. Early cataract formation is caused by alterations in α, β, and γ crystallin and related genes. Glycation, oxidative stress, and exposure to lipophilic substances all contribute to cataract formation by raising the calcium level in the lens and causing crystallin buildup. Hyperglycemia and hydroxyl radicals both contribute to oxidative stress. Nowadays, surgical removal of opaque lenses is the preferred therapeutic method. However, early therapy with an anti-cataract medication may reduce the need for surgery. Anti-cataract drugs are multifunctional antioxidants capable of both radical hunting and chelation [38]. Anti- cataract drugs include curcumin, lanosterol, resveratrol, and metformin [39].

Glaucoma

Glaucoma is a well-known optic neuropathy disorder. Symptoms begin with impaired vision and proceed to irreversible blindness in the late stage. It causes blindness due to the gradual degradation of optic nerve axons and the death of retinal ganglion cells [41]. It is frequently associated with an increase in intraocular pressure (IOP) due to abnormal development or blockage of the aqueous humor [42]. Risk factors include age, race, diabetes, heredity, nearsightedness, migraines, and retinal vascular caliber. Glaucoma is more common in women, accounting for 55% of open angle glaucoma, 70% of angle closure glaucoma, and 59% of total glaucoma cases in 2010 [40]. The global incidence is projected at 76 million in 2020 and is expected to increase to 112 million by 2040 [43].

Glaucoma is classified into two types: open angle and closed angle. Open angle glaucoma has no symptoms and is distinguished by enlarged optic disc cupping and visual field, resulting in increased inhibition of aqueous humor drainage through trabecular meshwork. However, closed angle is distinguished by higher pressure caused by the obstruction of outflow routes [41]. Glaucoma affected about 76 million people, with a projected increase to 112 million by 2040 [44]. Glaucoma began as a result of oxidative and nitrative processes. There are numerous antioxidant enzymes in aqueous humor, including superoxide dismutase, catalase, and glutathione peroxidase. As people age, their level decreases, resulting in an increase in IOP. Changes in the balance of oxidants and antioxidants influence the course of glaucoma [45]. Anti-glaucoma medications help to regulate either aqueous fluid production or drainage. Several studies were published to improve glaucoma treatment [42, 46, 47, 48]. Abd-Elsalam and ElKasabgy created topical agomelatine-loaded olaminosomes that shown impressive anti- glaucoma activity [42]. Eldepe et al. created topical proniosomal gel-derived niosomes to increase the ocular retention and action of brimonidine tartrate [49].

Age-related macular degeneration (AMD)

AMD is a major cause of visual loss in developed countries. It is more common among people over the age of fifty. [48]. AMD AMD causes approximately 8.7% of all blindness worldwide [49]. Nearly 196 million people afflicted from AMD in 2020, and the figure is anticipated to rise to 288 million by 2040 [50]. It is a multifactorial degenerative condition that affects the posterior portion of the eye. Aging, smoking, poor eating habits, high blood pressure, and immobility are all risk factors. There is currently no cure for AMD, however its progression can be slowed with appropriate treatments [51]. AMD is classified as either dry (atrophic or non-oxidative) or wet (neovascular or emulative). The major feature of AMD is irregular angiogenesis (the formation of new blood vessels) in the retinal epithelium, which causes drusen (yellow deposits under the retina), atrophy, and separation of Bruch's membrane [52]. Many cellular growth factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), and epithelial growth factor (EGF), are enhanced during angiogenesis as a result of anomalies in the respective metabolic processes. Juxtascleral injections of anecortave cortisone have been shown to have a 6-month release in the choroid and retina [53]. Furthermore, an intravitreal injection of a biodegradable Rho kinase and protein kinase C inhibitor for diabetic macular edema and neovascular age-related macular degeneration resulted in extended release for around 6 months [53].

Conjunctive

Conjunctivitis is typically the most common eye complaint. It is essentially an inflammation of the conjunctival tissue. It affects all ages, races, and genders [54]. It can be characterized as either infectious or non-infectious depending on the cause.Microbial infection causes infectious conjunctivitis, whereas allergens and irritants cause noninfectious conjunctivitis [55]. Conjunctivitis symptoms include red eyes, irritation, tears, and increased eye secretions. The prevalence of allergic conjunctivitis is about 40% of the global population [55]. Treatments for conjunctivitis include topical administration of antibiotic (infectious) or anti- inflammatory drugs (non-infectious).

Diabetic Retinopathy (DR)

Diabetes retinopathy is a vascular condition associated with both kinds of diabetes mellitus. After 20 years of diabetes, around 60% of type II patients and 100% of type I patients have some degree of retinopathy. Oxidative damage and inflammation caused by hyperglycemic conditions lead to the development of DR. It ranks as the third leading cause of blindness in the United States. After cataract and corneal blindness, the first and second causes of blindness. It is preventable if detected and treated early, along with adequate blood glucose and blood pressure management [65]. There are two types: proliferative and non-proliferative, and both cause progressive retinal injury. Nowadays, diabetic retinopathy is treated with laser photocoagulation, vitrectomy, and pharmaceutical agents.

Laser photocoagulation works by shutting leaky blood vessels, perhaps avoiding blindness, but leaves a laser scar. Vitrectomy is a surgical treatment that removes vitreous gel and blood from leaking capillaries in the back of the eye, however it only gives temporary comfort and does not prevent additional blood loss [66]. Intravitreous corticosteroid injections are one type of pharmacological treatment for macula edema. Additionally, a sustained release corticosteroid implant that disrupts inflammatory pathways. Modern therapy with anti-VEGF drugs (Ranibizumab and Aflibercept) inhibits VEGF expression, hence reducing blood leakage and edema [66].

Retinoblastoma

Retinoblastoma is a malignant tumor of the retina that most commonly affects children under the age of five. Untreated retinoblastoma causes blindness and eventually death (99%). It occurs in approximately one out of every 20,000 live births [56]. It occurs at an equal rate in both genders. It is caused by a mutation in the tumor suppressor gene RB1, which encodes for the retinoblastoma protein. It may be unilateral (60%) or bilateral (40%) [56]. Retinoblastoma treatment options include radiotherapy, cryotherapy, systemic chemotherapy, and surgery.

According to recent research, the formation of antigenic blood vessels and the production of compensatory proangiogenic factors are critical stages in the treatment of retinoblastoma [57].

Keratitis

Fungal Fungal keratitis develops only in traumatic corneas, as healthy corneas do not allow for fungal infection. It is caused by fungi such as Candida albicans, Candida glabrata, Candida tropicalis, Candida krusei, and Candida parapsilosis [58]. Fungal keratitis accounts for 40% of all infectious keratitis in underdeveloped third-world nations [59]. Trauma, contact lenses, past corneal surgery, and topical corticosteroids are examples of ocular risk factors, whereas systemic risk factors include diabetes, HIV positive, and leprosy. Fungal keratitis causes decreased wound healing, corneal ulceration, and stromal inflammatory infiltration. Corneal irritation may change miRNA expression[60].Fungal keratitis is treated with antifungal medications used orally or topically. When medications fail, a corneal surgical technique may be required. In certain cases, eyesight may not be recovered even after surgery. Many studies discuss the therapy of fungal keratitis. Younes et al. created topical Sertaconazole nitrate-loaded cubosomes and mixed micelles with increased safety and antifungal efficacy [60,61,62,63,64]. Figure 2 depicts several eye disorders [59]. Various ocular disorders affecting both parts of the eye [59]

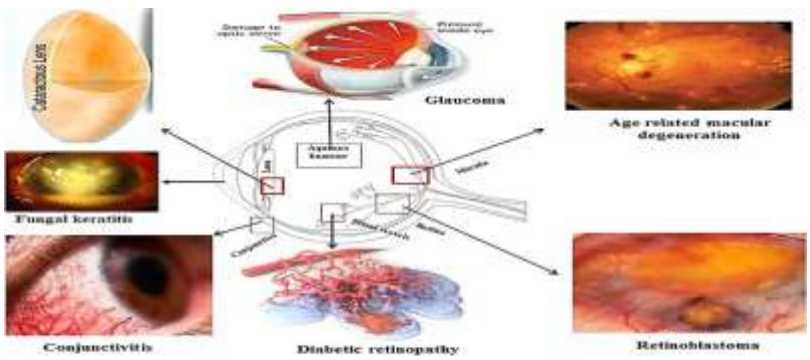

Fig 2 Diseases Of Eye

DISADVANTAGES

Disadvantages of Ophthalmic Drug Delivery Systems The main disadvantages of ophthalmic drug delivery systems are as follows: Drug solution has a short contact period with the eye surface. Poor bioavailability.occasioInstability of dissolved medicines.Preservatives are used in the installation and removal of dosage forms [12]. Ocular diseases can occur when sleeping or scratching one's eyes.

TREATMENT

Drug therapy, laser therapy, and surgical procedures are also used to reduce IOP. Certain parameters, such as IOP levels, illness stage and progression, treatment approaches used, and so on, influence the decision on the best therapy for the disease. Along with all of these considerations, satisfaction with the therapy delivered and patient compliance serve as the foundation for selecting the appropriate treatment. The conventional therapy depends primarily on topical medicine administration as eye drops or ointments.

CONCLUSION

The development of ocular drug delivery systems is critical for overcoming the limits of traditional medicines, such as eye drops and oral drugs. These old approaches frequently have low bioavailability, limited drug penetration, and require doses. Recent advances in ocular drug delivery technology, including nanocarriers, liposomes, microneedles, and injectable implants, have dramatically enhanced medication absorption, targeting, and controlled release within the eye. The goal of improving these systems is not only to enhance therapy outcomes for common ocular disorders such as glaucoma, macular degeneration, and dry eye disease, but also to reduce side effects and increase patient compliance. Biodegradable materials and sustained-release formulations are paving the way for more effective, non-invasive, and long- lasting therapies, reducing the need for frequent visits or repeated dosages.However, there are still hurdles to fully optimizing these systems, notably in terms of obtaining constant and effective medication distribution to diverse areas of the eye, overcoming ocular obstacles, and guaranteeing formulation stability over time. Continued research and development are required to solve these issues and improve ocular medication delivery techniques.

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