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INNOVATIVE APPROACHES OF OCULAR DRUG FORMULATION & DELIVERY

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ABSTRACT
Ocular drug delivery has made significant progress not just for fast developing gene therapy items but also for pharmaceutical chemicals such steroids, non-steroidal anti-inflammatory medications, immune modulators, antibiotics, and so on. While the main considerations for achieving adequate treatment outcomes for conventional non-gene therapy drugs are appropriate surgical techniques and release systems, the scope of "drug delivery" for gene therapy drugs is further expanded to include vector selection, vector engineering, and transgene construct optimization. Because it has so many benefits, the eye is an especially good organ to target with gene therapy. We will examine three key areas of ocular drug delivery in this review, pertaining to both conventional drugs and Aden-associated virus (AAV)-based gene therapy products: (1) the creation of AAV vector systems for ocular gene therapy, (2) novel drug carriers, and (3) the evolution of administration routes.

KEYWORDS: *Novel drug delivery system, approaches, conventional topical formulations, biotechnology.*

INTRODUCTION

The ocular globe is a unique organic structure with remarkable physiological, histological, and anatomical characteristics. Generally speaking, there are two main segments of the ocular globe: the anterior and posterior regions. The anterior portion of the eye comprises the choroid, neural retina, optic nerve, retinal pigment epithelium, sclera, and vitreous humor. The posterior portion occupies the remaining second-third of the eye and is composed of the aqueous humor, conjunctiva, cornea, iris, a ciliary body, and a lens [1-3]. Numerous illnesses can be identified based on the area of the eye that was evoked. A variety of conditions might be referred to as cataracts, anterior uveitis, or conjunctivitis for the anterior portion of the eye. Other conditions including diabetic retinopathy and age-related macular degeneration impact the posterior region of the eye. As a result, treating eye disorders is difficult since it requires creating medications that are tailored to address various issues relating to obstacles found in the structure of the eye [4-6].

In the last ten years, new medication delivery strategies have been developed to treat debilitating eye illnesses by targeting particular ocular tissues. Of eye disorders, the posterior region represents the source in 55% of cases [7]. The most common causes of vision impairment are retinal diseases, which include retinitis pigmentosa (RP), endophthalmitis, viral retinitis, proliferative vitreoretinopathy (PVR), age-related macular degeneration (AMD), diabetic retinopathy (DR), diabetic macular edema (DME), and inherited retinal diseases (Birds) [8,9]. The presence of dynamic barriers, such as conjunctival and choroidal blood flow, tear turnover, and lymphatic clearance, as well as static barriers, which are different layers of the cornea, sclera, retina, blood–aqueous (BAD) and blood–retinal barriers (BRB), pose a challenge to treating these retinal diseases and delivering drugs to specific ocular tissues. In recent years, there has been a significant growth in the field of research on ocular "drug delivery," which encompasses several novel approaches to target a retinal tissue and overcome ocular obstacles. Certain medication properties, target sites, and disease types can all affect how a medicine is delivered [10]. Derivatizing active pharmaceutical constituents (API) and enhancing their optical bioavailability using a conflation as a carrier system is another innovative strategy. This tactic might lessen eye vexation and enhance API's goods. Shen et al. (25) tried to increase the flurbiprofen's conflation biocompatibility in order to test this proposition. Flurbiprofen axetil, an outgrowth of flurbiprofen, was prepared as a conflation in this study using castor oil painting and tween- 80(30). Four distinct mixes were made and named F1, F2, F3, and F4 consequently. They had variable rates of castor oil painting (0.1 weight percent to 2.5 weight percent) and tween 80(0.08 weight percent to 4 weight percent). manly New Zealand albino rabbits were used in in vivo trials using topical drop instillation. Pharmacokinetic analyses of waterless humor revealed F2 conflation (castor oil painting) [11].

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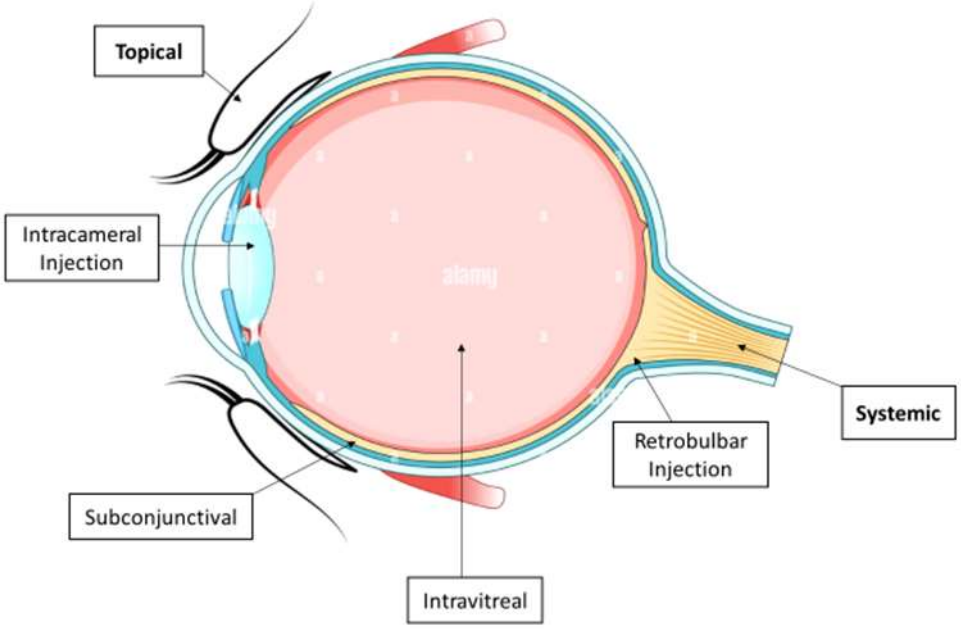
Fig no.1 Anatomy of the Eye



In this mini-review, we try to concentrate on and highlight effective methods that have been documented in the recent literature and are based on novel approaches to get through the physiological and anatomical barriers of the vitreoretinal structures. We also discuss the difficulties in identifying relevant and appropriate therapies for safely and effectively administering therapeutic agents to retinal tissues [12].

Novel formulation approaches for Ocular Delivery of Proteins and Peptides

Biodegradable Polymeric Micro Particles/Microspheres: Proteins, peptides, and tiny molecules are typically delivered to the eyes for a week or more using microparticles or microspheres. When the biocompatible polymers that make up the microspheres break down, they produce monomers and other harmless byproducts that are eventually removed safely from the eye and the circulation. The most often utilized polymers are poly (lactic-co-glycolic acid) (LPGA), which has excellent encapsulation efficiency, sustained release, biocompatibility, and the capacity to break down into toxicological acceptable compounds that are removed from ocular tissues [13]. PLGA microspheres produced significant vancomycin concentrations (0.81 mg/ml) in the rabbit aqueous humor 180 minutes after topical application, according to Gavini and colleagues [14].

Biodegradable Polymeric Nanoparticles/Ionospheres: Liposomes, dendrites, micelles, and nanowebers are examples of nanoparticles that are actively employed as carriers for the targeted distribution of proteins, peptides, and small molecules. Nanoparticles are often made of biodegradable polymers and lipids. Similar to microparticles, drug release from nanoparticles is influenced by molecular mass, the pace at which polymers degrade, and other physicochemical parameters. There are several ways to give nanoparticles, such as topical, particular, suprachoroidal, and intravitreal. However, because polymeric particles scatter light, intravitreal injection frequently results in vitreous clouding. Due to their larger molecular mass, nanoparticles are more likely to cause vitreous clouding than microparticles, which tend to sink to the lower portion of the virtual cavity. Additionally, reduced stability and potential loss of bioactivity of biopharmaceuticals [15]. By administering LPPR peptide, which binds exclusively to the VEGF receptor, NRP-1, as nanofibers, a team of researchers and B. Senturk (2016) have recently shown a considerable suppression of endothelial cell proliferation and migration as well as abnormal capillary formation. Additionally, on day 14, a subconjunctival injection of LPPR-PA nanofiber significantly reduced corneal neovascularization in a rat model (81.3%) in contrast to bevacizumab (51.2%), suggesting that it is a useful treatment for illnesses associated to angiogenesis [16].

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Route	Benefits	Challenges	Use in the management of illnesses
Systemic/Oral	patient's complaint and the non-invasive administration method.	High dosage results in toxicity, BAB, BRD, and BA<2%	PU, CMV retinitis, scleritis, and episcleritis
Topical	High patient compliance, noninvasive, and self-administrable	Increased tera dilution and turnover rate, efflux pumps, corneal barriers, and BA, 5%	Blepharitis, conjunctivitis, uveitis, and keratitis
Intravitreal	Direct administration to the retina and vitreous maintains medication levels and avoids BRB	Patient noncompliance, endophthalmitis, cataract, and retinal detachment hemorrhage	AMD, CMV retinitis, PU, BRVO, and CRVO.
Intracameral	Increase the dosage levels of the medicine. decreases corneal and systemic adverse effects, and does away with the need for topical drops in the anterior chamber.	Both toxic endothelial cell destruction syndrome (TECDS) and toxic anterior segment syndrome (TASS)	Anesthesia, inflammation, pupil dilatation, and endophthalmites prevention.

Table (1). Summary of Route of Administration, Benefits, and Challenges in Ocular Delivery.

OCULAR ROUTES FOR DRUG DELIVERY SYSTEM

Conventional Topical Formulations

Eye Drops: The eye drop formulations have several characteristics that make them a commonly prescribed form. They are non-invasive, safe, act right away when applied, have a high patient compliance rate, and are appropriate for the product. When eye drops are applied, the supported drug is absorbed through a pulsatile mechanism that happens after the drops are applied topically. This is followed by a rapid decline in drug concentration that roughly corresponds to a first order elimination process. By slightly disrupting the integrity of the stated tissue, the use of these chemicals is intended to increase the uptake by ocular tissues. Preservatives, cheating agents, bile salts, and surfactant molecules are just a few of the many substances that are said to have comparable qualities in this context and are used as permeation enhancers. The purpose of using these enhancers in an ocular solution is to significantly raise the compounds' bioavailability [17,18]. Studies conducted by Hornof et al. in 2002 revealed that polycarbophil-cysteine, a chemical used as an excipient, did not alter the tissue structure of the eye and was deemed safe enough to be employed in formulations for ocular route distribution [19].

Emulsions: A aphasic system made up of two immiscible phases is called an emulsion. Ophthalmic emulsions have the potential to increase the bioavailability and solubility of medications that were previously water-insoluble. Water in oil and oil in water (o/w) are two broad categories into which pharmaceutical emulsions can be divided. The o/w system, which comprises of a hydrophobic medication combined with oil and distributed in an aqueous media, is commonly used in ophthalmic formulations. Because of its exterior aqueous phase, an o/w emulsion has reduced ocular irritation and greater ocular tolerance than a water-in-oil emulsion [20,21]. Ophthalmic eye drops that are commercially available include Duel (Alton), Parasite (Akron), Refresh Endure (Allergan), and Restasis (Allergan) [22]. To lessen the impact on intraocular pressure in rabbits, Muchtar and associates created a submicron emulsion as an ocular carrier for delta-8-tetrahydrocannabinol because of the drug's poor solubility [23].

Suspension: Finely split insoluble drug particles suspended in an aqueous media with dispersing and solubilizing agents make up ocular suspensions. Drug particles are suspended in the precorneal cavity, lengthening the drug's duration of contact. The length of time needed for the drug molecules to absorb into a corneal tissue is determined by the medication's particle size, which ultimately affects the drug's bioavailability. For bacterial eye infections, Alcon, Inc.'s TobraDex ST suspension (0.3%) tobramycin and (0.05%) dexamethasone is recommended (Spiral.,2008) [24].

Ointments: Ointments fall under the category of topical formulations and are also utilized as drug delivery carriers. Because the composition of these systems is based on a mixture of solid and semisolid hydrocarbon molecules, their typical melting points are close to the ocular temperature of 34◦C. However, which hydrocarbon should we select for a particular use? This detail makes a big difference in a formulation's biocompatibility because the substance can't be rejected by the body to stop more organic side effects or even to ensure that the formulation's goals of increasing the drug's bioavailability and sustaining the delivery process are carried

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out [25,26]. In 2003, Fukuda and associates aimed to investigate the dynamics of vancomycin hydrochloride produced as ophthalmic ointments in the rabbit eye's internal environment, connecting this phenomenon to the MRSA extraocular infection. The researchers employed a control group of rabbits and an experimental group infected with Bacillus subtilis to ascertain the lowest concentration that prevents the growth of MRSA in bacterial infections. The latter group was created by injecting a Bacillus subtilis solution intracorneally into the parenchyma's central region. The previous parameter had a range of 1.56 µg/g [27].

Biotechnological Inspired Drug Technology:

Domicile: Colloidal drug delivery vehicles called Nano micelles self-assemble in aqueous solutions in an instant. Because of their hydrophilic surface, nanomicelles are perfect for delivering hydrophobic medications to the eye because they extend the duration of drug retention. Surfactant and polymeric nanomicelles are two broad categories for nanomicelles. Generally speaking, surfactant nanomicelle aggregates are weak and prone to physical instability upon dilution, whereas polymeric micelles are known to be more stable [28]. Panda et al. (2013) revealed that dipeptidic phenylalanine-alpha and beta-hydroxyphenilalalnine nanotubes were used as carriers to successfully administer pazopanib intraocularly. Using an intravitreal injection, the preparation produced a 15-day sustained pazopanib concentration in the vitreous, retina, RPE, and choroid [29].

Dendrimers: Synthetic polymers are arranged in branched and layered structures called dendrites, which have potential applications as nanocarriers in various biomedical fields. Compared to linear polymers, dendrites have entirely different properties due to their distinct branched topologies. G-1, G-2, and G-3 dendrites can be classified according to their size, number of branches, and end groups at the terminal. Any kind of polymer can make up a dendrites, and this will affect the material's solubility, stability, and biological activity. Polyamidoamines, polyamines, polyamides (polypeptides), poly (ARL ethers), polyesters, carbohydrates, and DNA are some of the frequently used dendrites. Of these, dendrites based on polyamidoamine (PA MAM) are the most widely used and commercially accessible. The multiagent characteristic of dendrites, in contrast to linear polymers, offers a way to achieve high concentrations of payloads, such as small molecules and biopharmaceuticals [30]. In order to investigate the impact of drug-release kinetics following modifications to the PAMAM dendrimer's size, molecular weight, carboxylate and hydroxyl surface groups, and total amount of amines, Vandamme and Brobeck (2005) trapped tropicamide and pilocarpine nitrate within the dendrimer. Results obtained in vivo in albino rabbits from New Zealand showed that dendrimers functionalized with carboxylic and hydroxyl functional groups have longer drug residence times [31].

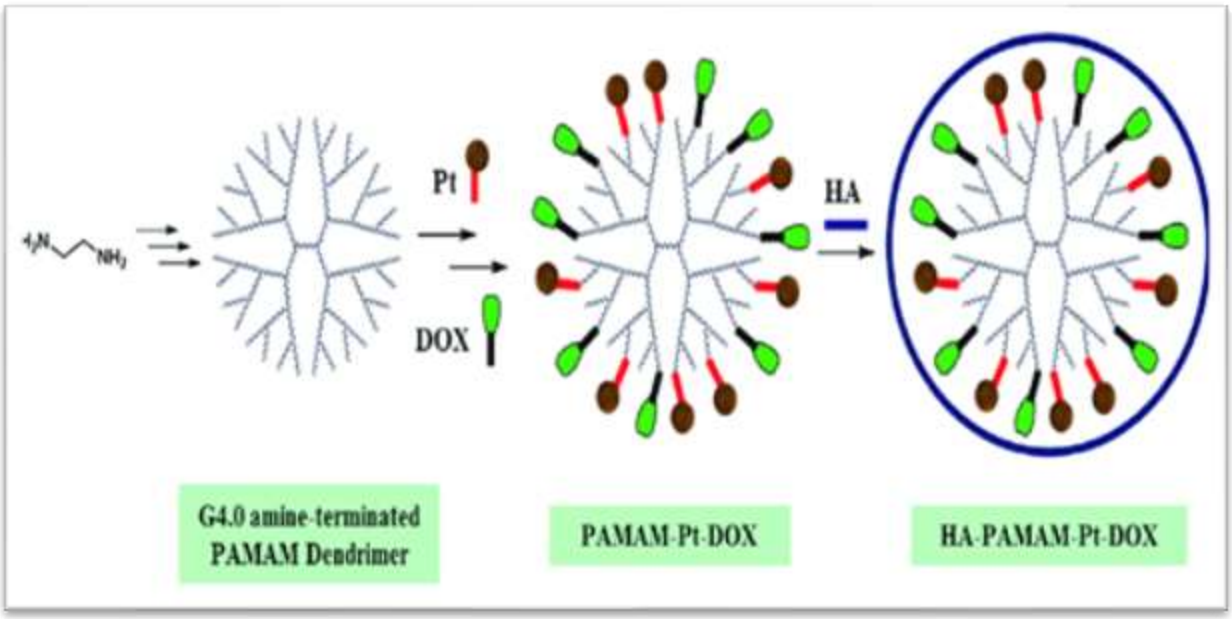

Fig no.2 Diagram showing how PAMAM dendrimers are made, with two medications (Pt and DOX) covalently bonded to the amine groups of the dendrimer's outer generation. The dendrimers' biocompatibility is enhanced by the addition of an external layer of HA, which is synchronized through electrostatic interactions with PAMAM [32]

Nano wafers: Nano wafers are small, transparent, circular discs made of different polymers, such as carboxymethyl cellulose (CMC), poly (vinyl alcohol) (PVA), polyvinylpyrrolidone (PVP), and (hydroxypropyl)methyl cellulose (HPMC). Unlike a topical eye drops, these can endure continuous blinking without becoming dislodged when applied with the fingertip on the ocular surface. Nanowebers are made up of arrays of drug-loaded nanoreservoirs that release the cargo over a few hours to several days under strict supervision. The polymers and the loaded medicine work in concert to produce a gradual release of the drug, which lengthens its residence time in the ocular tissues and improves its absorption. Crucially, the nanoweber disappears and dissolves at the conclusion

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of the prescribed medication release period, leaving the ocular surfaces free of polymers [33]. A dexamethasone-loaded nanowafer (Dex-NW) was created by Coursey et.al in 2015 and Bianetal in 2016 to treat dry eye condition. The carboxymethyl cellulose polymer was used to create the nanowafer, which was made up of many nano drug reservoirs that were loaded with dexamethasone. A mouse model of dry eye illness was used to investigate Dex-NW's in vivo effectiveness. For five days, Dex-NW was given as a once-daily therapy on alternate days [34].

Liposomes: Liposomes are spherical vesicles that self-assemble from cationic lipids. They have an aqueous core that can include hydrophilic particles, including tiny molecules, biologics, and DNA. Via either endocytosis or phagocytosis, liposomes enter the cell. As the endosome changes into a lysosome through the clathrin-mediated endoscopic pathway, endosome constituents are typically broken down. However, by selectively becoming cationic at a low pH (such as inside lysosomes), the usage of pH-dependent cationic lipids can aid escape from endosomes following endocytosis. In order to increase the vesicles' effectiveness of release, triggers like light, pH, heat, and ultrasonic waves have been employed recently to break the lipid bilayer of the vesicles [35]. Products like Tears Again® and Visudyne® (2017, 2018) are excellent examples of these formulations that are now on the market for the treatment of eye conditions. In contrast to isotonic saline solutions and triglyceride gels, the first product, a spray composed of phospholipid-based liposomes, has effectively shown clinically significant benefits for treating dry eye diseases [36].

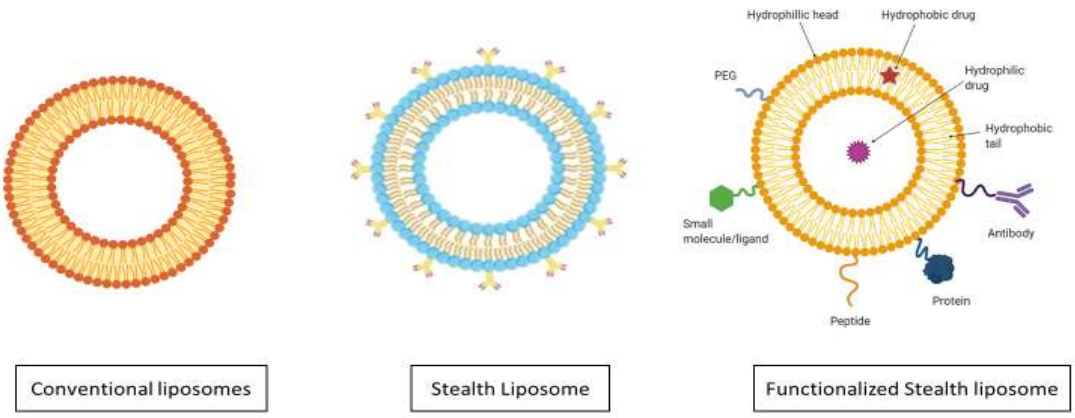

Fig no.4 Phospholipids in an aqueous solution from a liposome [37].

CONCLUSION

For many years, ophthalmologists have faced the difficulty of effectively delivering drugs into the eyes. The immunological privilege, accessibility, and compartmentalization of the eye still make it a great prospect for gene therapy research, despite the challenges. The field of drug delivery has increased with the research of viral and non-viral-based vector administration, spurred by the rise in the development and availability of gene therapy products. While there are benefits and drawbacks to both viral and non-viral vectors, Aden-associated viruses (AAV) are currently the subject of much research in the field of ocular medication administration. ATVs are effective at transducing RPE cells and photoreceptors (PRs), and future research should aim to reduce immunogenicity while increasing capacity. Ocular vector technology and carrier system technology have advanced [38].

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