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Intraocular Drug Delivery Systems for Diabetic Retinopathy

Harish R Changediya*[1], Prof. Randhawan B.B [2], Pruthviraj N Awate[3],
Naman K Gandhi[4], Komal A Dhakane[5]

Students[1,3,4,5] Assi. Professor[2]
Arihant College of Pharmacy, Kedgaon, Ahilyanagar – 414005.

Abstract

Novel drug delivery systems constitute a substantial advancement in pharmaceutical research and development, designed to optimize the efficacy of therapeutic agents via innovative delivery modalities. The primary purpose of these systems is the targeted delivery of therapeutic compounds to specific anatomical sites, such as tumors and affected tissues, with the dual objective of attenuating adverse effects and toxicity associated with the drugs while simultaneouslyamplifying therapeutic efficacy.

New ways of delivering drugs are being studied to make them work better. These new methods aim to get the medicine to the exact place where it needs to go, like tumors or sick tissues. This helps to reduce side effects and make the medicine stronger.

Numerous innovative drug delivery strategies have been investigated for their potential application in targeted ocular drug delivery. A variety of novel carriers, including implants, hydrogels, metal nanoparticles, nanoliposomes, micelles, solidlipid nanoparticles, emulsions, and biodegradable nanoparticles, have been employed to facilitate the controlled release of pharmaceutical agents to the retina and vitreous. These carriers offer distinct advantages such as enhanced intraocular drug delivery, precise control over drug release kinetics, increased stability, and superior entrapment efficiency. This comprehensive review aims to elucidate the current advancements in carriers and their contemporary applications in the treatment of diabetic retinopathy.

Keywords

Implant, Intraocular, Diabetes, Hydrogels, Nanocarriers, Retinopathy.

Introduction

Advanced drug delivery systems constitute a cutting-edge scientific field that has spurred progress in numerous scientific disciplines, notably in the pharmaceutical industry. These systems have successfully overcome the limitations inherent in traditional drug delivery methods, generating significant enthusiasm among pharmaceutical investigators who are pursuing innovative approaches for precise drug targeting.1-3 The primary goal of this paradigm is to deliver therapeutic agents in adequate amounts to specific locations, such as tumors and affected tissues, while concurrently minimizing unwanted adverse effects and toxicity, thereby augmenting therapeutic effectiveness.

Diabetes mellitus, a condition characterized by insufficient insulin production or resistance, resulting in elevated blood sugar levels, is a major global health concern. Diabetic retinopathy (DR), a microvascular complication, affects a significant portion of individuals with both type 1 and type 2 diabetes. DR is classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR, further divided into mild, moderate, and severe stages, is characterized by microaneurysms, hemorrhages, lipid deposits, cotton wool spots, intraretinal microvascular abnormalities, venous beading, and loopformation.

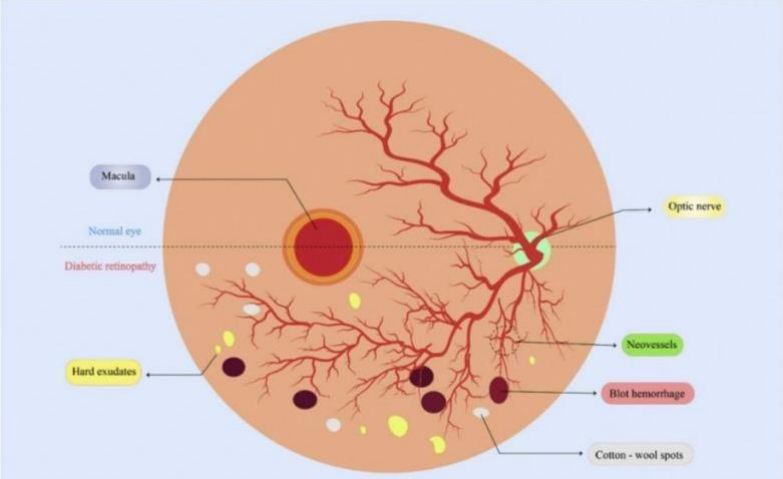

Fig 1: Schematic diagram of Diabetic Retinopathy

Non-proliferative diabetic retinopathy (NPDR) can advance to proliferative diabetic retinopathy (PDR), characterized by the development of new blood vessels in the retina and vitreous hemorrhage. This condition compromises the integrity of the blood-retinal barrier, resulting in increased vascular permeability, which can lead to diabetic macular edema (DME). Elevated vascular permeability further contributes to capillary occlusion, causing retinal ischemia and stimulating the production of vascular endothelial growth factor (VEGF). Recent studies have demonstrated the efficacy of VEGF inhibitors, such as pegaptanib sodium, ranibizumab, and bevacizumab, in suppressing ocular neovascularization, significantly reducing neovascular activity and vascular permeability in variousocular tissues.

Conventional drug formulations for the treatment of intraocular disorders often encounter significant challenges, including short half-lives, low solubility, and the needfor high doses to achieve therapeutic efficacy, aggregation, and susceptibility to degradation. The available repertoire of technologies for addressing intraocular diseases remains limited. While traditional delivery methods such as subconjunctival injection, intravitreal injection, and topical eye drops are utilized, numerous biological and physiological barriers present formidable obstacles that therapeutic payloads must overcome.

Within the realm of drug delivery and therapeutics, nanocarriers serve as specialized vehicles designed to transport drugs to precise anatomical targets within the body, encompassing sites affected by diabetic retinopathy. These nanocarriers possess the capability to encapsulate drugs within their structures, functioning as protective capsules that shield the drug from degradation, metabolism, or elimination, thereby prolonging circulation time and enhancing stability. A significant number of drugs utilized in the treatment of diabetic retinopathy exhibit poor solubility or limited bioavailability. Nanoparticles address this challenge by augmenting the solubility of hydrophobic drugs, resulting in improved drug absorption and distribution. Furthermore, nanoparticles offer protection against enzymatic degradation, leading to increased drug bioavailability and ensuring a more pronounced therapeutic effect. Notable advantages of nanocarriers include targeted drug delivery, controlled and sustained drug release, enhanced drug stability and protection, prolonged drug circulation, and improved solubility and bioavailability, ultimately facilitating enhanced drug absorption anddistribution.

Despite their potential benefits, nanocarriers are not without limitations. These include complex formulation and manufacturing processes, potential adverse immune reactions or toxicities associated with the nanoparticle materials, difficulties in scaling up production for widespread clinical use, and varying clearance rates from the body depending on the nanoparticle's properties and size. This review provides a thorough examination of innovative intraocular drug delivery systems for the treatment of diabetic retinopathy, a topic that has not been

extensively covered in previous reviews.

Tonicity, which is the concentration of solutes in a solution, is a crucial consideration in drug delivery systems for the treatment of diabetic retinopathy. To preserve the structural integrity of ocular tissues, the tonicity must be maintained within a tolerable range of 0.5% to 2% NaCl solution. Commonly used tonicity modifiers include 1.9% boric acid and sodium acid phosphate buffer.

Table 1: Different types of drugs that are currently available in the market for diabetic retinopathy

Drug	Dosage form	Mechanism	Drug delivery system
Triamcinolone acetonide	Injection suspension	Anti-inflammatoryeffect	Intravitreal
Dexamethasone	Implant	Anti-inflammatory effect	Extended-release implant
Bevacizumab	Injection suspension	VEGF inhibitors	Intravitreal
Ranibizumab	Injection suspension	VEGF inhibitors	Intravitreal
Hyaluronidase	Saline	Clearance of vitreous haemorrhage	Intravitreal

Anatomy of the Human Eye:-

The human eye is a complex organ designed to capture light and convert it intoelectrical signals that are transmitted to the brain, where they are interpreted as vision. It consists of several interconnected structures, each playing a crucial rolein the process of sight.

External Structures -

- Cornea: This transparent dome-shaped structure covers the front of the eye.

It acts as a natural lens, focusing light rays onto the retina. The cornea isresponsible for the refractive power of the eyes.

- Sclera: The sclera is the white outer layer of the eye. It protects the internalstructures and maintains the shape of the eye.
- Iris: It is the colored part of the eye. It contains a circular muscle that

controls the size of the pupil. The pupil is a black circular opening in the center of the iris which regulates the amount of light entering the eye.

- Conjunctiva: This thin, clear membrane covers the sclera and the innersurface of the eyelids. It protects the eye from injury and infection.

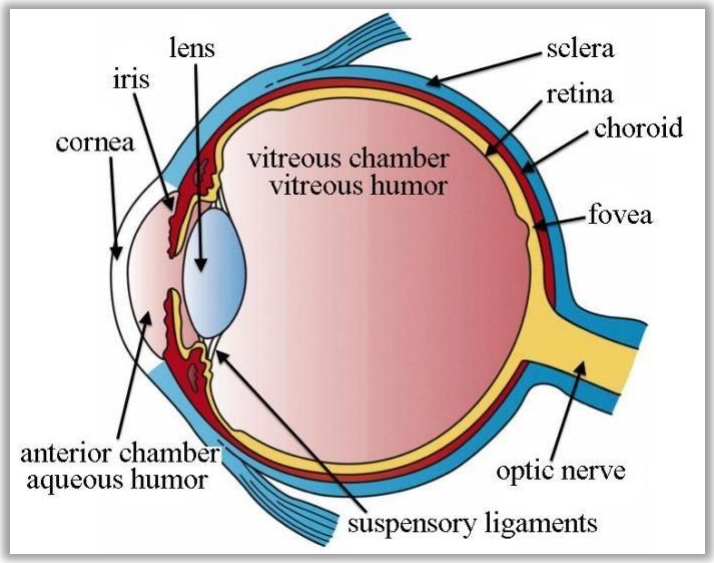

Fig 2: Anatomy of the Human Eye

Internal Structures -

- Anterior Chamber: This space between the cornea and the iris is filled witha clear fluid called aqueous humor. Aqueous humor nourishes the cornea and lens and helps maintain the eye's pressure.
- Lens: The lens is a transparent part of the eye located behind the pupil. It acts as a secondary lens, focusing light rays onto the retina. The lens can change its shape to accommodate objects at different distances.
- Posterior Chamber: This space between the lens and the retina is filled with vitreous humor. Vitreous humor is a jelly-like substance that helps maintainthe eye's shape and supports the retina.
- Retina: The retina is like a screen at the back of the eye that sees lightand turns it into messages for your brain. There are two kinds of specialcells on the retina: rods and cones. Rods help you see in the dark, while cones help you see colors.
- Optic Nerve: The optic nerve is a bundle of nerve fibers that carries the electrical signals from the retina to the brain. It exits the eye through theback of the sclera.

Accessory Structures -

- Eyelids: The eyelids protect the eye from injury and foreign objects. Theyhelp to spread tears over the surface of the eye.
- Lacrimal Apparatus: The lacrimal apparatus produces tears, which moistenthe eye and help to remove debris. Tears are drained through a series of ducts into the nasal cavity.
- Extraocular Muscles: Six extraocular muscles attach to the sclera and control the movement of the eye. These muscles allow the eye to move inall directions.

The anatomy of the human eye is a marvel of engineering. Each part of the eyeworks in harmony to produce clear and accurate vision. Understanding the anatomy of the eye is important for diagnosing and treating eye disorders.

Intraocular Delivery for Diabetes Retinopathy:-

Hydrogels –

The application of hydrogels in the biomedical field has undergone significant development since the 1960s when hydrogels were initially used in contact lenses. Hydrogels are a special type of polymeric material characterized by their exceptional ability to absorb and retain large amounts of water within their complex three-dimensional structure. This unique property has enabled the controlled delivery of biologically active substances through regulated drug release mechanisms.

Extensive research has been conducted to develop innovative hydrogel structures and chemically cross-linked networks. Among these, polyhydroxy ethyl methacrylate (PHEMA) has proven to be the most promising polymer. In the 1970s, a growing interest in stimuli-responsive hydrogels developed. These hydrogels possess the unique ability to undergo physical or chemical transformations in response to specific environmental cues, such as changes in pH, temperature, light exposure, and pressure. Thermosensitive hydrogels constitute one of themost thoroughly investigated and widely employed types of stimuli-responsive hydrogels. Thermosensitive hydrogels can be classified into lower critical solution temperature (LCST) and upper critical solution temperature (UCST) hydrogels. In LCST hydrogels, the system exists as a liquid below the critical temperature, while in UCST hydrogels, the system assumes a gel state below the critical temperature and transitionsto a liquid state above it.

To prevent adverse immune reactions, the polymers used in hydrogel formulations must exhibit specific essential properties, including biodegradability, biocompatibility, and non-cytotoxicity. Hydrogels are composed of cross-linked polymers capable of absorbing water, leading to swelling and the maintenance of a hydrated structure. Another critical

The category of stimuli-responsive hydrogels is the pH-responsive hydrogel. These systems possess ionizable pendant groups within the polymer backbone, enabling them to respond to changes in pH levels. Variations in environmental pH result in the ionization of these pendant groups, generating electrostatic repulsive forces between ionized groups and consequently inducing swelling. pH-responsive hydrogels can be furthercategorized into anionic and cationic hydrogels. Anionic hydrogels contain carboxylic or sulfonic acid groups that undergo deprotonation and swell as the pH increases, while cationic hydrogels incorporate amine groups that protonate and swell as the pH decreases. In the context of temperature-sensitive hydrogels, fluctuations in temperature induce either swelling or de-swelling within the system, which can be utilized for drug delivery applications. The interplay between hydrophobic and hydrophilic regions within the hydrogel structure playsa crucial role in this physical response.

Shear-thinning hydrogels represent a distinct avenue within hydrogel development. Characterized by a reduction in viscosity under elevated shear stress, these materials exhibit a remarkable ability to transition from a solid-like state to a liquid-like state when subjected to mechanicalforce. This property, known as shear-thinning, facilitates facile loading into syringes and extrusion, followed by a rapid return to the original state upon cessation of mechanical stress, a phenomenon termed self-healing. The inherent benefits of shear-thinning hydrogels extend to the preservation of material integrity post-injection and the facilitation of in situ gelation processes, while simultaneously mitigating the risk of embolization into the systemic circulation.

It is noteworthy that physical cross-linking often compromises self-healing capabilities and lacks the mechanical resilience observed in insitu cross-linking covalent systems. Consequently, researchers have investigated alternative cross-linking strategies to augment the stability of mechanically deployed hydrogels post-injection. Shear-thinning hydrogels have been extensively studied across diverse biomedical applications, including drug delivery, tissue regeneration, and intraoculardrug administration.

The development of In situ injectable hydrogels offers a promising approach to ocular drug delivery, enabling precise control over drug release kinetics and degradation profiles. Preclinical studies have demonstrated the efficacy of hydrogel-based tissue adhesives, vitreous replacements, and intravitreal drug delivery systems. Intraocular hydrogel administration has the potential to significantly advance the field, leading to refined hydrogel technologies and potential clinical approval. Concomitant development of injection systems capable of safely and efficiently handling in situ forming hydrogels is essential for their successful clinical application. Table 2 and Figure 3 summarize thevarious types of hydrogels discussed in this context.

Table 2: Hydrogels used in retinopathy drug delivery

Hydrogel type	Stimuli-responsive polymer	Drug	Property	Therapeutic outcome
Temperature-sensitive hydrogels	PLGA-PEG-PLGA	Bevacizumab	sol-to-gel transition with change in temperature	showed the beneficial effects of hydrogels in prolonging the residency of drugs in the vitreous and increasing the drug's efficiency
	Poloxamer	Bevacizumab		
	ESHU	Bevacizumab		
	PLGA-PEG-PLGA	Dexamethasone acetate		
	PEG-PCL-PEG	Bevacizumab		
	PLGA-PEG-PLGA	Insulin		
	Chitosan	Fluconazole		
Shear sensitive hydrogels	Tragacanthic acid		Gel-to-sol transition with shear	-

Nanocarriers:-

Nanocarriers represent a significant advancement in drug delivery, providing adaptable solutions that can be constructed from a diverse range of inorganic and organic materials, encompassing biodegradable and non-degradable polymers, metals, lipids, and self-assembling amphiphilic molecules.

This innovative development addresses a persistent challenge in pharmacotherapy, wherein bioactive substances, while demonstrating therapeutic advantages, frequently exhibit adverse side effects that constrain their clinical application.

A notable instance of non-selective targeting is chemotherapy, utilized in cancer therapy, where drugs indiscriminately affect both malignant and benign cells, leading to adverse consequences. The scientific community has striven to develop methods for selectively delivering bioactive substances to particular anatomical regions within the organism to optimize therapeutic efficacy while mitigating thesedeleterious outcomes. This pursuit has catalyzed extensive research into nanocarriers for precise drug and gene delivery, augmenting therapeutic effectiveness while reducing side effects. These nanoparticulate delivery systems offer several significant advantages, including elevated concentration ratios between the intended target and non-target sites, prolonged drug retention at the desired location, and enhanced cellular absorption and intracellular stability.

Nanocarriers have emerged as a favored drug delivery system owing to their exceptional capacity to mitigate toxicity and augment therapeutic efficacy. These systems are distinguished by their submicron particle dimensions, characteristically below 500 nm, which culminate in a substantial surface area-to-volume ratio. This distinctive attribute exerts a profound influence on the properties and bioactivityof the encapsulated drugs.

Critical attributes of Nanocarriers include :

Prolonged circulation time in the bloodstream.

Precise delivery of drugs to the intended target sites.Reduction in the required drug dosage.
Controlled drug release.

A variety of nanocarriers have been developed, including microemulsions, Nano suspensions, liposomes, micelles, solid lipid nanoparticles (SLN), dendrimers, and hydrogels.

The properties of nanocarriers can be modified through alterations in their composition, shape, size, and surface characteristics. These modifications include PEGylation, functional group introduction, surface charge adjustment, andtargeting moiety incorporation. Table 3 provides a summary of the various nanocarrier types.

The use of nanocarriers offers several advantages, such as enhanced drug bioavailability, improved drug permeation to specific retinal areas, prolonged drugresidence time, non-invasive drug delivery, and enhanced ocular tolerability.

Table 3: Different types of Nanocarriers used for drug delivery

Nanocarrier type	Materials	Drug
Polymeric nanoparticles	Chitosan	Bevacizumab
	CNAC	Ranibizumab
	Polycaprolactone and Pluronic® F68	Triamcinolone acetonide
	PGS	Sunitinib
	Generation-4 hydroxyl polyamidoamine dendrimer	Triamcinolone acetonide
	PLGA	Dexamethasone acetate
	PLGA	bevacizumab
Nanoliposome	NLC	Triamcinolone
	DPPC (C40H80NO8P)	Bevacizumab
	egg phosphatidylcholine	Bevacizumab
Albumin nanoparticles	HSA	Bevacizumab
Gold nanoparticles	HAuCl4	Resveratrol
zincoxide nanoparticles	zinc acetate	Cyperus rotundus leaf extract
magnetic nanoparticles	iron oxide core and an organic shell exposing carboxylic groups	Octreotide
Silver nanoparticles	AgNO3	-
silicate nanoparticles	tetraethoxysilane and Cyclohexane	-

Intraocular implants:-

Ocular drug delivery implants have attracted considerable attention as a potentialsolution to overcome the inherent limitations of traditional eye therapies. These implants offer several advantages, including ease of administration, precise drug delivery to ocular tissues, and minimal interference with the normal functioning ofthe eye.

Intravitreal implants are a type of drug delivery system designed for either injection or surgical implantation into the vitreous humor, enabling sustained drugrelease to the posterior and intermediate regions of the eye.

Implants can be categorized into two primary types: passive and active. Passive implants can be further subdivided into biodegradable and non-biodegradable varieties. Biodegradable implants are typically constructed from materials such as polycaprolactone (PCL), polylactic acid (PLA), and polylactic-co-glycolic acid (PLGA). Conversely, non-biodegradable implants are often fabricated from materials such as silicones, polyurethanes, polydactylies, and polyethylene vinylacetate.

A significant application of Implants is the sustained release of steroids, which have demonstrated efficacy in mitigating inflammation and managing macular edema associated with diabetic retinopathy. These implants offer extended therapeutic benefits while reducing the risk of systemic side effects compared to systemic steroid administration. However, it is crucial to acknowledge potential drawbacks, including the risk of cataract formation, elevated intraocular pressure,implant dislocation or migration, and the necessity for rigorous monitoring.
Prolonged use may necessitate the management of steroid-related complications.

Active implants utilize two primary mechanisms to regulate drug release: osmotic pressure gradients and electromechanical drives.

To illustrate the advancement in ocular implants, one can cite the research conducted by Maulvi et al. They developed a novel ocular implant for timolol maleate ™ delivery by encapsulating ethyl cellulose nanoparticles within hydrogel rings. This multi-step process facilitated controlled drug administration for the treatment of glaucoma. Initially, TM-ethyl cellulose nanoparticles were synthesized using the double emulsion method. Subsequently, hydrogel implants were fabricated through free radical polymerization, employing HEMA and ethylene glycol dimethacrylate. Finally, TM-encapsulated ethyl cellulose nanoparticles were dispersed within the acrylate hydrogel.

New contact lenses with a special medicine inside have been tested and found to work better than regular eye drops. These lenses keep the medicine in your eye fora longer time, and more of the medicine stays in your body. This has made peopleinterested in making similar lenses for treating eye problems like retinopathy.

Limitations and complexities of intraocular drug delivery systems:-

Nanotechnology has shown great promise in the field of intraocular drug delivery, with nanocarriers, hydrogels, and implants emerging as potential solutions. While laboratory studies have demonstrated encouraging results, the practical application of these carriers is still hindered by various challenges. Nanoparticles, in particular, have shown less promising outcomes due to their inherent heterogeneity, which can lead to therapeutic instability. Additionally, concerns regarding immunological responses and toxicity must be carefully addressed. Overall, the use of

nanocarriers, hydrogels, and implants in intraocular formulations offers significantpotential, but further research is necessary to overcome the challenges encountered in experimental applications. With continued exploration and advancement, these carriers could revolutionize the treatment of diabetic retinopathy.

Beyond traditional drug delivery methods, researchers are actively developing innovative approaches for treating diabetic retinopathy (DR). These include sustained-release implants, which can deliver medication directly to the eye over an extended period, reducing the need for frequent injections and improving patient adherence. Additionally, researchers are exploring the benefits of
combining different treatment modalities to address the various aspects of DR. Ongoing clinical trials are evaluating the effectiveness of combining anti-VEGF therapy with other drugs, laser therapy, or surgery to enhance visual outcomes andslow disease progression.

Future research will focus on addressing the challenges associated with scaling up the production of these novel drug delivery systems to ensure efficient and cost-effective manufacturing. This includes developing scalable production processes, optimizing manufacturing technologies, and implementing rigorous quality controlmeasures.

As these new drug delivery systems evolve, it will be crucial to conduct a comprehensive evaluation of their cost-effectiveness, considering factors such as healthcare expenditure, patient outcomes, and resource utilization. This information will be valuable for healthcare decision-makers and stakeholders.

Long-term safety studies will be crucial in future research on new drug delivery systems for diabetic retinopathy (DR). These studies will closely monitor the long-term effects of these systems, including any potential side effects and safety concerns. Advances in nanotechnology, sustained-release medications, targeted drug delivery, and gene therapy are leading to exciting new treatments for DR. As these innovative approaches develop, collaboration between researchers, pharmaceutical companies, regulatory agencies, and healthcare providers is essential for developing, approving, and effectively using new drug deliverysystems for managing DR.

Methodology for literature research:-

The systematic exploration of relevant studies was done through comprehensive searches across Web of Science, Scopus, Google Scholar, and PubMed. This exhaustive investigation spanned from 1993 through the conclusion of 2022. Thesearch queries were centered on the following keywords: nanotechnology, DR, nanoparticles, hydrogels, intraocular implants, and drug delivery. These queries were executed without imposing any language or date restrictions. The articles I referred to had titles and summaries about nanoparticles, hydrogels, intraocular implants, and how they work with drug delivery.

Conclusion

Novel intraocular delivery systems offer the promise of overcoming the shortcomings of conventional anti-neovascular treatments and exploring novel therapeutic avenues. The development of effective therapies is imminent, facilitated by innovative devices that extend the duration of intravitreal drug administration, deliver corrective genes to ocular tissues, or eliminate the need for direct ocular injections. There is great expectation that the promising preclinical findings will soon translate into successful clinical trials that definitively establish the safety and efficacy of these systems in human patients.

The newly discovered antiangiogenic properties associated with specific intraocular delivery methods offer promising avenues for developing composite materials that synergistically combat neovascular eye diseases. Nanocarriers, hydrogels, and implants, fabricated from diverse materials with varying physicochemical characteristics, have been meticulously engineered. Additionally, significant efforts have been invested in refining the structural attributes of these delivery systems to enhance their intraocular delivery efficiency. This optimization involves manipulating their internal and external morphologies, improving their stability, and modulating their drug release kinetics. Furthermore, the incorporationof biologically responsive components into nanocarriers, hydrogels, and implants has enabled the customization of their responsiveness to various stimuli. This technological advancement has paved the way for highly specialized therapies characterized by precise site-specific drug release and improved therapeutic outcomes. In conclusion, the field of novel intraocular delivery holds immense potential to revolutionize ocular antiangiogenic therapy.

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