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# Intraocular drug delivery systems for Diabetic retinopathy: Current and future prospective

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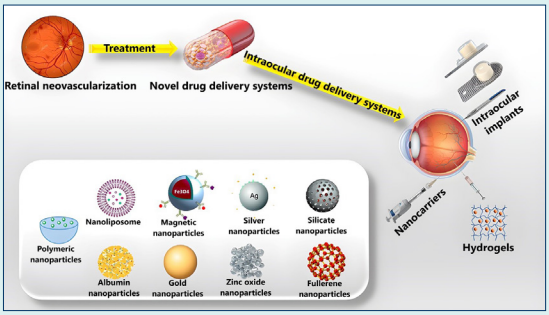
**Abstract**




In pharmaceutical research and development, novel drug delivery systems represent a significant advancement aimed at enhancing the efficacy of therapeutic agents through innovative delivery mechanisms. The primary objective of these systems is to transport therapeutic compounds to specific target sites, such as tumors and afflicted tissues, with the dual purpose of mitigating side effects and toxicity associated with the drugs while concurrently augmenting therapeutic effectiveness. Numerous innovative drug delivery strategies have been scrutinized for their applicability in the context of targeted ocular drug delivery. Diverse novel carriers, including but not limited to implants, hydrogels, metal nanoparticles, Nano-liposomes, micelles, solid lipid nanoparticles (SLN), emulsions, and biodegradable nanoparticles, have been harnessed 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, heightened stability, and superior entrapment efficiency. This comprehensive review seeks to elucidate the current strides made in the realm of carriers and their contemporary applications in treating diabetic retinopathy (DR). Furthermore, it underscores these carriers' pivotal role in achieving efficacious intraocular drug delivery. Additionally, this article explores the various administration routes, potential future advancements, and the multifaceted challenges confronting the domain of novel carriers in treating DR. In conclusion, novel formulations are introduced to surmount the challenges associated with intraocular drug delivery.

## Introduction

Novel drug delivery systems represent a contemporary scientific frontier that has catalyzed advancements across various scientific domains, particularly in pharmaceuticals. These systems have effectively surmounted challenges associated with drug delivery, sparking considerable interest among pharmaceutical researchers seeking innovative technologies for precision drug targeting.[1-3] The fundamental objective of this paradigm is to transport therapeutic agents in quantities sufficient to target specific sites, such as tumors and afflicted tissues, while simultaneously mitigating undesirable side effects and toxicity, thus enhancing therapeutic efficacy.[4-6]

Diabetes mellitus, characterized by inadequate insulin production or responsiveness leading to elevated blood glucose levels, is one of the most significant health epidemics of the 21st century.[7] Diabetes can be broadly categorized into type 1 (insulin-dependent) and type 2 (insulin-independent). Diabetic retinopathy (DR) emerges as a prevalent microvascular complication, affecting virtually all type 1 diabetes patients and over 60% of type 2 diabetes individuals during the first two decades of the disease.[8] Clinically, DR manifests in two primary forms: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR can be further stratified into mild, moderate, and severe stages, characterized by microaneurysms, hemorrhages, hard exudates (lipid deposits), cotton wool spots, intraretinal microvascular abnormalities, venous beading, and loop formation (Fig. 1).

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NPDR can progress to PDR, marked by retinal neovascularization and vitreous hemorrhage.[8] This condition disrupts the blood-retinal barrier (BRB) and increases vascular permeability, leading to leakage and diabetic macular edema (DME).[9] Elevated vascular permeability exacerbates capillary occlusion, causing retinal ischemia and upregulating vascular endothelial growth factor (VEGF) levels.[10] Recently, VEGF inhibitors like pegaptanib sodium, ranibizumab, and bevacizumab have demonstrated their effectiveness in suppressing ocular neovascularization, significantly reducing neovascular activity and vascular permeability in various ocular tissues.[11] Table 1 provides an overview of different drug types for retinopathy treatment.

Bevacizumab, also known as Avastin, stands out as the preferred anti-VEGF antibody fragment for PDR treatment. Although generally well-tolerated, bevacizumab is associated with common side effects such as hypertension, proteinuria, impaired wound healing, and thrombosis, raising concerns.[21] Consequently, intraocular injection is the prevailing method of bevacizumab administration. However, a significant drawback of intravitreal anti-VEGF treatment lies in the need for repetitive injections due to the short half-life of these drugs within the vitreous. This approach incurs challenges and costs, along with potential adverse effects, including intravitreal hemorrhage, endophthalmitis, cataract formation, and retinal detachment.[11,21]

Conventional drug formulations in treatment confront several hurdles, such as short half-lives, low solubility, efficacy at high doses, aggregation, and susceptibility to degradation.[22] A limited repertoire of technologies has been available for addressing intraocular disorders and diseases. While traditional delivery methods, such as subconjunctival injection, intravitreal injection, and topical eye drops, exist, numerous biological and physiological barriers pose formidable challenges that therapeutic payloads must surmount. Clinical studies

**Table 1.** A summary of the different types of drugs that are currently available in the market for diabetic retinopathy

| Drug | Dosage forms | Mechanism | Drug delivery system | References |
|---|---|---|---|---|
| Triamcinolone acetonide | 4 mg/0.1 mL (injection suspension) | Anti-inflammatory effects | intravitreal | 12 |
| Fluocinolone acetonide | 0.59 mg (implant) | Anti-inflammatory effects | intravitreal implant | 13 |
| Dexamethasone | 0.7 mg (implant) | Anti-inflammatory effects | Extended-release implant | 14 |
| Etanercept | 2.5 mg/0.1 mL (Injection Suspension) | Anti-inflammatory effects | intravitreal | 15 |
| Infliximab | 5 mg/kg (injection suspension) | Anti-inflammatory effects | Intravenous injection | 15 |
| Pegaptanib | 0.3 mg/0.09 mL (Injection Suspension) | VEGF inhibitors | intravitreal | 16 |
| Bevacizumab | 1.25 mg/0.05 mL (Injection Suspension) | VEGF inhibitors | intravitreal | 17 |
| Ranibizumab | 0.5 mg/0.05 mL (Injection Suspension) | VEGF inhibitors | intravitreal | 18 |
| Ruboxistaurin | 32 mg/day | inhibitor | oral | 19, 20 |
| Hyaluronidase | 75 IU/0.05 mL saline | Clearance of vitreous hemorrhage | intravitreal | 20 |

VEGF, vascular endothelial growth factor; PKC β, Protein kinase C β.

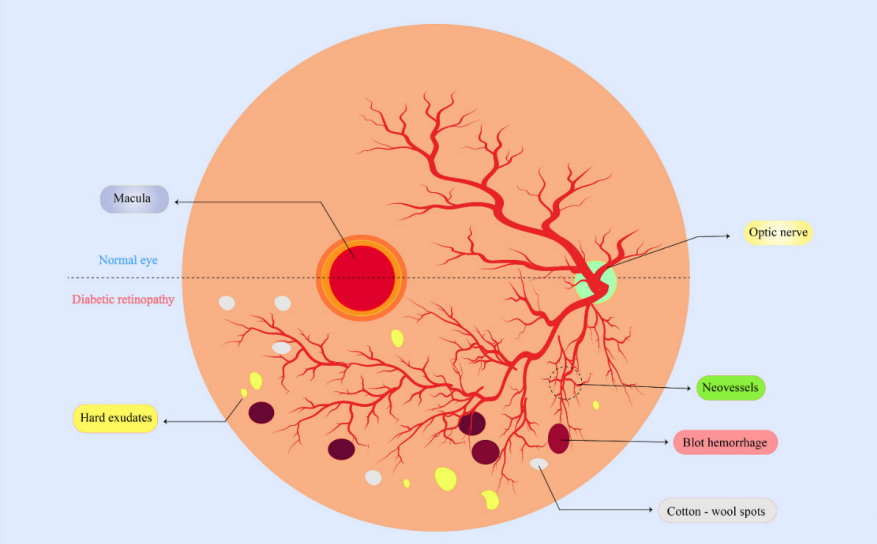


**Fig. 1.** Schematic of diabetic retinopathy.

employing these delivery vehicles have raised concerns regarding safety, including immunogenicity, broad tissue tropism, and genomic insertional mutagenesis.[23] Addressing these limitations necessitates the development of innovative intraocular drug delivery systems grounded in biodegradable carriers that offer heightened effectiveness and durability within the intraocular environment. A diverse array of drug delivery systems, including implants, hydrogels, nanoliposomes, micelles, solid lipid nanoparticles (SLNs), emulsions, and biodegradable nanoparticles, have been deployed for precise and controlled drug delivery to the retina and vitreous.[24-30] Several review articles covering ocular disorders have been published.[22,31,32]

Within drug delivery and therapeutics, nanocarriers are specialized vehicles for transporting drugs to specific anatomical targets within the body, including sites affected by DR. These nanocarriers can encapsulate drugs within their structures, serving as protective capsules that shield the drug from degradation, metabolism, or elimination, prolonging circulation time and enhancing stability.[33] Many drugs employed in DR treatment exhibit poor solubility or limited bioavailability. Nanoparticles address this issue by enhancing the solubility of hydrophobic drugs, leading to improved drug absorption and distribution. Additionally, nanoparticles offer protection against enzymatic degradation, augmenting drug bioavailability and ensuring a more pronounced therapeutic effect.[34] Notable nanocarrier advantages include targeted drug delivery, controlled and sustained drug release, enhanced drug stability and protection, prolonged drug circulation, and improved solubility and bioavailability, thus facilitating enhanced drug absorption and distribution.

However, nanocarriers have certain limitations, including intricate formulation and manufacturing processes, potential immunogenic responses or toxicities associated with nanoparticle carrier materials, challenges in scaling up production for large-scale clinical applications, and variable clearance from the body contingent upon nanoparticle characteristics and size.[35]

This review represents a comprehensive examination of emerging intraocular drug delivery systems for treating DR, a subject not comprehensively covered in prior reviews.

Tonicity, referring to the osmotic pressure or solute concentration in a solution, emerges as a pivotal factor in drug delivery systems for DR treatment. Maintaining the structural integrity of ocular tissues necessitates a tolerable tonicity range of 0.5% to 2% NaCl solution. Common tonicity modifiers include 1.9% boric acid and sodium acid phosphate buffer.[36,37]

Sterile drug delivery systems are pivotal in mitigating infection risks and ensuring patient safety when addressing DR. Given their direct contact with sensitive ocular tissues; microbial contamination can have severe consequences. Therefore, production processes must be executed within a sterile environment. Sterilization techniques such as filtration, autoclaving, or gamma irradiation may be employed to eliminate existing microbiological contaminants. Furthermore, ensuring the sterility of drug delivery systems until administration necessitates appropriate storage conditions, including regulated temperature and aseptic packaging.[36]

The meticulous engineering of drug delivery systems is imperative to ensure biocompatibility with ocular tissues and to maintain their integrity during ocular administration, thereby optimizing therapeutic efficacy while minimizing side effects. Biodegradable implantable technologies, including hydrogels and polymeric microspheres, hold promise as platforms for long-term drug delivery. Ideally, these systems should undergo gradual biodegradation, yielding non-irritating and non-toxic degradation byproducts, thus obviating surgical removal.[38]

The biodegradation of drug delivery systems significantly impacts their efficacy and safety in treating DR. Long-term drug release, reduced frequency of administration, and avoidance of complications associated with extended implantation are all contingent upon the capacity of a delivery system to biodegrade over time. Biodegradable materials such as polymeric microspheres, nanoparticles, and hydrogels are conventionally employed to encapsulate and release therapeutic agents.[39]

This comprehensive review delves into recent advancements in intraocular drug delivery systems for DR. Drawing from multiple articles, cutting-edge delivery methods for intraocular applications are introduced. The investigation encompasses nanocarriers and implants, each further segmented into subclasses, providing detailed insights. Additionally, current research developments and challenges linked to the use of carriers are addressed, along with specifics about DR treatments and regeneration incorporating carrier-based approaches.

## The human eye's anatomy

The human eye is an intricate organ crucial for vision, composed of several interconnected structures endowed with distinct functions. In Fig. 2, the primary components of the human eye are depicted. The cornea, a transparent and dome-shaped tissue, envelops the eye's anterior, facilitating light entry. The iris, which showcases the eye's coloration, governs the pupil's size, regulating the influx of light. The pupil, a malleable circular aperture at the iris's center, permits light passage. Positioned behind the iris, the lens concentrates light onto the retina, with its capacity to alter shape to accommodate near and far vision. The retina, a slender, light-sensitive layer at the eye's posterior, teems with specialized photoreceptor cells that convert light into electrical signals dispatched

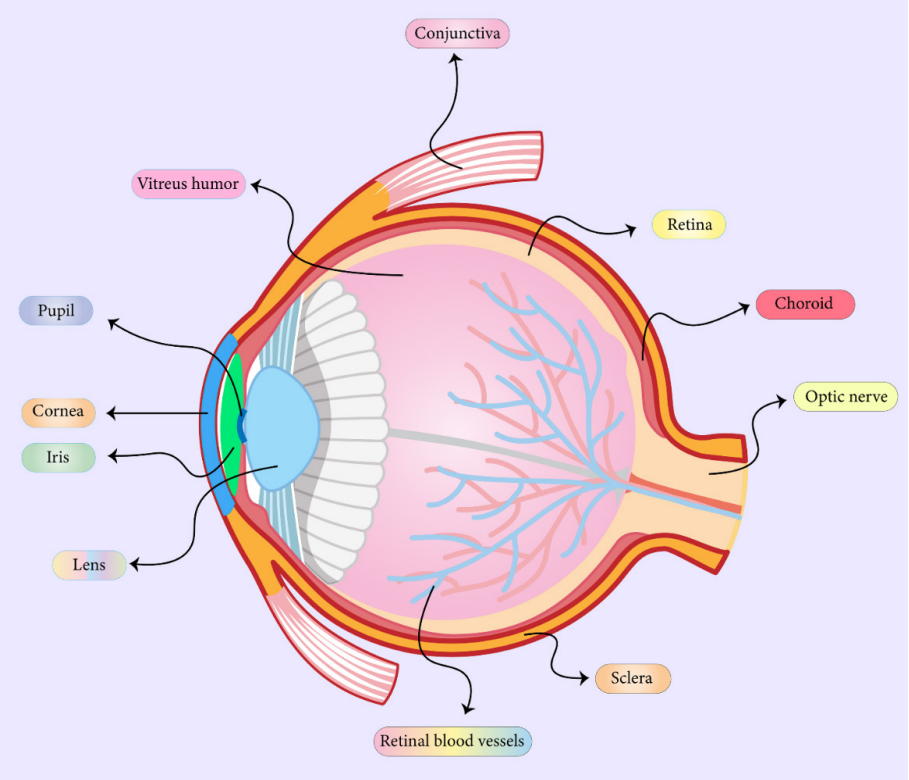


**Fig. 2.** Schematic of the human eye.

to the brain via the optic nerve. The optic nerve, a bundle of nerve fibers, is the conduit for visual information transmission from the retina to the brain. Filling the eye's central cavity, the vitreous humor is a gel-like substance that maintains the ocular structure and supports its internal components; the white outer layer, known as the scale, protects and sustains stain the eye's form.[40]

Challenges in Retinal Drug Delivery for DR The administration of drugs to the retina for DR treatment poses a formidable challenge due to many barriers, including the BRB, Limited Drug Permeability, Rapid Clearance, Ocular Dynamics, and Patient Compliance.[41] The retina's blood vessels are exceptionally selective, forming a formidable barricade called the BRB. This barrier imposes stringent restrictions on the transit of large molecules, including numerous drugs, from the bloodstream into the retina, rendering the delivery of therapeutic agents to the target location challenging. Even if a drug succeeds in traversing the BRB, it may encounter obstacles in permeating the diverse retinal layers to access the intended site of action. The retina's intricate architecture and tight junctions among retinal cells curtail drug permeability. The eye possesses highly efficient mechanisms for expeditiously expelling foreign substances, including drugs. This can curtail the duration and efficacy of drug action prior to its elimination from the eye. The perpetual motion and blinking of the eye pose mechanical hurdles in drug delivery. Tears and blinking can either rinse away or dilute drug formulations, thus diminishing their concentration and efficacy. In cases where drugs necessitate repeated and prolonged administration, patient adherence becomes a formidable obstacle.[42] Consistent and timely drug administration is imperative for the successful management of DR, with non-compliance serving as a hindrance to treatment outcomes. Surmounting these obstacles continues to be an area of active exploration within the realm of ocular drug delivery. Scientists are investigating many strategies, encompassing the development of innovative drug delivery systems, nanoparticles, and targeted drug carriers, all aimed at augmenting the efficiency and effectiveness of drug delivery to the retina in the context of DR and other ocular maladies.[43]

## Intraocular delivery for DR

### *Hydrogels*

The utilization of hydrogels in biomedical applications has been an evolutionary journey commencing in the 1960s when hydrogel first found its application as contact lenses.[44] Hydrogels represent a distinctive class of polymeric materials renowned for their remarkable capacity to absorb and retain substantial quantities of water within their intricate three-dimensional matrix.[45,46] This unique characteristic has paved the way for the effective delivery of biologically active substances through controlled drug release mechanisms.

Significant research efforts have been directed towards developing novel hydrogel structures and chemically

cross-linked networks.[47-49] Among these, polyhydroxy ethyl methacrylate (PHEMA) has emerged as the most compelling polymer.[50]

As the 1970s progressed, a newfound fascination with stimuli-responsive hydrogels emerged. These hydrogels exhibit an inherent ability to undergo physical or chemical transitions in response to specific environmental stimuli, such as changes in pH, temperature, light exposure, and pressure.[51] Thermosensitive hydrogel is one of the most extensively studied and utilized forms of stimuli-responsive hydrogels.[52,53] Thermosensitive hydrogels can be categorized into lower critical solution temperature (LCST) and upper critical solution temperature (UCST) hydrogels. In LCST hydrogels, the system exists as a liquid under critical temperature conditions, whereas in UCST hydrogels, the system assumes a gel state under critical temperature and becomes liquid at temperatures above the critical threshold.[54,55]

Crucially, to circumvent potential immune reactions, the polymers employed in hydrogel formulations must possess specific essential characteristics, including biodegradability, biocompatibility, and non-cytotoxicity.[56] Hydrogels are constructed from cross-linked polymers that can imbibe water, resulting in swelling and the maintenance of an expanded water-rich structure.[57,58]

Another vital category within the realm of stimuli-responsive hydrogels is the pH-responsive hydrogel. These systems feature ionizable pendant groups within the polymer backbone, allowing them to respond to variations in pH levels. Alterations in environmental pH lead to ionization of the pendant groups, creating electrostatic repulsive forces between ionized groups, thus inducing swelling. pH-responsive hydrogels can be further classified into anionic and cationic hydrogels. Anionic hydrogels incorporate 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.[59,60]

In the context of temperature-sensitive hydrogels, changes in temperature trigger either swelling or de-swelling within the system, which can be harnessed for drug delivery purposes. The interplay between hydrophobic and hydrophilic regions within the hydrogel structure plays a pivotal role in this physical response.

Shear-thinning hydrogels represent yet another facet of hydrogel engineering. Shear-thinning is a property wherein the material's viscosity decreases with increased shear forces. Such hydrogels can be readily loaded into syringes, extruded when subjected to shear, and swiftly regain their original form when mechanical forces cease, a phenomenon commonly referred to as self-healing. This property is highly advantageous for maintaining material integrity following injection and facilitating in situ gelation processes, with the benefit of minimizing potential embolization into the systemic circulation. However, it is worth noting that physical cross-linking often disrupts self-healing properties and fails to exhibit the mechanical integrity seen in in situ cross-linking covalent systems. Researchers have therefore explored alternative cross-linking methodologies to enhance the stability of mechanically deployed hydrogels after injection.[61,62] Shear-thinning hydrogels have been the subject of extensive investigation across various biomedical applications, encompassing drug delivery, tissue regeneration, and intraocular drug delivery.[63-65]

In summary, developing in situ injectable hydrogels, offering precise control over drug release rates and degradation, holds immense promise as a versatile drug carrier for ocular drug delivery.[66] Moreover, preclinical studies have yielded encouraging results in applying hydrogel-based tissue adhesives, vitreous replacements, and intravitreal drug delivery systems. The intraocular administration of hydrogels stands poised to bring about significant advancements in this field, ultimately contributing to the refinement of existing hydrogel technologies and the potential for future clinical approvals. It is imperative to concurrently advance injection systems capable of efficiently and safely handling in situ forming hydrogels in clinical settings.[67] Table 2 and Fig. 3 provide a succinct overview of the various types of hydrogels mentioned herein.

## *Exemplary instances of hydrogels*

### *Hydrogels with shear sensitivity*

In a study by Chegini et al, cross-linked and injectable hydrogels were formulated using tragacanth gum as a base material. This particular hydrogel demonstrated potential applicability for the targeted delivery of therapeutic agents to the posterior segment of the eye in conditions such as DR and macular edema. The formulation involved the utilization of tragacanthic acid (TA), the water-soluble component of tragacanth gum, and three distinct acetate salts.

The evaluations of this study revealed that the hydrogel formulation incorporating TA and sodium acetate (referred to as TA-NaOAc) exhibited biocompatibility, optical transparency, injectability, and adequate structural integrity in its quiescent state post-injection. Importantly, assessments conducted via the MTT assay demonstrated the absence of cytotoxicity toward human umbilical vein endothelial cells (HUVECs). Additionally, in vivo Draize tests and histological examinations of the retinas in rabbits and rats did not reveal any signs of allergic reactions or histopathological alterations.

The amalgamation of these in vitro and in vivo findings augurs well for the potential application of TA-NaOAc hydrogel in ocular drug delivery, holding significant promise in this domain.[65]

### *Temperature-sensitive hydrogels*

In the sphere of ocular drug delivery, a diverse array

**Table 2.** Various types of hydrogels used for retinopathy drug delivery

| Hydrogel type | Stimuli-responsive polymer | Drug | Property | Therapeutic outcome | Reference |
|---|---|---|---|---|---|
| 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 | 68 |
| | Poloxamer | Bevacizumab | | | 69 |
| | ESHU | Bevacizumab | | | 70 |
| | PLGA-PEG-PLGA | Dexamethasone acetate | | | 53 |
| | PEG-PCL-PEG | Bevacizumab | | | 71 |
| | PLGA-PEG-PLGA | Insulin | | | 72 |
| | Chitosan | Fluconazole | | | 73 |
| Shear sensitive hydrogels | Tragacanthic acid | | Gel-to-sol transition with shear | - | 65 |

PLGA-PEG-PLGA; Poly (lactic acid-co-glycolic acid)-poly (ethylene glycol)-poly (lactic acid-co-glycolic acid)), ESHU; poly (ethylene glycol)-poly-(serinol hexamethylene urethane), PEG-PCL-PEG; poly (ethylene glycol)-poly (ε-caprolactone)-poly (ethylene glycol)

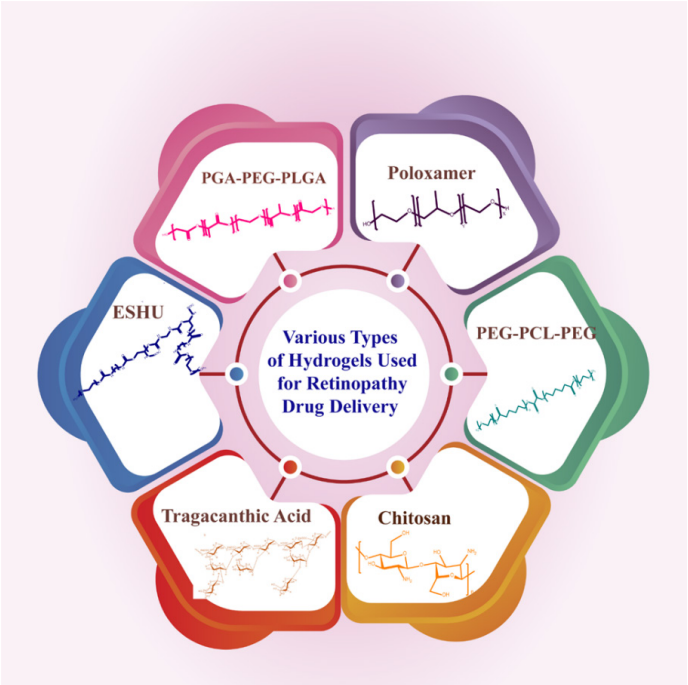


**Fig. 3.** Schematic diagram of the hydrogels used for retinopathy drug delivery.

of thermosensitive hydrogels has been developed, encompassing both natural polymers such as chitosan, alginate, and hyaluronic acid, as well as synthetic polymers like poloxamer, PEG/PLGA block polymers, PEG/PCL block polymers, and poly(N-isopropyl acrylamide).[67,74-77] Among these, poloxamers, recognized as triblock copolymers poly (ethylene glycol-b-propylene glycol-b-ethylene glycol) (PEG-PPG-PEG), have undergone extensive scrutiny due to their unique inverse thermosensitive properties. A significant transformation from a liquid to a gel state in aqueous poloxamer solutions materializes at the physiological temperature of 37 °C. This attribute renders them particularly attractive for applications as injectable agents in controlled-release drug delivery, tissue engineering, and cell therapy.[78]

Recent developments have also witnessed a growing interest in PEG-based hydrogels, augmented by including hydrophobic components such as PLGA and PCL. Consequently, PEG-based thermosensitive hydrogels have emerged as compelling candidates for exploration as injectable thermosensitive materials. Notably, PEG can be copolymerized alongside PLGA, PLA, and PCL, resulting in copolymers characterized by A-B-A or B-A-B structures.[25,79] In parenteral drug delivery, attributes such as biodegradability and biocompatibility assume paramount significance. Notably, PLGA has witnessed substantial investigation in combination with PEG to create block thermoreversible gelling polymers.[80,81] One remarkable study employed temperature-sensitive injectable hydrogels, specifically PLGA-PEG-PLGA, to facilitate the sustained release of Avastin into the ocular environment. Impressively, the in vitro drug release kinetics extended over two weeks, diverging significantly from the free drug release profile. Additionally, no toxicity or inflammation was discerned within the hydrogel system.[82]

### *Nanocarriers*

Nanocarriers represent a pivotal innovation in drug delivery, offering versatile solutions that can be crafted from a variety of inorganic and organic materials, including biodegradable and non-degradable polymers, metals, lipids, and self-assembling amphiphilic molecules.[83-85] This remarkable development addresses a longstanding challenge in pharmacotherapy, where bioactive substances, while exhibiting therapeutic benefits, often manifest undesirable side effects that restrict their clinical applicability.

One prominent example is chemotherapy, employed in cancer treatment, where drugs indiscriminately target both cancerous and healthy cells, resulting in adverse effects. The scientific community has sought ways to selectively deliver bioactives to specific anatomical sites within the body to optimize therapeutic potential while minimizing these detrimental outcomes. This endeavor has spurred extensive research into nanocarriers for precise drug and gene delivery, enhancing therapeutic efficacy while mitigating side effects. These nanoparticulate delivery systems offer several crucial advantages, including elevated target-to-non-target concentration ratios, prolonged drug residency at the intended site, and enhanced cellular uptake and intracellular stability.[86]

Nanocarriers have recently gained significant attention as a preferred drug delivery system due to their remarkable ability to reduce toxicity and enhance therapeutic effectiveness. These systems are characterized by submicron particle sizes, typically less than 500 nm, which results in a high surface area-to-volume ratio. This unique attribute profoundly influences the properties and bioactivity of encapsulated drugs. Critical attributes of nanocarriers include:

1. Prolonged circulation time in the bloodstream.
2. Precise delivery of drugs to the intended target sites.
3. Reduction in the required drug dosage.
4. Controlled drug release.

Various types of nanocarriers have been developed, such as microemulsions, nanosuspensions, liposomes, micelles, solid lipid nanoparticles (SLN), dendrimers, and hydrogels.[87-89] The properties of nanocarriers can be tailored through modifications in their composition, shape, size, and surface characteristics. These modifications encompass PEGylation, functional group introduction, surface charge adjustment, and targeting moieties incorporation.[90] Table 3 provides an overview of the diverse nanocarrier types.

Utilizing nanocarriers yields many benefits, including enhanced drug bioavailability, improved drug permeation to specific retinal areas, prolonged drug residence time, non-invasive drug delivery, and enhanced ocular tolerability. These advancements represent a substantial leap forward in achieving safer, more efficient, and more convenient medication delivery systems.

### *Exemplary instances of nanocarriers*

#### *Polymeric nanoparticles*

Polymeric nanoparticles (PNPs) are polymeric materials comprising nanoscale colloidal organic compounds. These PNPs exhibit configurations resembling nanospheres or nanocapsules.[108] Presently, a diverse array of polymers, including chitosan, polycaprolactone, hyaluronic acid, carbopol, eudragit, gelatin, poly butyl polylactic acid, and cyanoacrylate, are harnessed for the fabrication of nanoparticles intended for ocular drug delivery.[109-111] Chitosan, notable for its non-toxic, biodegradable, and biocompatible nature, emerges as a polymeric mucoadhesive capable of orchestrating drug release and averting abrupt drug discharges. Various investigations have scrutinized the therapeutic potential of chitosan nanoparticles encapsulating Avastin® for DR treatment, achieving regulated drug dispensation and enhanced intraocular drug transport.[112-115]

The antiangiogenic prowess of chitosan is ascribed to multiple mechanisms.[116, 117] It has inhibited tumor invasion and endothelial cell migration. Notably, chitosan has recently demonstrated its capability to mitigate lipopolysaccharide (LPS)-induced interleukin-8 (IL-8) production in endothelial cells, a phenomenon associated with the pathogenesis of vascular disorders.[111, 118,119] In an endeavor to further augment its efficacy, a chemically modified derivative of chitosan, namely chitosan-N-acetyl-L-cysteine (CNAC), was employed to fabricate nanoparticles for comparative assessment against unaltered chitosan-based nanoparticles in the context of Avastin® delivery via hydrogel.[120,121] CNAC distinguishes itself by the presence of N-acetyl-L-cysteine (NAC), a feature absent in unmodified chitosan. This addition introduces thiol groups that forge robust disulfide bonds with cysteine-rich domains in mucus glycoproteins, endowing CNAC with superior mucoadhesive attributes relative to chitosan.[120] Given that VEGF comprises cysteine residues, it is conceivable that CNAC may confer additional antiangiogenic activity via binding to VEGF.[121] Indeed, an investigation into N-acetylcysteine's antioxidant and antiangiogenic properties in a rat model of DR affirmed NAC's capacity for antiangiogenic and antioxidant actions.[122]

#### *Nanoliposomes*

Nanoliposomes are self-assembling, bilayered, circular particles that share similarities with cell membranes.[75] The synthesis of nanoliposome formulations varies depending on their intended application and functionality, with several methods available. These methods encompass thin-film hydration-sonication, ethanol injection, reverse phase evaporation, supercritical fluid technology, heating, and the Mozafari technique.[123,124]

Liposomes offer numerous advantages, including low toxicity, biodegradability, and non-immunogenicity, rendering them an ideal choice for drug delivery

**Table 3.** Summary of the different types of nanocarrier used for drug delivery

| Nanocarrier type | Materials | Drug | References |
|---|---|---|---|
| Polymeric nanoparticles | Chitosan | Bevacizumab | 91 |
| | CNAC | Ranibizumab | 92 |
| | Polycaprolactone and Pluronic® F68 | Triamcinolone acetonide | 93 |
| | PGS | Sunitinib | 94 |
| | Generation-4 hydroxyl polyamidoamine dendrimer | Triamcinolone acetonide | 95 |
| | PLGA | Dexamethasone acetate | 96 |
| | PLGA | bevacizumab | 97 |
| Nanoliposome | NLC | Triamcinolone | 98 |
| | DPPC (C40H80NO8P) | Bevacizumab | 99 |
| | egg phosphatidylcholine | Bevacizumab | 100 |
| Albumin nanoparticles | HSA | Bevacizumab | 101 |
| Gold nanoparticles | HAuCl4 | Resveratrol | 102 |
| zincoxide nanoparticles | zinc acetate | Cyperus rotundus leaf extract | 103 |
| magnetic nanoparticles | iron oxide core and an organic shell exposing carboxylic groups | Octreotide | 104 |
| Silver nanoparticles | AgNO3 | - | 105 |
| silicate nanoparticles | tetraethoxysilane and Cyclohexane | - | 106 |
| Fullerene nanoparticles | C60 fullerene (C60) | - | 107 |

Chitosan-N-acetyl-L-cysteine (CNAC), Polyglycerol sebacate (PGS), Human serum albumin (HSA), 1, 2-Dipalimitoyl-Sn-glycero-3-phosphocholine (DPPC), nanostructured lipid carrier (NLC; Lipophilic solid lipids used included C16, C18, and a mixture of monoglycerides, diglycerides, and triglycerides, Hydrophilic solid lipids used included Ethylene oxide, propylene oxide copolymer, and surfactant)

systems.[125] Employing liposomes for intravitreal injections enables a controlled and gradual drug release into the vitreous, potentially reducing the frequency of injections.[126] Several studies have investigated the use of liposomes for intravitreal administration.[127] Abrishami et al. conducted a study examining the impact of nanoliposome encapsulation on bevacizumab following intravitreal injection in rabbits. Their findings revealed that intravitreal nanoliposome injections containing bevacizumab were well-tolerated in rabbits for 42 days. Notably, the clearance rate of this drug from the vitreous when delivered through nanoliposomal formulations was significantly slower than its soluble counterpart. The concentration of bevacizumab following intravitreal injection indicated that this delivery system maintained appropriate therapeutic drug levels for up to six weeks, particularly for diabetic neovascularization and potentially other neovascular eye disorders. These results suggest that the use of nanoliposomes has a beneficial impact in extending the presence of bevacizumab in the vitreous.[128]

*Albumin nanoparticles*

Human serum albumin (HSA) is a protein with a molecular weight of 66 kD that is abundantly found in plasma and is widely employed in the pharmaceutical industry as an excipient for various purposes. It boasts remarkable stability in fluid environments and possesses amphiphilic properties. Consequently, HSA proves to be a suitable choice for formulating numerous therapeutic proteins as an additive, serving to mitigate irreversible adsorption to containers or the occurrence of aggregation phenomena.[129,130] Standard techniques for generating albumin nanoparticles encompass the desolvation method, thermal-induced aggregation, self-assembly, and albumin-bound technology.[131] Owing to its notably high glass transition temperature, HSA can function effectively as a cryoprotectant during freeze-drying processes.[132] Moreover, it plays a pivotal role in producing micro- and nanoparticles like Albunex®,[133] Abraxane®,[134] and bevacizumab-loaded albumin. The latter is created through a desolvation process followed by freeze-drying. Remarkably, these resulting nanoparticles exhibit stability without requiring additional measures, such as cross-linking with glutaraldehyde. This stability is primarily attributed to reinforcing protein-protein interactions between the antibody and albumin. Notably, assessments conducted on ARPE-19 cells revealed these nanoparticles to be non-cytotoxic. Furthermore, when administered as eye drops to laboratory animals, they exhibit a sustained presence on the ocular surface for at least four hours. These collective findings strongly indicate that albumin-based nanoparticles hold significant promise for the ocular delivery of bevacizumab, thereby paving the way for further in vivo evaluations.[135]

*Gold nanoparticles*

Gold nanoparticles (GNPs) are agglomerations of particles varying in size from a few to several hundred nanometers, comprising a central gold core enveloped by a surface coating.[136] Two fundamental approaches are employed in the synthesis of AuNPs, namely chemical synthesis and biological synthesis. Chemical synthesis methods

encompass Turkevich, Brust, seed-mediated growth, and digestive ripening. On the other hand, biological synthesis exploits microorganisms such as bacteria and fungi, as well as plants, algae, and biomolecules.[137]

The resulting morphology of these nanoparticles can vary, encompassing quasi-spherical, spherical, cubic, triangular, pentagonal, rod-shaped, hexagonal, and plate-like structures, although spherical GNPs have been the most frequently documented.[138]

Due to their diminutive dimensions and distinct physicochemical attributes, GNPs have garnered considerable attention in drug delivery, bio-imaging, bio-sensing, and nanomedicine.[139-141] Investigations have indicated that GNPs can impede VEGF-induced endothelial cell migration through modulation of the Akt pathway, also known as protein kinase B (PKB).[142] Generally, GNPs can trigger nanostructural modifications of vascular endothelial growth factor receptor 2 (VEGFR2), thereby hindering VEGFR2 activation and suppressing angiogenesis. Further examinations have suggested that GNPs can inhibit both in vitro and in vivo angiogenesis by inducing autophagy.[143,144] The interplay between autophagy and angiogenesis is intricate, as heightened autophagy can either promote or obstruct angiogenesis. Inhibitory autophagy of angiogenesis is often associated with lysosomal dysfunction.[145,146] Key proteins involved in autophagosome formation and autophagic cell death,[147] such as Autophagy-related protein 5 (ATG5) and Beclin1, displayed increased expression upon GNPs administration, underscoring GNPs' potential as a therapeutic nanomedicine for angiogenesis treatment and offering novel insights into ocular angiogenesis therapy.[148] Notably, GNPs have exhibited no detrimental effects on the cellular viability of retinal microvascular endothelial cells, as supported by Jin Hyoung Kim et al. Additionally, intravenous administration of GNPs has not induced any toxicity towards retinal cells, including retinal microvascular cells, retinal neurons, endothelial cells, and astrocytes. Furthermore, when administered at high doses directly into the vitreous cavity, GNPs did not manifest any retinal toxicity. These findings collectively suggest that GNPs may be safely employed in treating various retinopathies without causing harm to the retina or normal retinal vessels.[149]

### *Magnetic nanoparticles*

Magnetic nanoparticles (MNPs) represent nanoscale materials of magnetic elements, such as nickel, iron, manganese, cobalt, gadolinium, chromium, and various chemical compounds. Owing to their nanoscale dimensions, MNPs exhibit superparamagnetic properties. They hold immense potential across diverse applications in their unmodified form. However, selecting functional groups and applying surface coatings are imperative for specific applications. Among MNPs, ferrite nanoparticles have garnered substantial research attention.[150,151] Various synthetic techniques are employed to attain the desired shape, size, stability, and biocompatibility of MNPs. Standard methods for MNP synthesis include ball milling, thermal decomposition, coprecipitation, microemulsion, hydrothermal, sol-gel processes, and biological approaches.[152]

MNPs hold promise for intraocular drug delivery.[153] Intraocular MNPs have demonstrated rapid and sustained penetration into the retina, explicitly targeting the retinal pigment epithelium (RPE) without inducing any tissue damage.[154] Furthermore, MNPs possess significant capabilities in loading and delivering specific molecules. Notably, MNPs have been effective carriers for brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), enhancing their efficacy in preventing retinal oxidative damage.[155]

Amato R et al. conducted a study to assess the feasibility of employing magnetic nanoparticle-octreotide (MNP-OCT) to treat DR. Their evaluation examined MNP-OCT's ability to suppress VEGF-induced pro-angiogenic responses in human retinal endothelial cells (HRECs) and its effectiveness in safeguarding ex-vivo retinal explants from oxidative stress (OS)-induced apoptosis. Furthermore, they investigated the actual localization of MNP-OCT in retinas in vivo following intraocular injection. The results of their experiments in animal models demonstrated that MNPs exhibit no toxicity to ocular tissues. Furthermore, the biocompatibility of MNPs was corroborated in ex-vivo mouse retinal explants, where no apoptotic activity was observed in the presence of MNPs.[104]

### *Silver nanoparticles*

Silver nanoparticles (Ag NPs) have emerged as a prominent subject of investigation within the realm of nanoparticles in recent decades. These Ag NPs typically comprise 20 to 15,000 silver atoms and exhibit diameters below the 100 nm threshold.[109] Silver, a naturally occurring element, is characterized by its distinctive white appearance, softness, lustrous sheen, and notable thermal and electrical conductivity.

Various methodologies can be employed to synthesize Ag NPs, encompassing physical, chemical, biological, and mechanical approaches. Among these, chemical processes have gained prominence as a standard and straightforward means of Ag NP fabrication.[156]

Due to their remarkable antimicrobial attributes, Ag NPs find application in many domains, including wound dressings, contraceptive devices, surgical equipment, and bone prostheses. Moreover, Ag NPs are extensively utilized to coat ocular lenses, effectively thwarting microbial activity. Additionally, these nanoparticles have been recognized for their antifungal characteristics, anti-viral efficacy, and anti-inflammatory properties.[157-163]

Gurunathan et al have presented compelling evidence suggesting that Ag NPs function as potent antiangiogenic

agents, effectively suppressing angiogenesis initiated by VEGF via the PI3K/Akt pathway.[164]

Pathological conditions often manifest with heightened permeability in choroidal and retinal vessels, as seen in age-related macular degeneration and diabetes.[165] Sheikpranbabu et al have elucidated that Ag NPs possess the capability to inhibit retinal vascular hyperpermeability induced by advanced glycation end-products-bovine serum albumin (AGE-BSA), a condition characterized by the suppression of intracellular adhesion molecule-1 (ICAM-1) expression and the upregulation of tight junction proteins ZO-1 and occludin[166]. Additionally, their study unveiled Ag NPs' potential to counteract permeability induced by VEGF and interleukin-1β (IL-1β) via the deactivation of the Src kinase pathway, thus presenting a promising therapeutic avenue for ocular diseases such as DR.[167]

Kalishwaralal et al have contributed further insights by reporting that Ag NPs exert inhibitory effects on cell survival through the PI3K/Akt-dependent pathway in retinal endothelial cells.[168]

*Silicate nanoparticles*

Silica nanoparticles (SiNPs) are non-crystalline, spherical particles in various forms and sizes with easily modifiable surface properties to cater to diverse applications. In their nonporous state, SiNPs exhibit abrasive and absorbent characteristics. However, mesoporous SiNPs, characterized by hexagonal pore architectures, hold significant promise within nanomedicine and therapeutic interventions.[124] Several methods exist for synthesizing SiNPs, resulting in a range of sizes from 10 to 500 nm and diverse morphologies and physicochemical attributes. Stober's procedure and microemulsion synthesis are among the widely employed synthesis techniques.[169]

SiNPs find utility in gene therapy and drug delivery, whether used independently or with other treatment modalities.[170-172] A study by Mohammadpour et al posited that the small size of SiNPs allows them to permeate corneal epithelial tight junctions effectively, suggesting their potential efficacy in treating and preventing corneal neovascularization. Further investigations could explore the application of SiNPs in controlling retinal neovascularization associated with vascular disorders and DR.[173]

Jo et al demonstrated that SiNPs hold promise for the treatment of retinal neovascularization without inducing toxicity. SiNPs effectively inhibited VEGF-induced retinal neovascularization and suppressed the activation of extracellular signal-regulated protein kinase (ERK 1/2) by inhibiting VEGFR-2 phosphorylation. Pathological angiogenesis, driven by angiogenic molecules like VEGF, contributes to angiogenesis-related blindness (ARB), making SiNPs and siRNAs potential candidates for preventing vision loss.[174]

Observational research has shown that magnesium silicate nanoparticles exhibit low toxicity. Specifically, Emodin–$MgSiO_3$ effectively impedes the expression of both protein and the VEGF gene. This suggests that magnesium silicate hollow spheres hold promise as safe drug carriers.[175]

*Zinc oxide nanoparticles*

Zinc oxide (ZnO) is categorized as an n-type semiconducting metal oxide with commendable biocompatibility, safety, and enduring efficacy, rendering it a viable option for addressing various medical conditions. In the context of diabetes mellitus, zinc oxide nanoparticles (ZnO NPs) have garnered significant attention owing to their capability to administer zinc ions, as substantiated by references.[176-178] An array of investigations have unequivocally demonstrated that ZnO NPs exhibit negligible toxicity towards human cells, as corroborated.[179]

ZnO NPs can be synthesized through diverse chemical methodologies encompassing vapor transfer, precipitation, and hydrothermal routes. However, it is noteworthy that the contemporary focus of research lies in the burgeoning domain of biogenic synthesis of ZnO NPs, which entails the utilization of various plant extracts or microorganisms. This biological approach to nanoparticle synthesis offers many advantages when compared to conventional chemical and physical methods, as elaborated.[180]

In a recent study, DR in rats was targeted for treatment using zinc oxide nanoparticles loaded with extracts from Cyperus rotundus (CR-ZnONPs). The experimental findings demonstrated significant improvements in key parameters, including fasting blood sugar (FBS), retina thickness, insulin levels, and HbA1c, all of which returned to average values. These outcomes suggest that CR-ZnONPs possess remarkable anti-inflammatory and anti-diabetic properties.[181]

*Fullerene nanoparticles*

Fullerenes represent the third naturally occurring allotropic variation of carbon.[181] The pseudo-aromatic structure of C60 molecules, characterized by the delocalization of π-electrons over its carbon core, is primarily determined by the presence of $sp^{2,5}$-bonds.[182]

Numerous scientific publications have detailed various methodologies for synthesizing fullerenes, which can possess varying degrees of hydroxylation while conforming to the general formula C60. These methods predominantly involve the solubilization of fullerenes in water through solvent exchange utilizing diverse organic solvents such as toluene, ethanol, acetone, and THF, often aided by sonication or mechanical stirring. Furthermore, it has been documented that C60 can be directly solubilized in water through prolonged stirring or sonication.[183]

Fullerene has recently garnered significant attention as an up-and-coming candidate for numerous medical applications.[184] Ever since research commenced on

C60's antioxidant properties, it has been posited that the extensive electron-conjugation system is a unique characteristic of fullerene molecules. Until recently, fullerene was regarded as a groundbreaking "structural" antioxidant, a notion articulated by Krusic, who referred to it as a "radical sponge".[185]

The principal mechanism by which C60 benefits astrocytes is through its capacity to neutralize free radicals and safeguard cellular membranes from oxidative damage. This property has significant implications for astrocyte survival. Strikingly, fullerene also exerts a profound influence on signaling pathways associated with the regulation of apoptosis, offering a novel therapeutic approach for addressing cellular dysfunction in DR.[107]

Concurrently with the progression of DR, there is a noteworthy occurrence of pro-inflammatory and pro-oxidative alterations in retinal cells, including astrocytes and Muller cells. Glial reactivity has been recognized as a pivotal pathogenetic factor in various neural tissue disorders. The anti-inflammatory and antioxidant attributes of fullerene C60 nanoparticles have been empirically substantiated. Nedzvetsky et al investigated the glioprotective efficacy of water-soluble hydrated fullerene C60 (C60HyFn) in a 12-week STZ-diabetes model. Their findings indicated that C60HyFn treatment ameliorated astrocyte reactivity in the STZ-diabetic rat group, as evidenced by reduced S100β and PARP1 overexpression. Additionally, the retinas of STZ-diabetic rats subjected to C60HyFn treatment exhibited diminished TNFα production. These results underscore the glioprotective potential of C60HyFn on retinal cells, suggesting its viability as a prospective nano-strategy for DR therapy.[186]

### *Intraocular implants*

Ocular drug delivery implants have garnered significant attention as a solution to address the inherent limitations associated with conventional eye therapies.[187-190] These implants offer distinct advantages, such as ease of administration, precise drug delivery to ocular tissues, and minimal interference with the normal functioning of the eye.[191] Specifically, intravitreal implants represent a class of drug delivery systems designed for either injection or surgical implantation into the vitreous humor, facilitating sustained drug release to the posterior and intermediate regions of the eye.[192]

Over the past few decades, the medical community has witnessed a burgeoning interest in bioimplants. Bioimplants encompass diverse technologies to enhance the functionality of damaged natural organs. These encompass brain/neural implants, [193] sensory implants,[194] spinal implants,[195] organ stimulation implants,[196] subcutaneous implants,[197] dental implants,[198] cosmetic implants, [199] and convenience implants. Additionally, structural implants such as rods, braces, heart valves, pins, bones, hip prostheses, ear implants, ocular implants, skull implants, and knee replacements have played pivotal roles in improving patients' quality of life. Bioimplants have ushered in a new era of drug delivery systems, enhancing therapeutic outcomes while mitigating side effects through targeted and localized drug administration.[200] This localized approach has improved drug bioavailability at the desired site, reduced dosing frequency, and eliminated systemic side effects. Furthermore, an essential feature of these implants is their ability to be removed in the event of adverse effects.

Implants can be classified into two primary categories: passive and active implants. Passive implants, in turn, can be further divided into biodegradable and non-biodegradable varieties. Biodegradable implants have been crafted using materials like polycaprolactone (PCL), polylactic acid (PLA), and polylactic-co-glycolic acid (PLGA).[201,202] Conversely, non-biodegradable implants are typically manufactured from materials such as silicones, polyurethanes, polyacrylates, and polyethylene vinyl acetate.[203-209]

One notable application of implants is sustained-release steroids, which have proven effective in reducing inflammation and managing macular edema associated with DR. These implants provide extended therapeutic effects while minimizing the risk of systemic side effects compared to systemic steroid administration. Nevertheless, it is essential to acknowledge potential drawbacks, including the risk of cataract formation, elevated intraocular pressure as a side effect of steroid use, implant dislocation or migration, and the need for meticulous monitoring. Prolonged use may necessitate the management of steroid-related complications.[210]

Active implants harness two principal mechanisms to control drug release: osmotic pressure gradients and electromechanical drives.[211]

To exemplify the innovation in ocular implants, one can reference the work of Maulvi et al.[211.] They devised a novel ocular implant for timolol maleate (TM) delivery, starting with loading ethyl cellulose nanoparticles within hydrogel rings in a multi-step process for controlled drug administration in the treatment of Glaucoma. The initial step involved the synthesis of TM-ethyl cellulose nanoparticles using the double emulsion method. Subsequently, hydrogel implants were crafted through a free radical polymerization process, employing HEMA (hydroxyethyl-methyl acrylate) as monomers and ethylene glycol dimethacrylate as a cross-linker. In the final step, TM-encapsulated ethyl cellulose nanoparticles were dispersed within an acrylate hydrogel. Compared to traditional eye drop therapy, in vivo pharmacokinetic assessments demonstrated an increase in mean residence time (MRT) and area under the curve (AUC) with TM implant contact lenses.[212] The success of this innovative approach has ignited interest in developing similar

implants for treating retinopathy and other ocular diseases.

### *Exemplary instances of intraocular implants*

Various sustained-release corticosteroid delivery systems have undergone scrutiny for therapeutic purposes. The fluocinolone acetonide intravitreal implant, commercially available as Retisert, is the pioneering device in this domain. This particular implant is the subject of investigation for its efficacy in treating DME and autoimmune retinopathy.[213,214] A more compact device, designed for in-clinic administration under the name Iluvien, is also examined for DME treatment.[215] Another noteworthy option is the biodegradable, extended-release dexamethasone implant known as Ozurdex, which can be introduced in a clinical setting to address macular edema. Ozurdex comprises a biodegradable copolymer encompassing lactic acid and glycolic acid, laden with an adjustable quantity of dexamethasone. Many in vitro and in vivo studies have firmly established its biocompatibility.[216,217] Furthermore, the triamcinolone-eluting intravitreal implant, named I-vation, has also been explored as a therapeutic approach for DME.[218]

## Constraints and complexities of intraocular drug delivery systems

### *Hydrogels*

Despite their broad potential applications in ophthalmology, the commercialization of products based on hydrogels has remained relatively limited. In contrast, hydrogel-based soft contact lenses (SCLs) and foldable intraocular lenses (IOLs) have showcased exceptional efficacy. However, the practical deployment of hydrogel-based vitreous substitutes or intravitreal medication delivery systems currently faces substantial challenges. Several factors contribute to this situation. First and foremost, sterilizing hydrogels poses a formidable challenge.[219,220] Conventional thermal sterilization tends to degrade most natural and synthetic polymers, while radiation or chemical sterilization may trigger side reactions that alter the inherent characteristics of the hydrogel. These issues are exacerbated when incorporating proteins or other biopharmaceuticals.[221]

Aseptic processing offers a viable solution for sterilizing hydrogel drug delivery systems. Maintaining aseptic conditions throughout the manufacturing process, encompassing material handling, formulation, and packaging, minimizes the risk of introducing contaminants while preserving the delicate attributes of the hydrogel and any incorporated biopharmaceuticals. Filtration represents another standard method for sterilizing heat-sensitive materials and solutions in hydrogel drug delivery systems. This method passes the product through sterile filters to eliminate microorganisms and particulate matter.[222]

Furthermore, pre-formed hydrogels exhibit a finite shelf life, and the reactivity of in situ cross-linkable polymers may diminish during storage. The shelf life of a hydrogel largely hinges on its composition and the cross-linking methodology employed. Hydrogels featuring stable, covalently cross-linked polymer networks exhibit superior long-term stability to those with physically cross-linked structures, which may be more susceptible to degradation over time. Environmental factors, such as temperature, humidity, and light exposure, can significantly influence hydrogel stability. Commercially available hydrogel formulations are typically engineered to withstand various environmental conditions, and packaging considerations may further contribute to overall stability.[223]

Moreover, the selection and quantity of medications that can be integrated into hydrogels remain constrained.[224] While physical cross-linking may enhance the stability of encapsulated therapeutic proteins, it may simultaneously limit control over gel degradation and drug release.[225] Finally, antibodies released from hydrogels at a slower rate may display instability over several weeks.[226]

### *Nanocarriers*

Ophthalmic drug delivery faces numerous challenges attributed to the eyes' distinctive physiological and anatomical features. These intricate organs present several formidable barriers that must be surmounted to target specific ocular tissues.[227] Additionally, emerging scenarios, such as the initial burst release from nanoparticles, compound the limitations of ocular drug delivery. Furthermore, investigating toxicity in retinal cells remains incomplete, primarily conducted in vitro, leaving essential gaps in the understanding.[228,229] While nanoparticles are generally biocompatible, factors such as their charge, particle size, drug concentration, and duration of exposure significantly influence their potential toxicity to the retina. Typically, the interaction between cationic surfaces of nanoparticles and negatively charged cell membranes serves as the predominant catalyst for toxicity.[230] These limitations are not exclusive to nanoparticles; other types of formulations also face similar obstacles when delivering drugs to the specific tissues within the eye. For instance, traditional eye drops encounter difficulties in achieving targeted delivery to the intended ocular tissues. Additionally, challenges exist for ointments, gels, and intravitreal injections in ensuring effective and sustained drug delivery while minimizing potential side effects.[231]

### *Intraocular implants: surgical considerations and challenges*

The implantation procedure for intraocular implants necessitates a surgical intervention, inherently carrying associated risks. Moreover, post-surgical complications, such as infection, inflammation, elevated intraocular

pressure, and cataract formation, may manifest. In certain instances, the extraction of intraocular implants can be a formidable task, mainly when complications arise, or implant replacement is imperative.[217]

### *Limitations and complexities in intraocular drug delivery systems*

Nanotechnology has brought substantial promise in intraocular drug delivery, encompassing nanocarriers, hydrogels, and implants. Despite promising outcomes in laboratory settings, the practical utilization of these carriers remains encumbered by difficulties. Notably, attempts involving nanoparticles have yielded less sanguine results. The heterogeneity inherent to these carriers, potentially leading to therapeutic instability, is a significant challenge.[232] Furthermore, paramount concerns concerning immunological responses and toxicity must be addressed. In sum, using nanocarriers, hydrogels, and implants in intraocular formulations holds excellent potential, necessitating further extensive investigation to surmount the challenges encountered during experimental application. With persistent exploration and advancement, these carriers can revolutionize the treatment of DR.

Beyond traditional dosage forms, ongoing clinical trials and innovative formulations are under development for DR treatment. Some researchers are exploring sustained-release implants, such as Retisert and Ozurdex, designed to administer medications directly into the eye over an extended period. These implants can reduce the required injection frequency and enhance patient compliance.[213,216]

Researchers are also investigating the potential advantages of combining diverse treatment modalities to address multiple facets of DR. Concurrently; clinical trials are underway to assess the efficacy of combining anti-VEGF therapy with other pharmaceutical agents like Bevacizumab and Triamcinolone, as well as laser therapy or surgical interventions. The aim is to improve visual outcomes and disease progression substantially.[233]

Future research endeavors will tackle the challenges of scaling up and industrial production, ensuring efficient and cost-effective manufacturing of novel drug delivery systems. This may encompass the development of scalable production processes, optimization of manufacturing technologies, and tailored implementation of quality control measures in line with the specific requirements of DR treatments. As novel drug delivery systems for DR continue to evolve, a comprehensive assessment of cost-benefit considerations will be imperative. Researchers will scrutinize the overall impact on healthcare expenditure, patient outcomes, and resource utilization, offering valuable insights to healthcare decision-makers and stakeholders.

In forthcoming research endeavors, there will be a pronounced emphasis on the rigorous conduct of clinical trials aimed at appraising the safety, efficacy, and relative effectiveness of innovative drug delivery methodologies for treating DR. These trials will not solely gauge the therapeutic advantages inherent in the novel delivery systems but will also delve into ancillary aspects such as patient adherence, quality of life enhancements, and the enduring consequences of treatment.

Long-term safety assessments will emerge as an imperative sphere of concentration in prospective research endeavors. This undertaking encompasses the meticulous surveillance of the cumulative ramifications stemming from the employment of pioneering drug delivery systems for DR across protracted timeframes. It comprehensively scrutinizes potential adversities and the safety profile of these therapeutic modalities.

Significant strides in nanotechnology, sustained-release formulations, targeted drug delivery, and gene therapy are propelling groundbreaking innovations within the ambit of DR treatment. As these innovative approaches continue their evolutionary trajectory, the symbiotic partnership between researchers, pharmaceutical entities, regulatory authorities, and healthcare providers is pivotal in propelling the development, acceptance, and efficacious integration of pioneering drug delivery solutions for managing DR.

## Methodology for literature search

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. The search 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 screened articles encompassed titles and abstracts, focusing on those elucidating the roles of nanoparticles, hydrogels, intraocular implants, and the effects of drug delivery.

## Concluding remarks

The advent of novel intraocular delivery systems has the potential to address the limitations inherent in traditional anti-neovascular therapies while simultaneously forging innovative therapeutic avenues. The realization of efficacious treatments is now on the horizon, thanks to the emergence of novel intraocular delivery devices capable of extending intravitreal drug administration intervals, facilitating the introduction of corrective genes into ocular tissues, or eliminating the necessity for direct ocular injections. In the coming years, there is eager anticipation for translating promising preclinical evidence into successful clinical trials that can unequivocally demonstrate safety and efficacy in the context of human patients.

## Review Highlights

**What is the current knowledge?**

√ Various novel drug delivery strategies have been examined for targeted ocular drug delivery.

√ Novel carriers such as implants, hydrogels, and nanocarriers have been employed to deliver drugs in a controlled manner to the retina and vitreous.

**What is new here?**

√ Current progress and contemporary applications of carriers in treating diabetic retinopathy.

√ Administration routes, prospective future developments, and challenges in the field of novel carriers for treating diabetic retinopathy.

Furthermore, the newfound antiangiogenic attributes associated with selected intraocular delivery methods may pave the way for integrating intriguing composite materials that synergistically combat neovascular eye diseases. Nanocarriers, hydrogels, and implants have all been meticulously crafted from diverse materials possessing a spectrum of physicochemical characteristics. In addition, concerted efforts have been dedicated to refining the structural attributes of nanocarriers, hydrogels, and implants, primarily enhancing their intraocular delivery efficiency. This optimization involves manipulating their internal and external morphologies, enhancing their stability, and modulating their release kinetics.

Moreover, incorporating biologically responsive components into nanocarriers, hydrogels, and implants has enabled the customization of their responsiveness to various stimuli, including magnetic fields, ultrasound, pH fluctuations, and even dual or multi-stimuli responsiveness. This technological advancement has opened doors to highly specialized therapies characterized by precise site-specific drug release and improved therapeutic outcomes. In summary, the realm of novel intraocular delivery harbors tremendous potential to shape the future landscape of ocular antiangiogenic therapy.

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