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RECENT ADVANCEMENTS IN OCULAR DRUG DELIVERY FOR DIABETIC RETINOPATHY: A COMPHRENSIVE REVIEW

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ABSTRACT

Due to changing lifestyles, an increased number of individuals, including children and young adults are developing diabetes. These individuals have a risk of vision loss from diabetic retinopathy (DR) and diabetic macular edema (DME). The key risk factors for DR are increased duration of diabetes, poor control of blood sugar level, and blood pressure. There is strong evidence for reducing the occurrence of vision-threatening DR by controlling blood sugar levels and hypertension. There is good evidence from systematic reviews of randomized clinical trials that controlling hyperglycemia and hypertension lowers the incidence of DR. In fact, each 1% reduction in updated mean HbA1c was associated with a decrease in risk of 21%. The vision-threatening DR and 98% of blindness can be prevented by laser treatment and vitreous surgery and the use of nanotechnology in ocular drug delivery systems. This review summarizes what diabetic retinopathy means, and innovative nanostructured technology used to treat diabetic retinopathy. Further, it is interesting to note that Autoimmune rheumatic disease (ARD) related to dry eyes is also associated with some retinal diseases directly or indirectly. Significantly, because of the direct or indirect associations of ARD pertaining to dry eye with some retinal diseases, a comprehensive understanding of dry eye, ARDs, and relative complications is necessary.

KEYWORDS: Hyperglycemia, Diabetic Retinopathy, Ocular drug delivery system, Vitreous surgery, Nanostructured technology.

INTRODUCTION

One will not be able to live normally once the vision is adversely affected and the life is significantly changed by visual impairment. This may have resulted from various diseases like Cataracts, Glaucoma, Diabetic retinopathy (DR) etc.[1] Diabetes is a metabolic disorder characterized by high blood glucose levels caused by genetic and environmental factors that result in the loss of β-cells in the pancreas.[2] It occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. In fact, Diabetes is one of the four priority non-communicable diseases of concern in the world. The global burden of diabetes has been steadily rising. In 2014, 422 million adults all over the world were reported to be living with diabetes and it is anticipated that by 2045, the prevalence rate will reach 629 million, the populations from low- and middle-income countries being the most affected.[3,4] Diabetes prevalence will continue to increase with economic and social consequences for the patients, families and society due to the dearth of effective preventive measures.

The DR is generally asymptomatic in the early stages, with the patients becoming aware of the first symptoms when the pathology is already significantly advanced. Since therapy can improve the symptoms and reduce the rate of disease progression, it is essential to regularly screen the eyes of diabetic patients to timely diagnose this complication and delay the occurrence of permanent damage. Over the years, several strategies have been developed to prevent and manage DR. Overcoming the physiological barriers inborn to ocular delivery and the constraints of the available delivery routes have been the challenges that steered researchers to develop novel and innovative drug delivery systems.

DIABETIC RETINOPATHY (DR)

Diabetic retinopathy is a complication of diabetes that affects the eyes by damaging the retinal blood vessels. It occurs due to high blood sugar levels that progressively damage blood vessels. It is one of the major causes of vision impairment and blindness, however, early detection and appropriate treatment can help slow its progression and prevent serious consequences.

Microvascular changes

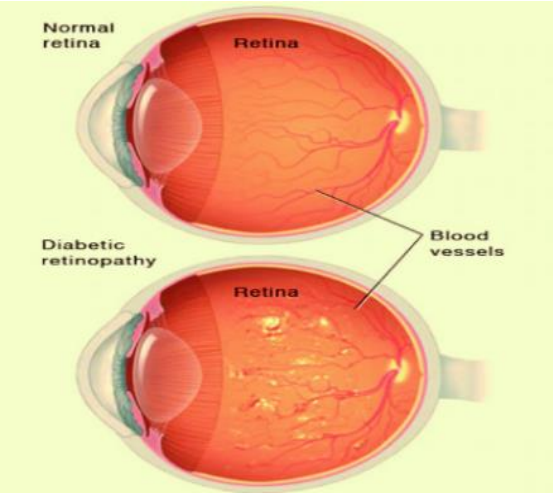

Fig 1.

The changes in the small blood vessels, present in the retina are called microvascular changes. These are mainly associated with diabetes, but they can also arise from other diseases like hypertension, retinal vein occlusions, retinal microaneurysms, use of blood thinners, and some systemic conditions like carotid atherosclerosis, blood dyscrasias, systemic infections, anemia, and post-radiotherapy. Identifying these changes is important for diagnosing and managing eye complications. Signs of vascular occlusion include cotton wool spots, closure of retinal capillaries, and neovascularization, while hemorrhage, exudates, and edema reflect increased vascular permeability.[5]

ETIOPATHOGENESIS OF DIABETIC RETINOPATHY

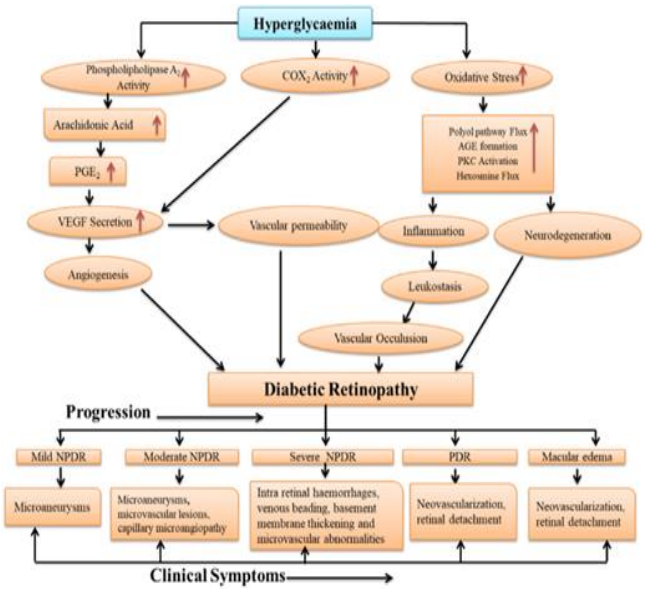

Fig 2.

Alteration in the glucose metabolism and high sugar levels affect different metabolic pathways like vascular endothelial growth factor expression, aldose reductase, protein glycation, and epigenetic changes which increase the activity of phospholipase A2 and COX2. Oxidative stress also activates various pathways like polyol, AGE, PKC, and hexosamine flux pathways, resulting in inflammation, neurodegeneration, and increased vascular permeability, ultimately leading to diabetic retinopathy.[6]

(Abbreviations**:** COX – Cyclooxygenase, AGE – Advanced glycation end products, PKC – Protein kinase C)

RISK FACTORS FOR DIABETIC RETINOPATHY[7,8,9]

1. **Long duration of Diabetes**: Longer the duration of diabetes, greater is the risk of developing retinopathy. About 90% of individuals with type 1 diabetes for a period of 10 years will show some degree of diabetic retinopathy, while 67% of those with type 2 diabetes for over 10 years who do not use insulin are also at risk.
2. **Blood Glucose Levels**: The primary factor for developing diabetic retinopathy is persistent high blood glucose levels or even extreme fluctuations in the blood glucose level.
3. **Blood Pressure**: High blood pressure can damage the retinal blood vessels, a condition known as hypertensive retinopathy. Thus, individuals with both high blood glucose and high blood pressure face a greater risk of diabetic retinopathy.
4. **Smoking**: Smoking increases the possibility of vascular disorders, including retinopathy.
5. **Gestational Diabetes**: Pregnant women with gestational diabetes are also at risk of developing diabetic retinopathy.
6. **Genetic factors**: Traditional risk factors, such as glycemic control and duration of diabetes, are unable to explain why some individuals remain protected from DR while others progress to a more severe form of the disease. Differences are also observed in DR heritability as well as the response to anti-vascular endothelial growth factor (VEGF) treatment. This indicates the involvement of genetic factors in the causation of DR. Gene studies have highlighted various candidate genes associated with the disease, such as *AKR1B1*, *VEGFA*, *AGER*, *EPO*, and *NOS3*.

TYPES OF DIABETIC RETINOPATHY

Diabetic retinopathy is classified into two types:

1. Non-Proliferative Diabetic Retinopathy (NPDR)

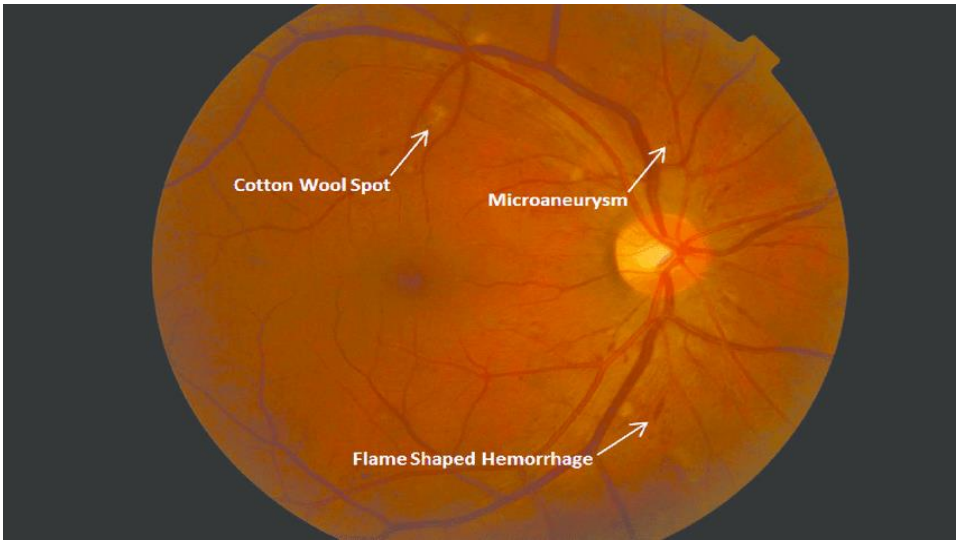

Fig. 3.

This early stage is characterized by swelling and damage to the small blood vessels in the retina. It can result in the formation of microaneurysms (small bulges in the blood vessels), retinal hemorrhages, and fluid leakage.[10]

There are four stages of Diabetic retinopathy, of which the first three fall in the category of non-proliferative DR, and stage 4 is the proliferative DR.

- **Early NPDR** – This stage is characterized by swelling in small areas of the retinal blood vessels, with one microaneurysm visible during examination.
- **Moderate NPDR –** In this stage, there is an increased number of microaneurysms, dot retinal hemorrhages, venous dilation and thinning of the venous walls, and cotton wool spots.
- **Severe NPDR** – This final and most advanced stage is characterized by blockages in larger sections of the retinal blood vessels, leading to reduced blood flow and then body start signaling for growth of new blood vessel in the retina. Patients with severe NPDR have a 52% risk of progressing to Proliferative Diabetic Retinopathy (PDR) within a year, making blood sugar control and close monitoring essential.[11,12]

2. Proliferative Diabetic Retinopathy (PDR)

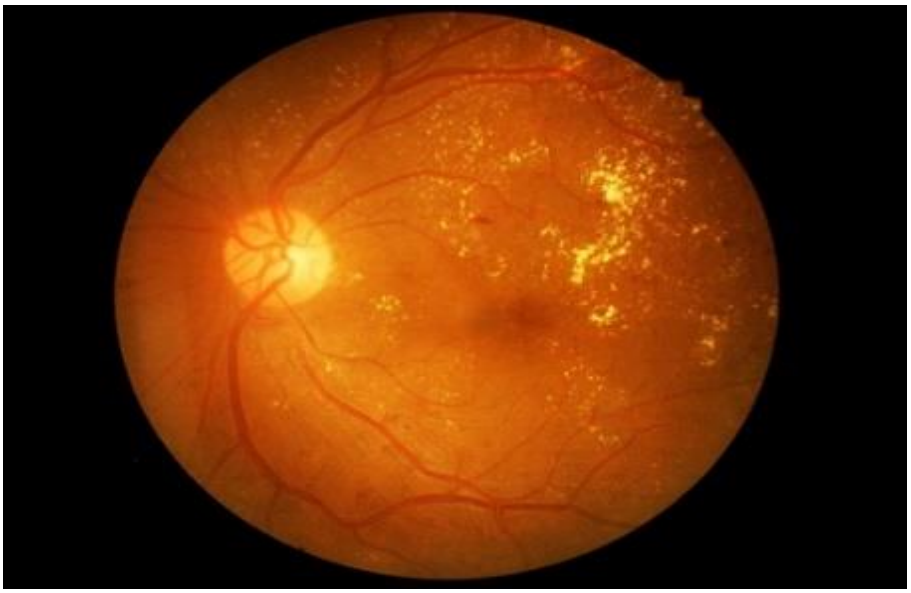

Fig 4.

This advanced stage occurs when abnormal blood vessels start growing on the retina and vitreous (the gel-like substance in the eye). These fragile vessels can bleed easily and frequent vitreous and retinal hemorrhage induce fibrotic proliferation and development of vitreous bands and can cause tractional retinal detachment and vision loss.

PDR is divided into the following stages.

- **Stage 1: Background Retinopathy:** Small bulges appear in the retinal blood vessels, potentially causing mild bleeding.
- **Stage 2: Pre-proliferative Retinopathy:** This stage shows more severe and widespread changes in the retina, leading to bleeding.
- **Stage 3: Proliferative Retinopathy:** In this stage, new blood vessels and scar tissues develop on the retina, which results in significant bleeding and retinal detachment, where the retina pulls away from the back of the eye.

DIAGNOSIS

- **Eye Exam:** Dilated fundus Examination, plays a very important role in detecting diabetic retinopathy. It is a type of eye test that examines the posterior segment of the eye and helps to diagnose the conditions that impact the retina, such as diabetic retinopathy. Pregnant women with diabetes should have a dilated eye examination before conception, early in the first trimester, and then every 3 months until delivery.[13]

- **Imaging:** Techniques like Optical Coherence Tomography (OCT) or fluorescein angiography may be used to observe the retinal damage.

TREATMENT

- **Controlled Blood Sugar:** Maintaining normal blood glucose levels is essential in reducing the development of and managing diabetic retinopathy.
- **Medications:** Anti-VEGF (vascular endothelial growth factor) injections can help reduce abnormal blood vessel growth and leakage in severe cases, Dexamethasone implants (intravitreal) can reduce retinal edema and fibrovascular proliferation.
- **Surgery:** A vitrectomy is done on patients with non-resolving vitreous hemorrhages or severe traction causing retinal detachment. In this procedure, the vitreous gel and hemorrhage are removed from the eye and replaced either with gas or silicon oil.
- **Fluorescein angiography (FA):** It is an eye test that uses a special dye and camera to see the blood flow in the retina and choroid.
- **Laser Therapy:** It can be used to seal leaked blood vessels or to reduce the growth of abnormal blood vessels thereby reducing ischemic areas.
- **Use of nanostructured Ocular dosage forms** aids in precisely administering the drug to the target site. These are effective alternatives to conventional ocular delivery systems.

PREVENTION AND MANAGEMENT

- **Regular Monitoring:** Regular eye examination is important for people with diabetes to monitor for diabetic retinopathy.
- **Effective Management of Diabetes:** For those who are diagnosed with diabetes, a no. of cost-effective interventions can improve the outcomes and these interventions include control of blood glucose through a combination of diet, physical activity, other lifestyle changes, medications if needed, and regular screening for damage to the eyes, kidneys, feet, etc. Control of blood pressure and lipids is important to reduce cardiac risks and other complications. Each 1% reduction in updated mean HbA1c was associated with a reduction in risk of 21%.

OCULAR DRUG DELIVERY SYSTEM

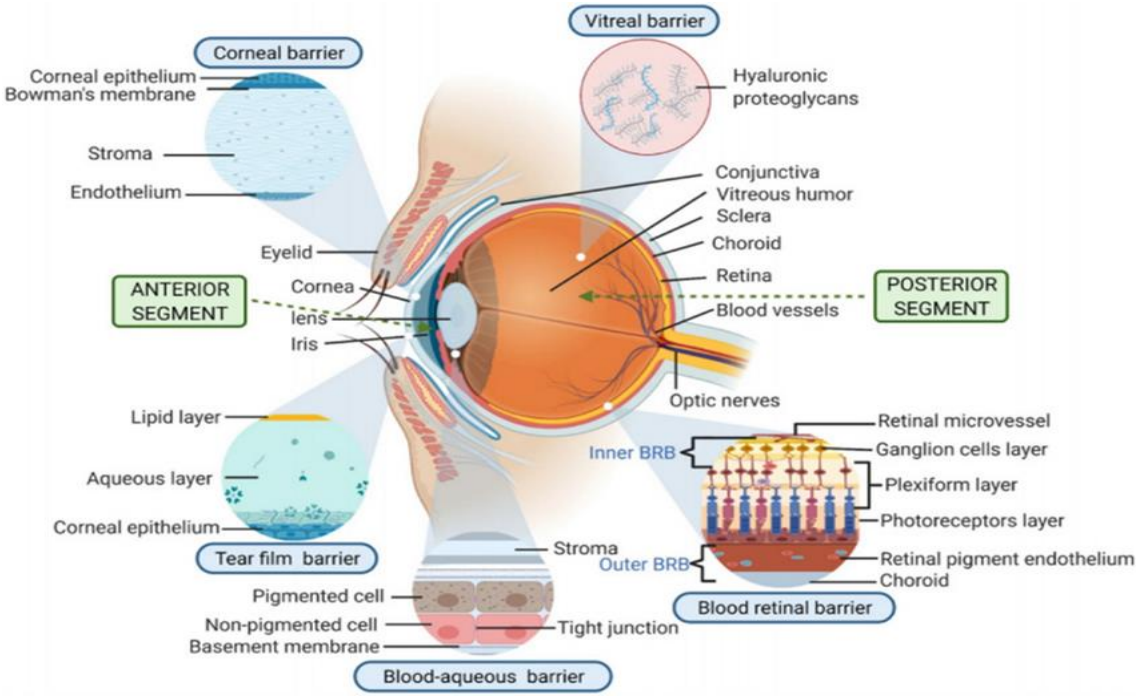

Fig 5. Drug delivery barriers in Ocular routes.

The eye is a unique organ with distinct anatomy and physiology. It is divided into two primary parts: the anterior segment and the posterior segment. The anterior segment makes up one-third of the eye, while the posterior segment comprises the remaining two-thirds. The anterior segment includes structures such as the cornea, conjunctiva, aqueous humor, iris, ciliary body, and lens. In contrast, the posterior segment contains the sclera, choroid, retinal pigment epithelium, neural retina, optic nerve, and vitreous humor.

To address conditions affecting the anterior and posterior segments, such as diabetic retinopathy, glaucoma, age-related macular degeneration (AMD), and uveitis, ocular drug delivery systems have been developed to target therapeutic agents directly to the eye. The primary goal of these systems is to effectively deliver medication to the intended tissues while minimizing systemic side effects and enhancing patient adherence.

KEY OCULAR DRUG DELIVERY SYSTEMS

1. Topical delivery: This is the most common method for administering drugs to treat conditions affecting the anterior segment of the eye. About 90% of available ophthalmic formulations consist of traditional dosage forms like eye drops, gels, or ointments. This method of drug delivery is easy to use, non-invasive, and generally promotes patient compliance.[14,15] However, with these, ocular bioavailability is quite low, and factors such as

tear turnover, nasolacrimal drainage, reflex blinking, and both static and dynamic ocular barriers can delay deeper drug penetration.[16] As a result, less than 5% of the topically applied dose actually reaches the deeper ocular tissues.[17]

These barriers make it challenging to achieve therapeutic drug concentrations in the posterior segment by instilling the drug using topical eye drops.

2. Intravitreal delivery: Intravitreal and periocular injections are the most commonly recommended methods for treating diseases of the posterior eye. In this approach, the drug is injected into the vitreous humor, allowing for direct targeting of the retina and vitreous body. This method is effective for conditions such as macular degeneration and diabetic retinopathy, but it requires sterile techniques and carries risks of infection and retinal detachment. Repeated injections can lead to complications like endophthalmitis, hemorrhage, retinal detachment, and decreased patient tolerance.[18]

3. Transscleral drug delivery: Transscleral delivery is relatively significant, less invasive, and promotes patient compliance. However, drug permeation is limited by ocular barriers, which include static barriers like the sclera, choroid, and retinal pigment epithelium (RPE), as well as dynamic barriers such as blood flow in the conjunctiva and choroid, along with lymphatic flow in the conjunctiva and episclera.[19]

To address the challenges of ocular drug delivery and enhance bioavailability, various conventional and innovative drug delivery systems have been developed. These include emulsions, ointments, suspensions, aqueous gels, nano micelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and in-situ thermosensitive gels specifically for ocular diseases.[20]

LIMITATIONS OF INTRAOCULAR DRUG DELIVERY SYSTEMS

Intraocular drug delivery systems are critical for treating various eye diseases, especially those affecting the retina and vitreous body. However, these systems face several limitations and intricacies that impact their efficacy and safety. Here's an in-depth look at these challenges.

1. **Invasiveness**

- **Surgical Procedures:** Many intraocular drug delivery methods, such as implants or injections, involve invasive techniques that can lead to risks such as infection, retinal detachment, or other complications.
- **Patient Compliance:** The requirement for surgical insertion and the associated discomfort may impact a patient's willingness to pursue treatment.

2. **Complications and Side Effects**

- **Infection:** Invasive procedures like vitrectomy, fluorescein angiography, and laser therapy carry a risk of intraocular infections.
- **Retinal Detachment:** Surgical procedures and devices can sometimes cause retinal detachment or other retinal injuries.
- **Intraocular Pressure (IOP) Changes:** The ocular drug delivery system may increase intraocular pressure, potentially leading to glaucoma.

3. Drug Distribution and Retention

- **Limited Drug Penetration:** Achieving uniform drug distribution across the retina and other intraocular tissues can be challenging due to the eye's complex anatomy and barriers.
- **Short Duration of Action:** Some systems may not provide prolonged drug release, necessitating frequent re-administration or replacement.

4. Device-Related Issues

- **Size and Design:** For effectiveness with minimal invasiveness, the size and design of intraocular devices must be balanced. Large-sized devices may be more effective but difficult to insert and remove.
- **Biocompatibility:** To avoid adverse reactions or chronic inflammation, materials like hydroxy-apatite (coral-like), polyethylene (Medpor), and Aluminium oxide (Alumina) used in making implants or delivery systems must be biocompatible.

5. Formulation Challenges

- **Stability of Drugs:** Some drugs may be unstable in the intraocular environment, affecting their efficacy and safety.
- **Controlled Release:** Achieving a precise and sustained release of the drug is technically challenging and requires sophisticated formulation strategies.

INNOVATIVE NANOTECHNOLOGY IN DRUG DELIVERY SYSTEMS FOR DR

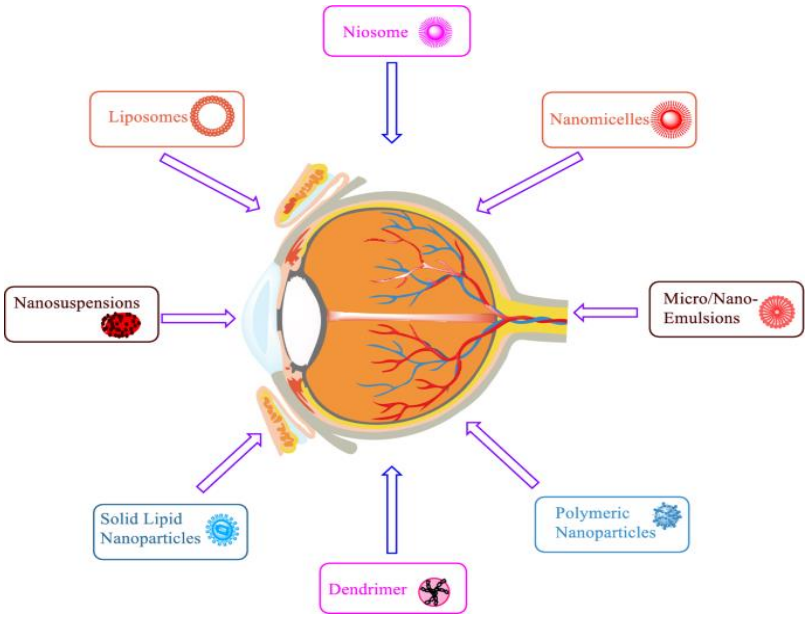

Fig 6.

Various Nano techniques for Ocular Drug Delivery System

Diabetic Retinopathy (DR) and Age-Related Macular Degeneration (AMD) are two major retinal diseases that can lead to vision loss if not managed effectively. Delivering drugs to the posterior segment of the eye remains a challenge due to the presence of multiple physiological and anatomical barriers. Nano-therapeutics are characterized by their small size, large surface area, tunable properties, and biocompatibility, enhancing the permeability, stability, and targeting of drugs**.**

Nanomicelles

Nanomicelles have become a popular method for ocular drug delivery across various indications, due to the benefits such as controlled drug release, effective penetration of ocular barriers, and enhanced bioavailability with minimal toxicity. Their unique structure allows them to encapsulate highly hydrophobic drugs, improving solubility and facilitating drug delivery to target tissues. Mixed amphiphilic nano micelles exhibit strong hydrophobic interactions and robust hydrogen bonding with surrounding polymers.[21] For instance, Tacrolimus formulated in nano micelles has been shown to reduce inflammatory markers and inhibit the NF-kB pathway in multiple cell lines. Additionally, this formulation has demonstrated the ability to prevent early retinal neovascularization in mouse models of streptozotocin-induced diabetic retinopathy.[22]

Liposomes

Liposomes are spherical vesicles made from a phospholipid bilayer that can encapsulate both hydrophilic and hydrophobic drugs. Their biodegradability and biocompatibility make them ideal candidates for topical ocular delivery. Liposomes are especially effective for large molecular weight and poorly water-soluble drugs, as they enhance drug permeation through ocular tissues due to their superior spreading ability and rheological properties, which prolong drug availability on the eye's surface. When liposomes interact with tear lipid components, their amphiphilic lipids create a sublayer that facilitates drug distribution across the ocular surface. Extensive research has highlighted the advantages of liposomes in reducing potential drug toxicity and improving absorption and bioavailability compared to encapsulated drugs. Examples of such drugs include vancomycin, tobramycin, ganciclovir, fluconazole, brinzolamide, triamcinolone acetonide, and cyclosporine A. Intravitreal injections of drug-loaded liposomal formulations offer several benefits, including extended drug half-life, protection of sensitive compounds, and prolonged retention within ocular tissues.[23]

Polymeric Nanoparticles

Polymeric nanoparticles, which range in size from 10 to 1000 nm, serve as colloidal carriers for ophthalmic delivery. They can be composed of lipids, proteins, or natural and synthetic polymers such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA), and polycaprolactone. These nanoparticles have been effectively utilized for long-term drug delivery to posterior segment ocular tissues. The distribution of nanoparticles in the posterior segment is influenced by their size and surface properties.[23]

Mucoadhesive polymers like hyaluronic acid, polyethylene glycol, and chitosan can modify nanoparticles to extend their residence time in the cornea. Furthermore, mucus-penetrating nanoparticles—characterized by low surface tension, low viscosity, and high hydration can enhance the delivery of therapeutic agents through the cornea, improving bioavailability and resulting in better therapeutic outcomes. Consequently, these nanoparticles have the potential to significantly improve the treatment of posterior ocular conditions such as posterior uveitis, CMV retinitis, and retinal disorders.[24]

Hydrogels

Hydrogels are commonly used as a solution for managing drug delivery limitations. They are similar to natural tissues consist with high water content, ranges from 70 to 99% of the gel

weight, making them compatible with the vitreous structure in the posterior segment area. Hydrogels are semi-solid used as drug carrier, cell carrier, vitreous substitute, and corneal contact lens in the treatment of ophthalmic diseases and not easily injected into the vitreous. These are required to ensure the long-term sustained release of active drug load to extend injection intervals and to reduce morbidity risks and side effects while targeting the retina. The use of injectable aqueous biodegradable gel is formulated using hydrophilic polymers (hydrogels) and of in situ-forming hydrogels (stimuli-responsive HGs, SRHGs) are used as delivery vehicles for intraocular treatments as sustained release platforms for drugs and proteins.[25]

The following types of hydrogels used for retinopathy drug delivery.

Table 1

Sr.No	Types of hydrogels	Stimuli-responsive polymer	Drug
1	Heat–sensitive hydrogels	Poloxamer	Bevacizumab
		PLGA-PEG-PLGA	Bevacizumab
		ESHU	Bevacizumab
		PLGA-PEG-PLGA	Dexamethasone acetate
		PLGA-PEG-PLGA	Insulin
		Chitosan	Fluconazole
2	Shear- sensitive hydrogels	Tragacanthic acid	Tragacanth gum

[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)]

Dendrimers

Dendrimers are nano-sized, highly branched, star-shaped polymeric structures available in various molecular weights, featuring terminal functional groups such as amine, hydroxyl, or carboxyl. These terminal groups can be used to attach targeting moieties. Dendrimers serve as effective carrier systems in drug delivery, with factors such as molecular weight, size, surface charge, geometry, and functional groups playing crucial roles in drug delivery efficacy. Their branched structure enables the incorporation of a wide range of both hydrophobic and hydrophilic drugs. Poly-amidoamine-based dendrimers are particularly common in ocular drug delivery; for example, subconjunctival injections of dexamethasone-poly-amidoamine conjugates have been shown to enhance the ocular permeability and bioavailability of dexamethasone in ocular tissues.[26]

Nanosuspensions

Nanosuspensions consist of a colloidal dispersion of submicron drug particles stabilized by polymers or surfactants, emerging as a promising approach for delivering hydrophobic drugs. In ocular applications, they offer several benefits, including sterilization, ease of formulation as eye drops, reduced irritation, prolonged precorneal residence time, and improved ocular bioavailability of drugs that are insoluble in tear fluid.[27] Several studies have demonstrated the effectiveness of nanosuspensions in enhancing the ocular bioavailability of glucocorticoids.

CHALLENGES AND CONSIDERATIONS

- **Safety and Biocompatibility:** It is essential to ensure that nanoparticles are safe for long-term use and do not cause any adverse reactions.
- **Manufacturing and Scalability** Developing nanotechnology-based treatments requires advanced manufacturing processes and the ability to scale from laboratory settings to clinical applications.
- **Regulatory Approval:** Securing regulatory approval for new nanotechnology-based treatments involves extensive testing and validation to meet the safety and efficacy standards.

CONCLUSION

Effectively managing ophthalmic diseases presents significant challenges due to the various ocular barriers in both the anterior and posterior segments of the eye. This review provides an overview of diabetic retinopathy and highlights emerging technologies in ocular drug delivery aimed at halting the progression of the disease. The incidence of diabetic retinopathy is rising sharply among individuals, underscoring the need for improved therapeutic approaches. By enhancing the efficacy of existing systems and integrating conventional methods with innovative nanotechnology, new research opportunities may arise. Nanotechnology shows considerable promise for advancing the management of diabetic retinopathy through improved drug delivery, enhanced diagnostics, and novel therapeutic strategies. Continued research and development could lead to safe, effective, and patient-friendly potential treatments for this condition.

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