

DIABETIC RETINOPATHY: AN INCLUSIVE REVIEW ON CURRENT TREATMENT AND MANAGEMENT APPROACHES

JYOTHI S L, VISHAL GUPTA N*

Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, JSS Medical Institutions Campus, Sri Shivarathreshwara Nagara, Mysuru - 570 015, Karnataka, India. Email: vkguptajss@gmail.com

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ABSTRACT

Diabetic retinopathy (DR) is a complication which occurs due to diabetes mellitus leading to loss of vision and hindering the quality of patient life by damaging the layer of retina at the posterior segment of the eye. According to the survey around 285 million peoples are suffering from visual loss out of these 65% of people are more than 50 years old and 82% of blind patients are more than 50 years old. The diseases that occur in the posterior segment of the eye like, cytomegalovirus retinitis, posterior uveitis, age related macular degeneration and diabetic retinopathy needs a novel delivery system that can improve the concentration of drugs that reaches posterior segment of the eye. The development of new drug delivery system gained more importance in the field of research in which nanotechnology is the most considered approach. The nanotechnology-based systems such as nanoparticles, nanoliposomes, niosomes, nanomicelles, nanoemulsions, nanogels, cyclodextrins, dendrimers, and quantum dots are developed as a new formulation for drug delivery. The rationale behind the nanoparticle systems is its ability to formulate a sustained, controlled release dosage form, painless, safe, non-invasive system to overcome the major barriers in the treatment of DR. Based on the nanoparticles, some approaches are exploited for more effective conveyance of drug toward the posterior segment. Thus, these advanced delivery systems progress the therapeutic efficacy of the drug and patient's obedience and life quality. In this review, the new therapeutic treatments and their managements were discussed and methods of drug delivery to reach the posterior segment of eye.

Keywords: Diabetic retinopathy, Posterior segment of the eye, Diabetic macular edema, Nanoparticles.

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INTRODUCTION

Diabetic retinopathy (DR) arises in people having diabetes for prolonged period, and it causes vision loss. It affects the retina by damaging the layer, and at the back of the eye, light-sensitive lining appears. In the retina, minute blood vessels leak blood, extrafluids, and tissues present in the retina swells, results in gloomy or blurred vision and if untreated leads to vision loss (Fig. 1) [1]. The diseases such as glaucoma, age-related macular degeneration, and DR affect the posterior segment of the eye and if not treated in time cause permanent vision loss. The therapeutic agents that affect the posterior segment are administered through intravitreally [2,3]. The administered drug shows short half-life and less tissue permeation with chronicity of diseases, maintain visual acuity, frequent drug administration, and to avoid disease progression [4]. For the researchers, significant challenge remains in maintaining and assuring the therapeutic dosage of the drug in the target tissue and drug delivery approaches specifically to the back of the eye. There are many advanced biomedical applications in nanotechnology-based treatment for DR such as gene therapy, novel drug discovery techniques, and drug delivery [5]. Several advantages of nanoparticle relatively to drug administration alone or to classic drug delivery systems such as (1) delivery of drugs to specific cells and tissues, (2) sustained drug delivery, and (3) reduced side effects are present. In the pathophysiology of DR, increased level of adenosine in the retina is seen. The selective adenosine receptor antagonist inhibits the proliferation of endothelial cells, tube formation, migration of cell, and neovascularization [6].

CLASSIFICATION OF DR

Non-proliferative DR (NPDR)

NPDR is the preliminary stage, in which symptoms occurring will be mild or not existed and blood vessels are weakened in the retina. In blood vessels, the minute bulges called microaneurysms appear in blood vessels, this causes leakage of fluids in the retina and it leads to swelling of the macula.

Proliferative DR (PDR)

PDR is the advanced form of the disease. In this phase, oxygen in retina is deprived due to circulation problem, thus resulting in development of new fragile blood vessels in the vitreous and in the retina, at the back of the eye. Gel-like fluids fills into the vitreous; the new blood vessels leak blood and form blurred or cloudy vision (Fig. 2).

PDR

The people suffering from diabetes are affected by PDR which is very common disease and causes vision loss. The abnormal growth of blood vessels in the retina called neovascularization occurs along with bleeding and formation of the fibrous tissue. The foremost contribution for DR includes production of more vascular endothelial growth factor (VEGF); new blood vessel is induced by growth factor and rises the permeability of the existing blood vessels [9]. In some cases of severe NPDR and PDR, panretinal laser photocoagulation is the backbone for treatment in DR. About 50% of the vitreous hemorrhage and risk of DR is reduced and in 12 months, about 50% of severe visual loss is reduced by giving the treatment by panretinal laser photocoagulation [10]. The use of anti-VEGF treatment for PDR affects individuals like vitrectomy intended for vitreous hemorrhage, for diabetic macular edema (DME), and for anterior segment neovascularization and as substitute for panretinal laser photocoagulation for PDR similarly present [11]. After 2 years of treatment with intravitreal ranibizumab, an anti-VEGF agent is demonstrated to improve the visual acuity in people as compared through panretinal laser photocoagulation treatment [12]. For the treatment of the last-stage complication of vitreous hemorrhage and retinal detachment, the vitreoretinal surgery is used (Fig. 3).

DME

DME remains as the main reason for diabetes correlated to loss of vision [13,14]. In macula of the retina, the accretion of extravasated lipids and proteins occurs and breakdown of tight blood-retinal barrier is seen. The DME can be treated by intravitreal injections of anti-VEGF agents, corticosteroids, and laser photocoagulation. The aim

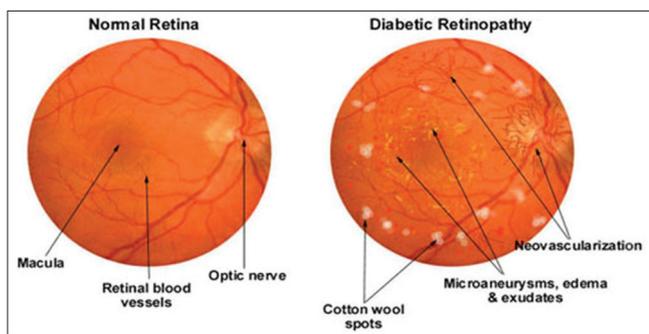


Fig. 1: Normal retina vs. diabetic retinopathy [7]

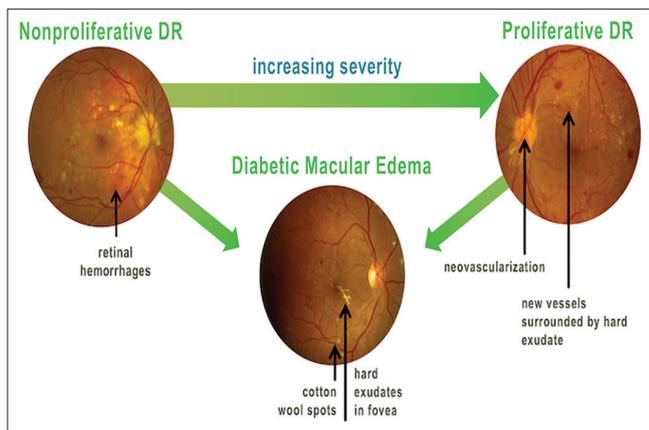


Fig. 2: Schematic representation of classification of diabetic retinopathy [8]

of this therapy is to improve and maintain the visual acuity [15,16]. The anti-VEGF shows the better visual acuity when compared to laser photocoagulation [17]. For inhibiting the inflammation and reducing capillary permeability, patients of DME are treated with corticosteroids [18]. Recent studies suggested that intravitreal triamcinolone acetonide or microimplants loaded with corticosteroids like dexamethasone has shown significant improvement in visual acuity for DME when used over 3 years [19,20].

Mechanism of DR

Diabetes can be characterized by means of resistance to insulin, hyperglycemia, absolute or relative lack of insulin action, and growth of diabetes detailed pathology in the retina [22]. The elementary trade of the disease comprises of loss of pericytes, neovascularization, thickening of the basement membrane, microaneurysms, and breakdown of blood-retinal barrier [23] (Fig. 4).

Polyol pathway

The polyol pathway can be explained by a number of mechanisms such as osmotic pressure induced by sorbitol, decrease in ATPase activity, increase in cytosolic NADH/NAD⁺, and decrease in cytosolic nicotinamide adenine dinucleotide phosphate (NADPH). It is a metabolic pathway which consists of two steps, first, the glucose is reduced to sorbitol and second, the sorbitol converted to fructose (Fig. 5) [25]. The rate-limiting enzyme in the polyol pathway is aldose reductase enzyme. The cofactor called NADPH reduces glucose to sorbitol with the help of aldose reductase enzyme and the cofactor called NAD⁺ metabolize sorbitol to fructose using sorbitol dehydrogenase. Sorbitol dehydrogenase has a low capacity and high affinity toward sorbitol and aldose reductase has low affinity and high capacity toward glucose.

Protein kinase C (PKC) pathway

In this pathway, the family of multifunctional serine/threonine kinase is present which are involved in protein control. In patients with

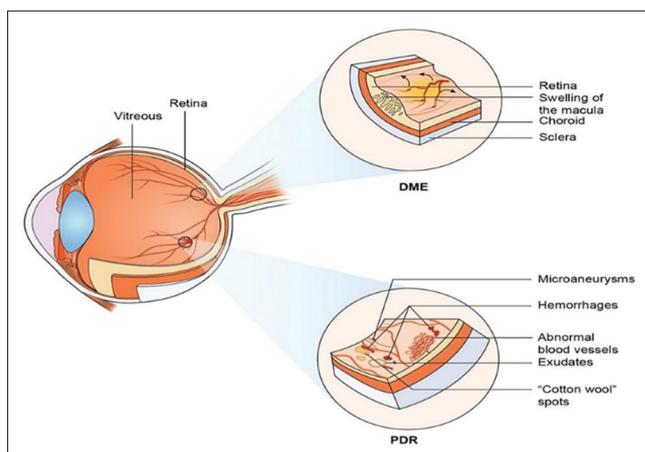


Fig. 3: Schematic illustration of diabetic retinopathy comprises of diabetic macular edema and proliferative diabetic retinopathy [21]

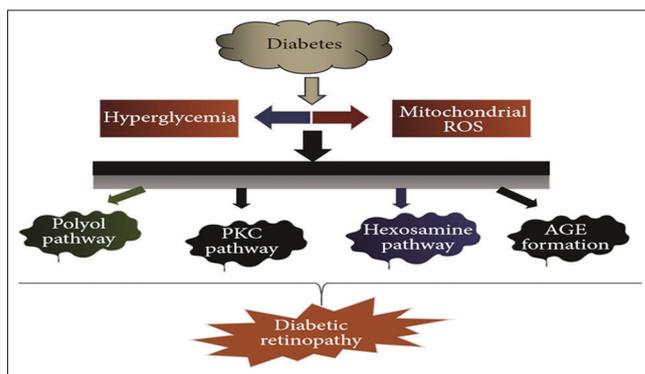


Fig. 4: Schematic illustration of mechanisms complexed in diabetic retinopathy [24]

diabetes microvascular modification rises from hyperglycemia-induced activation of PKC. In this family, 12 PKC isoforms are identified and are subdivided into 3 groups: Atypical, classical, and novel [26]. There are several isoforms that functions in a different biological system. The activation of PKC also occurs in plasma membrane when the messenger isoforms binds to the regulator domain. Diacylglycerol (DAG) enhances the classical isoforms such as PKC- α , - β 1/2, and PKC- δ . Nine isoforms are activated by DAG, a lipid messenger and alteration of DAG-PKC pathway are the important role in diabetic diseases. PKC- β plays an important role in signaling component for endothelial cell permeability and VEGF. Several isoforms which are involved in PKC activation are responsible for pathogenesis for DR [27].

Hexosamine pathway

In retinal tissues of rats and humans, the hexosamine content is more with diabetes. The glucose flux has been increased in *in vitro* and *in vivo* studies through hexosamine pathway have been concerned in diabetic vascular problems, insulin resistance, and synthesis of growth factor stimulates [28]. In this pathway the conversion of fructose- 6-phosphate to glucosamine- 6-phosphate, an essential precursor for glycosylation of lipids and proteins by glutamine fructose- 6-phosphate amido-transferase (GFAT) a rate limiting enzyme [29]. The transcription of TGF- β 1 and plasminogen activator inhibitor-1 increases when conversion of glucose to GFAT blocks hyperglycemia-induced which inhibits the rate-limiting enzyme. Hexosamine pathway which is activated by hyperglycemia results in many alterations of protein level and gene, which are contributed to the pathogenesis of DR [30].

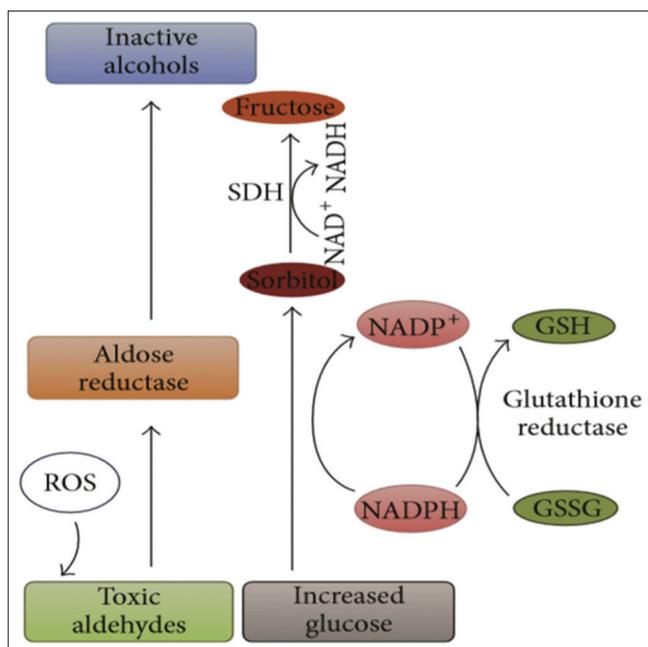


Fig. 5: Schematic illustration of polyol pathway and aldose reductase [22]

Advanced glycation end-product (AGE) formation

The accumulation of advanced glycation end products occurs when the retina is more exposed to hyperglycemia and it leads to DR. AGEs are lipids and proteins which are oxidized and non-enzymatically glycosylated after it is exposed to aldose sugars. In humans, the chemically characterized AGEs are present such as carboxymethyl lysine, carboxyethyl lysine, and pentosidine. These chemically characterized AGEs help in the formation of AGEs in hyperglycemic patients. The Schiff bases and Amadori products are formed by the process of glycation and oxidation [31].

Current treatments for DR

Treatment for hyperglycemia and hypertension are suggested for averting or striking development of DR, previously for the treatment of laser photocoagulation, anti-VEGF agents, or intravitreal injections of corticosteroids and vitreoretinal surgery are executed. Therefore, new treatments are required for the early stages of DR [32,33]. The laser photocoagulation directly treats to the leaky blood vessels by photocoagulation or by removing newly formed blood vessels in the retina. The peripheral retina of eye is involved in the formation of VEGF responsible for neovascularization. The animal studies of reduced hypoxia and improved retinal function in mice are supported recently to this concept with degenerated or chemically ablated photoreceptors and anti-angiogenic therapy was used to improve the vision in patients through DME and PDR [34,35].

Treating the classical risk factor

In type 2 diabetic patients population of UK Prospective Diabetes Study, 39% of reduction is seen in the risk of laser photocoagulation was associated with intensive versus conventional management [36]. In type 1 diabetic population of diabetes regulator and complication trials, the risk of new retinopathy was reduced about 76% and progression of existing retinopathy of about 54% by tight against less tight glycemic control by means of insulin [37]. Serum lipids have a reduced amount of impacting the development of DME or PDR [38]. For preventing or arresting DR, the tight control of the blood pressure is important, this results in ADVANCE and ACCORD Eye proved ambiguous for DR with managing blood pressure in clinical trials [39]. Recent studies show that, there is also a development of DR with control of glucose level in blood and without hypertension. For PDR, the heritability evaluation ranging from 25% to 50% [40,41].

Anti-VEGF in DR

VEGF stands as a homodimeric protein in the range of 35–45 kDa, which exist in several isoforms. The production of vascular permeability factor and endothelial cell-specific angiogenic factors are increased by hypoxia. In recent studies, monoclonal antibodies which are administered through intravitreal injection for treating ocular diseases because these neutralizes the VEGFs. In DR, VEGFs are more expressed due to hypoxia and the capability to rise the penetrability of the blood-tissue barriers which occur in retinal cells are main stimulation for the growth of retinal neovascularization [42]. The drugs which are used as anti-VEGF are bevacizumab, ranibizumab, and pegaptanib.

Bevacizumab

It is a recombinant humanized antibody which shows activity in isoforms of VEGF-A. For DR, iris neovascularization, and DME, the bevacizumab, a monoclonal antibody, is very effective treatment [43]. The stability of monoclonal antibodies at the stage of production, drug release, and *in vivo* performances are limited when these drugs are loaded into nanoparticles. Polymeric nanoparticles are very useful system for ophthalmic drug delivery because of its biocompatibility, non-toxicity, and diversity [44].

Ranibizumab

In the treatment of DME, the ranibizumab is effective when it is administered through intravitreal injection. These drugs rapidly improve the vision and further vision loss is reduced and non-ocular side effects [45]. The combination of intravitreal injection of ranibizumab and panretinal photocoagulation shows effective treatment for PDR [46]. The hypertension and renal side effects that include glomerular thrombotic microangiopathy and proteinuria are caused when chronic anti-VEGF therapy is given [47]. The use of ranibizumab in the treatment of DME over 5-year period was not related with ocular or systemic effects [48].

Pegaptanib

It is an aptamer which binds to the isoforms of VEGF-A. In patients with DR, the intravitreal pegaptanib shows regression of neovascularization on retinal neovascularization [49]. In patients having DME, this drug blocks 165 amino acid isoforms of VEGF, this results in improved visual acuity, thickness of central retina is reduced and reduction in the supplementary therapy with photocoagulation associated with sham injection [50].

Corticosteroids

These are the class of drugs which has more anti-inflammatory activity. It reduces the vascular permeability and reduces the breakdown of blood-retinal barrier and it also reduces the VEGF expression [51]. Various corticosteroids that are used in the DR are triamcinolone acetonide, dexamethasone, and fluocinolone acetonide.

Triamcinolone acetonide

In management of DR, the common corticosteroid is triamcinolone acetonide delivered by intravitreal route and it is more suitable approach for delivery of drug to the posterior segment [52]. In posterior segment, the intraocular concentration is achieved by triamcinolone acetonide. Around 56% of patients have improved their visual acuity by intravitreal triamcinolone acetonide when compared with 26% of patients with placebo [53].

Dexamethasone

It is the well-known corticosteroids which has a high anti-inflammatory effect used in the treatment of chronic and acute eye disease [54]. The dose of the dexamethasone is instillation of 0.1% 3–4 times per day. If the dose extended for more than 4 times a day, it causes glaucoma and damage to optic nerve and also effects on visual acuity and posterior sub-capsular cataract development and cornea become thin [55].

Fluocinolone acetonide

It is the potent corticosteroid which is used in the treatment of eye diseases and it is applicable in the treatment of DME [56]. In patients with DME, clinical trials indicate the significant reduction in ocular edema [57].

Antioxidants

The pathogenesis of several diseases such as hypertension, DR, and ischemic cardiovascular diseases caused due to imbalance between the antioxidants mechanism and reactive oxygen species (ROS) [58,59]. In diabetic patient's, retinal inflammation are caused due to increase in oxidative stress [60]. The inflammatory responses are mediated by ROS through modifying the inflammatory genes expression. In retina, the concentration of polyunsaturated fatty acids is high and oxygen demand is also high. In human, the retina consumes 300-600% of oxygen as compared with the cerebral cortex and cardiac muscle [61]. There are several ROS generated are free-radical superoxide, peroxy, hydroxyl and hydroperoxyl, and non-radical hydrogen peroxide [62] (Table 1).

Route of administration to eye for DR

The route of administration is selected based on the target site of action and on convenience. There are some of the routes which are predicted for ocular delivery includes topical, systemic, intravitreal, and in recent studies, based on periocular routes are used. For anterior segments, topical route is preferred, and for the posterior segment, both periocular and intravitreal routes have been used [73].

Topical route

It is the most frequently used route which is more convenient route for the patients. This route has a major limitation for anterior segment such as bioavailability of the drug is low, limited contact time, and transcorneal permeation is low [74]. Recent studies have discovered that a small molecule of nepafenac formulated as topical drops for treating initial stages of retinopathy to retina. The study describes the inhibition of abnormalities in DR within 2 months of nepafenac as a topical drop in diabetic rats [75]. In other study, the topical drop instillation of ranibizumab reaches the retina adequately through transscleral route. The low concentration of ranibizumab can able to prevent VEGF in vitreous, frequency of administration is high, cost is high [76].

Intravitreal route

For intraocular administration of non-anti-VEGF and anti-VEGF therapeutics, the intravitreal route is maintained as the best route. The application of this route includes, avoidance of blood-ocular barrier to attain higher drug concentration in vitreous and it also avoid adverse effects resulting from systemic administration. The drugs which are present in the vitreous are rapidly cleared therefore repeated administration are necessary to maintain effective therapy, but there is an adverse effect for repeated administration [77]. The

anti-VEGF injections causes economic problem on both patient and health services, and this can be reduced if studies support the use of low-priced and easier-to-administer injections.

Periocular

The periocular offers a good option for drug delivery to the retina or vitreous humor. The administration of drug from periocular route is done through peribulbar, subconjunctival, posterior juxta-sclera, subtenon, and retrobulbar spaces [78]. The periocular route is relatively a longer route and it has to cross the barriers such as sclera, Bruch's membrane, episclera, and choroid to reach the retina or vitreous humor. Subtenon triamcinolone acetonide shows high level in vitreous humor of retinopathic patients than with idiopathic molecular hole patients, rheumatogenous retinal detachment, and macular epithelial membrane [79]. Novel drug delivery system can sustain or improve the periocular therapeutics. Considering these studies, periocular route has more adopted route for delivering drugs to retinopathic patients than compared to intravitreal injections.

Non-invasive ocular drug delivery system

The eye is a delicate sensory organ that is comparatively isolated from systemic access by blood-retinal, blood-vitreous barriers, and blood-aqueous; as a result, the eye exhibits some unusual pharmacokinetic and pharmacodynamic properties [80]. New technologies for ophthalmic drug delivery have received much attention over the past few years such as microspheres, prodrugs, nanotechnology, polymeric gels, liposomes, and inserts. These vehicles have been designed to increase the amount of drug that can penetrate the cornea by minimizing physiological factors such as drainage, blinking, and tearing. The two main approaches in improving the ocular bioavailability are by prolonging the contact time on ocular surface and increasing the corneal permeability.

Nanotechnology applied to ocular delivery

Nanoparticles

Nanoparticles are nanometer-sized particles in the range of 0.1-100 nm. In medical purposes, nanoparticles have potential application such as gene therapy, drug delivery, and imaging [5]. Nanoparticles can afford various advantages as a drug delivery system such as (1) sustained delivery, (2) delivery of drug to the specific sites or tissues, (3) water-insoluble drugs are delivered and large biomolecular drugs are improved, and (4) toxicological reactions and side effects are reduced [81]. In ocular diseases, the nanoparticles bypass the biological barriers such as blood-retinal barriers and blood-brain barriers included in the blood-neural barriers. In the biological system, the determinants for therapeutic effects are physicochemical properties such as surface charge, shape, and size. The size of nanoparticles in the range of 2 and 100 nm are suitable for systemic administration and for the therapeutic purposes. Smaller nanoparticles in the range of <5 nm is susceptible for clearance from the targeted tissues and renal excretion [82]. Gold nanoparticles in the range of 20 nm are suitable

Table 1: Antioxidants used in the treatment of diabetic retinopathy

Antioxidants	Mechanism	Formulation	References
Ascorbic acid	It acts as a free-radical scavenger	Polymeric nanoparticles	[63]
α-tocopherol	It prevents lipid peroxidation	Liposomes	[64]
		Nanoemulsion	[65]
Resveratrol	It reduces the oxidative stress in retina Retinal cell loss is reduced	Gelatin nanoparticles	[66]
		SLN/NLC	[67]
α-lipoic acid	Oxidative stress in retina is reduced Expression of VEGF is reduced	Liposomes	[68]
		Nanocapsules	[69]
Curcumin	It reduces the oxidative stress in retina VEGF production is reduced	Nanoemulsion	[70]
		Microcapsules and nanocapsules	[71]
		Nanoemulsion	[72]

SLN: Solid-lipid nanoparticles, NLC: Nanostructured lipid carriers, VEGF: Vascular endothelial growth factor

for bypassing through blood-retinal barrier and gold nanoparticles are in the range of 100 nm were not detected in retinal layers when administered the drugs intravenously [83].

Nanoliposomes

Nanoliposomes are single or multiple bilayer lipidic membrane surrounded by an aqueous core or compartment. These are artificial vesicles formed from synthetic or natural cholesterol and non-toxic phospholipids. The properties of the liposomes are depending on the lipid composition, size, surface charge, fluidity of bilayers, and preparation method [84]. The liposomes are suitable for delivery of therapeutics dual times due to non-covalent encapsulation of lipophobic drugs which are present in core and hydrophobic drugs which are present in bilayers. A cholesterol-poly(ethylene) glycol formulation was used to the delivery of sirolimus, a lipophilic multitargeted agent, whose poor water solubility is a barrier to effective topical delivery [85]. Particle size was very small, compared to liposomal preparations containing cholesterol, and size was uniformly distributed. Further applications on eye cell-based treatments can take benefit of this non-viral gene delivery Nanosystem vector. Nevertheless, it is known that *in vivo* drug release from nanoliposomes may be affected by environmental conditions making this phenomenon quite complex and, somehow, not stable nor effective [86]. Recently, there are 11 liposomal formulations accepted for medical use, being several under clinical and preclinical development [87].

Niosomes

Niosomes are lamellar (bilayer) structures, similar to liposomes, composed of non-ionic surfactant molecules surrounding an aqueous compartment [88]. In ocular delivery, lamellar structures are favored over vesicular system because chemically they are stable; raw materials are easily available and less expensive; unlike phospholipids, does not require any conditions and precautions for handling of surfactants, which make them more attractive for industrial manufacturing; they are biocompatible, biodegradable, and non-immunogenic [89].

Nanomicelles

Nanomicelles contains amphiphilic molecules, in aqueous media, they are self-assembled to form organized structure where the polar head groups are in connection with the surrounding solvent, and the hydrophobic single-tail regions are oriented toward the nanomicelle center. The self-assembly occurs at concentrations greater than the critical micelle concentration [4]. Nanomicelles are similar to liposomes, whereas liposomes are composed of lipid bilayers and nanomicelles are made of monolayers [90]. In ocular drug delivery, nanomicelles offer unique advantages due to their nanoscale size and permeation over ocular epithelia is increased with no irritation. Nanomicelles can be formed with either: (1) Surfactants like anionic surfactants (e.g., sodium dodecyl sulfate), non-ionic surfactants (e.g., n-dodecyl tetraethylenemonoether), and cationic surfactant (e.g., dodecyl trimethylammonium bromide) or (2) polymeric systems [91]. The sustained dexamethasone delivery from nanomicelles for *in vitro* transscleral iontophoresis was investigated using a mixed micellar solution constituted by mixed and simple micelles prepared with addition of sodium taurocholate alone along with egg lecithin [92]. The nanomicelle preparation method was optimized focusing the effect of drug-polymer interaction on drug solubilization in nanomicelle core, in order to achieve higher solubility of dexamethasone (>1 mg/mL). These results suggest that this nanomicellar formulation may be able to provide therapeutic levels of dexamethasone and other hydrophobic anti-inflammatory agents to the back of the eye subsequent topical administration, such as for the treatment of uveitis. Future improvements on this formulation are planned to study the effect of nanomicelle size on transport across the excised rabbit sclera aiming the delivery of drugs to the intermediate and posterior eye segments following topical administration [93].

Nanoemulsions

Nanoemulsions is an oil-in-water emulsions, in which droplets consisting of lipid monolayer enclosing liquid lipid core is formed. These structures are stabilized by the use of surfactants, which, along with the small size of nanoemulsions, provide increased membrane permeability, thus permeation is higher in the deeper layers of ocular structure and facilitated drug uptake. Hence, these systems offer a faster therapeutic action using smaller doses which means fewer ocular side effects and less applications per day, enhancing patient compliance [94]. Nevertheless, nanoemulsions are not suitable for sustained drug release [95]. The *in situ*-forming gels are polymeric solutions that undergo gelation after instillation in the eye because of the phase transition properties of polymers [96]. Thus, by incorporating a nanoemulsion into an *in situ*-forming gel, an increase in the residence time of nanoemulsion in eyes, improving the therapeutic performance of the drug, may be achieved. For this purpose, an *in situ* poloxamer-based nanoemulsion gel of loteprednol etabonate, an ester-based corticosteroid used for topical management of several ocular inflammatory diseases, and inflammation after cataract surgery, was developed to upgrade the performance of this drug relatively to conventional eye suspensions [97]. Polymeric NPs are colloidal particles able to encapsulate (dissolved or dispersed) bioactive or drug molecules, including chemotherapeutic agents, proteins, and nucleic acid, for biomedical application [98]. Light-responsive NPs were formulated based in a far ultraviolet light-sensitive polymer 57 to encapsulate a small molecule angiogenesis inhibitor, nintedanib (BIBF 1120). Furthermore, this light-responsive NPs maintained drug release ability and angiogenesis inhibition 10 weeks after the implantation. This work demonstrated a promising clinical significance of this nanosystem for intravitreal drug delivery [99].

Nanogels

Nanogels are also called as hydrogels made of nanoscale system with lipophobic polymers (e.g., nisopropylacrylamide and 2-hydroxyl methacrylate-lactide-dextran macromer), directly loaded with the drug, both hydrophilic and hydrophobic drugs. The kinetics for the release of administered drug from nanogels can be controlled through degradation rate of the cross-links and through peripheral stimuli such as pH and temperature [90]. Previously described nanogels were found to be able to bypass the ocular biological barriers, and thus to be used as intraocular drug delivery carriers and deliver drugs to the retina [100]. More recently, nanogels presenting promising properties for ocular drug delivery and constituting viable alternatives to conventional eye drops for the treatment of ocular diseases were reported [101].

Cyclodextrins (CD)

Nanosystems based on CD are capable of delivering the drugs from the surface of eye into its posterior segment [102]. The molecule has a water-soluble hydrophilic exterior, and an apolar cavity that provides a hydrophobic matrix capable of hosting a wide range of guest molecules, ranging from polar molecules to a polar molecule [103]. CD (cyclic oligosaccharides, CDs) have been proposed as a new attractive biomaterial to obtain hydrogels, combining both, the favorable property of CDs to form inclusion complexes and the swelling behavior of hydrogels [104]. The potential use of a CD-based nanosystem for enhanced stability, efficacy in the treatment of ocular allergic conjunctivitis, and ocular bioavailability of loteprednol etabonate were described recently [105]. In this study, the authors prepared complexes of loteprednol etabonate with each of hydroxypropyl- β -CD and β -CD. These complexes were then incorporated into different ophthalmic preparations, namely, gels, eye drops, and ocuserts based on hydroxypropyl methylcellulose, methylcellulose, and sodium alginate. It was found that higher drug release was obtained from the hydroxypropyl- β -CD complex. Regarding stability, anti-inflammatory activity against allergic conjunctivitis and bioavailability in rabbits' eyes, more satisfactory results were obtained with hydroxypropyl methylcellulose-based formulations with the hydroxypropyl- β -CD complex. It is also important to mention that cyclodextrin derivatives-based therapies *per se* are currently a very promising route of intervention for ocular diseases [106].

Dendrimers

Dendrimers are highly branched, star-like, typically water soluble, chemically tunable macromolecule systems with three components, namely, (1) a central core, (2) an exterior surface with the functional surface groups, and (3) an interior dendritic structure. Dendrimers are mainly prepared from polyamidoamine (PAMAM). The efficiency of PAMAM dendrimer in DNA delivery, has been shown to be improved on by partial PEGylation, acetylation, and alkylation [107]. Drugs are also being captured in dendrimer network through hydrogen bonds, interaction of ions, and conjugated through covalent bonds or hydrophobic interactions [90]. Dendrimers can able to provide a sustainable delivery of drug to posterior segment. Nonetheless, their cytotoxicity, which depends on the functional group, seems to be a limitation. In previous studies using the intravitreal management of PAMAM dendrimers in animal models of neuroinflammation, dendrimers were selectively localized in the activated microglia, suggesting that they are appropriate deliver drug systems to these cells and hence potentially useful in the treatment of retinal neuroinflammation for a sustained period [108]. PAMAM dendrimers by cationic and anionic functional groups are used to prepare different formulations to examine their effect on ocular delivery followed by topical and subconjunctival applications, less invasive than intravitreal route. Authors observed an improved concentration of the dexamethasone within the retina, after topical or subconjunctival application of dexamethasone-PAMAM complex formulations. Some of these complexes also enhanced *in vitro* permeability and *in vivo* ocular distribution of dexamethasone, in addition to *ex vivo* transport through both the sclera tissues and cornea of dexamethasone. Accordingly, these nanosystems seem to be capable delivery systems for dexamethasone to retina by topical application, since this is safest and relaxed ocular route for application [109].

Quantum dots (QDs)

QDs have a significant influence on research in many different fields such as chemical, physical, and biological sciences. These are semiconductor nanocrystals whose measurements are in the range of 2-6 nm [110]. The QDs consist of heavy metal core (e.g., cadmium selenide), with a transitional unreactive zinc sulfide shell and an outer coating of various bioactive molecules, aiming to definite application. Their composition and small size grant unique fluorescent and optical properties that cannot be attained with traditional fluorophores: (1) Higher signal-to-noise ratio and minimal photobleaching and (2) broad absorption spectra but actual narrow emission spectra [111]. Thus, the main application that is known for QDs, namely in ophthalmology, is as imaging agents for labeling, for instance, neurons, glia, and endothelial cells in retinal capillaries [112]. Another approach involving QDs that has been under development is the neuronal activation with optical stimulation of photoresponsive surfaces. Recently, it was reported that it has facility to transport electrical stimulus to retinal cells by silicon-based QDs in retinal degeneration [113]. Therefore, improvements need to be done in drug loading, release, biodistribution, toxicity, ocular irritation, and patient compliance.

CONCLUSION

Concerning about the ocular diseases such as DR and DME, the common treatments are intravitreal anti-VEGF drugs and surgery. The significant number of drugs which are deliver to the posterior segment of the eye like intravitreal injections are needed. Nanotechnology is the contemporary topic because of its potential applications in many fields such as biology and medicine. For the posterior segments diseases, nanometer-scaled particles can be used. Nanotechnology seem to be a promising route since they are able to bypass the blood-retinal barrier, reducing the treatment administration, and remains longer period in the eye. Nanotechnology described as a very effective therapy of posterior eye segment diseases like DR. In this review, the current strategies for the treatment of DR using nanotechnology-based system include nanoparticles, nanoemulsions, nanogels, CD, QDs, dendrimers, and nanomicelles are explained.

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AUTHOR CONTRIBUTIONS

The first author has collected and compiled the information. The second author has reviewed the manuscript.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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