Unveiling the Nanotechnology-Based Drug Delivery Systems and Patent Literature for Diabetic Retinopathy

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Abstract: Diabetes mellitus is a principal reason for globally developing chronic microvascular disorders defined as diabetic retinopathy (DR). Proliferative retinopathy and non-proliferative retinopathy are the two types of DR. Long-term diabetes, and poor blood sugar and arterial blood pressure regulation are the key risk factors for the onset and advancement of DR. A variety of biochemical pathways are involved in the pathogenesis of DR, which includes increased polyol pathway fluxes, advanced glycation end product growth, protein kinase C isoform activation, and increased hexosamine pathway flux. The varieties of cells are involved in diabetic retinopathy, including glial cells, retinal ganglion cells, endothelial cells, and pericytes. Surgical treatment of DR includes laser treatment, panretinal photocoagulation, focal laser photocoagulation, and vitrectomy surgery. The systemic treatment of DR includes glycemic management and control of blood pressure and hyperlipidemia. Nanotechnology-based formulations like nanoparticles, polymeric nanomicelles, and nanocarrier composite, and various patented formulations have been investigated for the treatment of DR.

Keywords: diabetes mellitus; diabetic retinopathy; laser treatment; panretinal photocoagulation; vitrectomy surgery; nanotechnology.

1. Introduction

Diabetes mellitus (DM) is a leading cause of diabetic retinopathy (DR) and promptly developing chronic diseases worldwide. DR is the microvascular complication of diabetes, continues to be the leading cause of acquired vision loss in middle-aged and, therefore, economically involved people around the world [1]. With the prevalence of diabetes, the number of people with DR and vision-threatening DR (VTDR), which involves extreme non-proliferative DR (NPDR) and proliferative DR (PDR), is expected to increase to 191 million and 56.3 million by 2030. The enhanced vascular permeation and capillary blockage are imperative causes that lead to alteration in the vasculature of the retina in NPDR, which characterize the initial phase of DR. Fundus photography may perhaps diagnose retinal disorders like micro-aneurysms, hemorrhages, and hard exudates. PDR is a progressive stage and is distinguished by neovascularization. Patients can experience severe vision loss if the dysfunctional vessels bleed into the vitreous or if the tractional retinal detachment is there. Diabetic macular edema (DME) is the most frequent cause of vision loss in DR patients. DME is marked by swelling or thickening of the macula as a result of sub- and intra-retinal fluid...
deposition in the macula attributable to a weakening of the blood-retinal barrier. DME may happen at whichever DR stage, resulting in visual deformations and loss of sight acuity [2-5].

2. Risk Considerations for Diabetic Retinopathy

The risk parameters for DR can be widely categorized into two types (Figures 1 and 2). Hyperglycemia, hypertension, hyperlipidemia, and obesity are modifiable risk factors. Non-modifiable risk factors for DR growth and development include diabetes duration, puberty, and pregnancy [6-11].

![Figure 1. Modifiable risk factors and interventions in diabetic retinopathy.](image1)

![Figure 2. Non-modifiable risk factors and interference in diabetic retinopathy.](image2)
3. Clinical Pathophysiology of Diabetic Retinopathy

BRB malfunctioning generally occurs in diabetic retinopathy (DR). The seepage of blood components within the neuropile of the retina happens concurrently in consequence of weakening of an internal BRB, which recurrently results in diabetic macular edema. VEGF has been linked to blood vessel leakage and serves as a persuasive vascular permeability factor [12]. The increased expression of collagen, fibronectin, and laminin contributes to improvements in the microenvironmental conditions mediating development and longevity, including the role of pericytes and endothelial cells, which is thought to cause thickening of the vascular basement membrane in DR [13]. The lack of pericyte function is core to the pathophysiology of degenerative capillaries seen in DR. Pericytes are essential for normal retinal function because they help angiogenic endothelial cells differentiate, migrate, and proliferate [14]. Pericyte deficiency and the appearance of "pericyte ghosts" are thus considered important histopathological features of DR [15].

4. Molecular Mechanisms for Diabetes Associated Retinopathy

The most common reason for microvascular problems is hyperglycemia. The induction of chronic, low-grade inflammatory signaling and metabolic instability caused by high glucose play a key role in the development of DR. Hemorrhages, microaneurysms, cotton-wool spots, lipid exudates, macular edema, capillary occlusion, and eventually neovascularization are all clinical symptoms of retinopathy [16]. The pathogenesis of DR involves a number of biochemical pathways like polyol flux, advanced glycation end (AGE) product development, oxidative stress, and activation of protein kinase C (PKC). Figure 3 represents sequential pathophysiology leading to retinal neovascularization and eventually vision loss [17-25].

![Figure 3](https://biointerfaceresearch.com/)
4.1. Advanced glycation end product (AGEs) formation.

The provocative occurrence for the formation of AGEs is intracellular hyperglycemia, which is present in higher concentrations in diabetic retinal blood vessels [26] and glomeruli [27]. They are formed when intracellular glucose is auto-oxidized to glyoxal and further decomposed and fragmented to methylglyoxal, which reacts with amino residues of intra- and extracellular proteins to produce AGEs [28,29].

4.2. Polyol pathway.

Hyperglycemia causes an increase in the conversion of glucose to sorbitol, as well as a reduction in NADPH (nicotinamide adenine dinucleotide phosphate). Sorbitol oxygenation is thought to boost the ratio of NADH and NAD+ within the cytosol, which causes inhibition of glyceraldehyde-3-aldehyde dehydrogenase (GAPDH) activity. This results in higher levels of triose phosphate, which promotes the production of methylglyoxal, AGE precursor, and diacylglycerol, therefore triggering PKC [30]. Moreover, as NADPH is needed for the regeneration of reduced glutathione, therefore, reducing glucose to sorbitol absorbs NADPH which causes potential exacerbation of oxidative stress.

4.3. Oxidative stress.

The hyperglycemia causes an increase in reactive oxygen species (ROS) activities which lead to activation of poly-(ADP-ribose) polymerase (PARP) enzyme. This causes a decrease in GAPDH activity which accelerates methylglyoxal formation and AGEs production [31,32].

4.4. Protein kinase C (PKC) activation.

Excess glucose flux through the glycolysis pathway is also a result of hyperglycemia. The PKC pathway is activated due to this increase in diacylglycerol synthesis [33-35]. High expression of PKC in DR causes overexpression of NADPH oxidase in vascular endothelial cells, which aggravate oxidative stresses and ROS activities [36].

5. Cells Involved in Diabetic Retinopathy

The cells which are implicated in the diabetic retinopathy process are shown in Figure 4. Glial cells, retinal ganglion cells (RGCs), and other neuronal cells make up the neural unit [37]. Energy balance and synaptic transfer modulation are made possible by their close relationship. They also play a role in producing BRBs, which have high selectivity as a controlling barrier [38].

5.1. Role of glial cells and retinal ganglion cells in diabetic retinopathy.

Glial cells comprise astrocytes, microglia, and muller cells, which play a potential role in preserving retinal homeostasis. They play a role in phagocytosis of neuronal fragments, metabolism and in releasing numerous transmitters, dietary factors, potassium ion uptake, and imparts structural integrity [39]. RGCs are the only efferent neuron that can transfer sensory input to the brain via retina since their cell bodies are situated in the ganglion cell layer and their dendrites are located in multiple inner plexiform layers to interact with different presynaptic neurons [40-43].
RGC deficiency is a common pathological characteristic in diabetic retinal neurodegeneration [44], and may contribute to early neurovascular unit disturbance [45,46]. One of the main mechanisms of RGC deficiency is the aggregation of ROSs and oxidative stress that can be exacerbated by the diabetic environment [47-50].

5.2. Astrocytes for upholding blood-retinal-barrier integrity.

Astrocytes comprise the innermost coating of the retina and play a fundamental function in maintaining BRB integrity. The majority of these cells are found in vascular regions of the retina, while avascular zones have fewer astrocytes. Astrocytes appear to play a role in neuronal signal transduction, ion homeostasis and are an important component of BRB. Stimulated astrocytes lead to proliferation leading to hypertrophic conditions and taking on a stellate morphology. Astrocytes, T-cells, microglia, and monocytes/macrophages are stimulated and develop several pro-inflammatory cytokines and chemokines in the diabetic environment, which is marked by dysmetabolic and hypoxic conditions augmenting the inflammatory response [51]. Astrocytes are among key producers of vascular endothelial growth factors (VEGF). Reactive gliosis increases the expression of the glial fibrillary acidic protein (GFAP) inside astrocytes. After that, the lack of astrocytes causes inner BRB deficiency and retinal vascular leakage [52].

5.3. Involvement of microglia and Muller cells in diabetic retinopathy.

Microglia, the retina’s resident inflammatory cells, plays a role in neural network production and maintenance in addition to immunologic action. Microglia cells are present practically in each layer of a normal retina. The subdivisions of microglia remained aligned along optic nerve fibers, but this kind of alignment gets disordered in DM [53]. During the activated state, the distribution and composition of microglia change in a variety of pathological conditions. Microglia cells use phagocytic and cytotoxic pathways, similar to macrophages, to degrade foreign materials. Based on the intensity and type of tissue dysfunction or inflammation, these cells transform from resting to active [54]. Enhanced perivascular microglia cells settle inside the plexiform of the retina—microglia cells gathered in large numbers in ischemic areas and newly dilated blood vessels in PDR. Microglia and
RGC interaction can also be observed in epiretinal membranes [55]. The retina is inflamed for a long time as a result of DR. The chronic inflammation raises expression of interleukin-6 (IL-6) in ocular fluids of DR patients, which leads to interaction among microglia and retinal pigment epithelium (RPE), causing outer BRB disturbance [56,57]. IL-6 increases the VEGF expression in RPE, which causes mobilization of microglia to RPE ensuing larger secretion of tumor necrosis factor (TNF)-α, which contributes directly to oBRB disruption [58,59].

Muller cells cover the whole retina from the interior side, restraining membrane from the outside makes it a perfect supervisor for controlling pathological and physiological responses of retinal neurons as well as vasculature [39,60]. Muller cells can serve their role in retinal metabolism, functions, repair, and defense via removing metabolic wastes, supplying nutrition, and releasing neurotransmitters engaged in vision cycles, controlling BRB activity, and modulating innate immunity [61]. Muller cells serve as the center of the neurovascular complex, where nutrients and oxygen are exchanged. Furthermore, Muller cells provide the eye with the majority of its dietary support [62]. Retinoschisis is caused by the selective removal of Muller cells from the retina, implying that these can provide elasticity to the retina [63,64]. During DR, the interaction occurs between Muller cells as well as vascular unit is disrupted, and they develop significant quantities of factors, some of which have a protective effect, while others, such as VEGF, exacerbate the problem [65]. The up-regulation of VEGF occurs during preliminary phases of DR and exerts neuroprotective outcomes. Muller cells secrete VEGF, which improves the blood supply and contributes to BRB collapse during DM [66]. These cells develop dynamic, specific, and reactive phenotypes in DR, which generates a persistent inflammatory environment [67]. Hypoxia-inducible factor-1 rises in vitreous, which stimulates Muller cells, ultimately creating the chronic inflammatory environment and leading to accumulation and overexpression of fibroblast growth factor, ultimately leading to retinal fibrosis and pathological neovascularization [68].

5.4. Pericytes and endothelial cells: the fundamental vascular units.

Pericytes are blood microvessels that exhibit an important role in angiogenesis, blood flow regulation, and BRB integrity [69,70]. Pericytes insert themselves in the endothelial basal layer, develop structured bonding with ECs, and contribute to platelet-derived growth factor receptor signal transduction [71]. Hyperglycemia causes depletion of this signaling system, resulting in pericytes apoptosis, resulting in a lack of structural support for retinal capillaries and leading to a localized failure of the vascular membrane [72].

Amongst the most significant components of inner BRB are close dynamic connections of endothelial cells (ECs). The endothelial form in the retina differs greatly depending on the type of vessel. ECs are a complex, semi-selective barrier that regulates fluid and macromolecule transfer between the blood and the interstitium and regulates inflammatory reaction and angiogenesis [73]. Over-expression of many cytokines, including TNF-α, VEGF, IL-6, with vascular cellular adhesion molecule-1 is linked to retinal microvascular dysfunction [74]. In high-glucose conditions, the expression of Toll-like receptors, which play an important role in modulating inflammatory responses, is dramatically increased in retinal ECs [75]. Retinal ischemia is caused by increased capillary occlusion, and hypoxia in DR induces an increase in VEGF levels, which facilitates pathological neovascularization. VEGF activates the receptors on ECs, promoting EC durability, multiplication, and porosity against VEGF sources, which are necessary steps in producing and maintaining blood vessels [76-80].
6. Treatment Strategies for Diabetic Retinopathy

The classification of various treatment strategies for DR includes numerous surgical procedures, systemic therapies, and nanotechnology-based strategies, as described in Figure 5.

6.1. Surgical management.


Vitrectomy is a surgical procedure that removes the vitreous gel from the eye. A translucent jelly-like fluid called vitreous holds about two-thirds of the eye between the lens and the retina. Vitrectomy stops more vitreous hemorrhage by destroying the dysfunctional blood vessels that cause bleeding as well as the scar tissue and avoiding progressive vision loss [81-83]. The success rate of vitrectomy surgery is very high. Any surgical operation carries the risk of complications such as vitreous hemorrhage, cancer, retinal tears, cataract progression, and retinal detachment [84,85].

6.1.2. Laser photocoagulation and panretinal photocoagulation (PRP).

Laser photocoagulation has been shown to be a successful therapy for maintaining eyesight as well as decreasing the likelihood of vision loss from DR over the last few decades [86]. The primary goal of laser photocoagulation in the retina should be the reversal of dysfunctional capillaries and angiogenesis. An argon laser can be used with two different laser techniques. PRP is a kind of laser therapy that is utilized to treat anomalous blood capillaries in either retina or drainage configuration inside the eyeball. It entails tissue oxygenation and overturns hypoxia [87].
6.1.3. Focal laser photocoagulation.

Individually bleeding blood vessels in the eye are targeted with focal laser therapy. The retina was treated with slighter intense and less laser energy spots in this method [86]. The laser therapy takes between 15-20 minutes. Laser therapy is not approved for slight to severe non-proliferative DR. While laser therapy will not be sufficient to replace lost visual, it is meant to avoid further vision loss. While laser therapy has been shown to improve or stabilize visual perception if used properly, effectively, and well-timed, however, this method has several adverse consequences like moderate vision failure and diminished night and color visualization [88], decreased contrast sensitivity [89], and decreased ability to concentrate [90].


Few experimental therapies for DR have shown promising outcomes in animals and/or human patients. Any biochemical mechanisms linked to hyperglycemia and DR are inhibited by the medications. A variety of targets must be met in order to lower a sufferer's chance of developing retinopathy. Topical, systemic, and local administration of eye medications is some options (intravitreal, subretinal, subconjunctival, sub-tendon, peribulbar, and retrobulbar routes). The growth and progression of DR may be slowed by controlling systemic glucose [91-93], blood pressure [94-98], and lipid levels [99-102]. However, these medicines used for such treatments have severe side effects.

6.3. Nanotechnology-based therapeutic approaches.

Nanotechnology performs together at atomic and molecular levels and has been proficient in science and technology for therapeutics, diagnosis [103,104], and biomedical application [105,106]. Nowadays, this has been gaining enormous significance in the field of pharmaceuticals in various routes like oral, ocular, inhalable, parenteral, rectal, and topical [107] and types of drug delivery systems like immediate, sustained, and controlled drug delivery [108]. It has the prospective to unlock innovative strategies for the treatment of diabetic retinopathy [109-112]. Nanomedicines incorporate nanoparticles to achieve superior drug targeting, diminished toxicity, and improved efficiency of therapeutic or diagnostic agents. Polymeric nanoparticles are sub-micron carriers having approximately 1-100 nm scale comprised of biodegradable and biocompatible polymers and are considered strategic tools for specific drug delivery at the site of action and advanced bioavailability [110-113]. Polymeric nanomicelles are produced self-assembling amphiphilic polymers and designate as a pioneering tool to conquer numerous problems associated with drug delivery from poorly permeable drugs across biological barriers, such as in ocular drug delivery for diabetic patients retinopathy management [114,115]. Polymeric biodegradable nanocomposites are heterogeneous materials that are synthesized using the blends of biocompatible and biodegradable polymers at a nanometric scale [116,117]. The application of nanotechnology approaches like nanoparticles, polymeric nanomicelles, and polymeric nanocarrier composite in drug therapeutics have been investigated by several researchers and have discovered their superior efficacy with an outcome of improved treatment of DR as summarized in Table 1.
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database and
diagnosis of DR and associated problems have been searched from the PATENTSCOPE
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Formulations comprising a compound that for diabetic
Advan
topical ophthalmic peptide formulation treating diabetic retinopathy
A novel formulation of 5
treating diabetic retinopathy

Traditional
Pharmaceutical composition and formulation for treatment of diabetic retinopathy
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nanoparticles have a
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α-Lipoic acid in soluplus® polymeric nanomicelles for the ocular treatment of diabetes-associated corneal diseases

Chitosan-sodium alginate-fatty acid nanocarrier composite for treatment of DR

Formulation of PPAR-gamma agonist as surface-modified polyactic acid-co-glycolic acid (PLGA) nanoparticles and concluded that pioglitazone loaded surface-modified PLGA nanoparticles have great potential to treat DR

Enhancement of scutellarin oral delivery efficacy by vitamin B12-modified amphiphilic chitosan derivatives for treatment type II diabetes induced-retinopathy

Intravitreal injection of bevacizumab-chitosan nanoparticles inhibited angiogenesis of DR. Research indicated that the intravitreal injection of bevacizumab inhibited the VEGF-expression in the retina, and bevacizumab-chitosan nanoparticles have a longer duration of action

7. Patents Reported for Treatment and Diagnosis of Diabetic Retinopathy

The recent patents based on various herbal and synthetic formulations for treatment or diagnosis of DR and associated problems have been searched from the PATENTSCOPE database and summarized in Table 2. This patent literature indicates that continuous efforts are under process for exploring several additional therapeutic measures for DR.

Table 1. Nano-based formulations investigated for the treatment of diabetic retinopathy.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Method</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenofibrate, poly(lactic-co-glycolic acid), Tween 80, dichloromethane</td>
<td>Emulsification</td>
<td>[111]</td>
</tr>
<tr>
<td>Triamcinolone acetonide, Polycaprolactone, pluronic® F-68, , Poly (l, l-lactide-co-glycolide)</td>
<td>Nanoprecipitation</td>
<td>[112]</td>
</tr>
<tr>
<td>Celecoxib, chitosan, sodium alginate, poly-ε-caprolactone (PCL), poly-L-lactide, and poly-D,L-lactide-co-glycolide</td>
<td>Emulsification solvent diffusion</td>
<td>[113]</td>
</tr>
<tr>
<td>α-Lipoic acid (ALA), sodium dioctylsulfosuccinate, Soluplus</td>
<td>Freeze drying</td>
<td>[115]</td>
</tr>
<tr>
<td>Lutein, chitosan, oleic acid</td>
<td>Ionotropic gelation</td>
<td>[117]</td>
</tr>
<tr>
<td>Pioglitazone, dichloromethane, polysorbate 80, Polyvinyl alcohol and mannitol</td>
<td>Single emulsion solvent evaporation</td>
<td>[118]</td>
</tr>
<tr>
<td>Scutellarin, Chitosan, Deoxycholic acid, Vitamin B12</td>
<td>Self-assembly in aqueous medium</td>
<td>[119]</td>
</tr>
<tr>
<td>Bevacizumab, chitosan</td>
<td>Emulsification evaporation</td>
<td>[120]</td>
</tr>
</tbody>
</table>

Table 2. Patented formulations for diabetic retinopathy.

<table>
<thead>
<tr>
<th>Patent title</th>
<th>Patent number</th>
<th>Applicant</th>
<th>Publication date</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marker for diagnosing diabetic retinopathy and use thereof</td>
<td>WO2014003343</td>
<td>LG Electronics Inc.</td>
<td>03.04.2014</td>
<td>[123]</td>
</tr>
<tr>
<td>Traditional Chinese medicine formulation for treating diabetic retinopathy</td>
<td>CN106309841</td>
<td>Wang Yongchao</td>
<td>01.01.2017</td>
<td>[124]</td>
</tr>
<tr>
<td>A novel formulation of 5-fluorouracil for treating diabetic retinopathy</td>
<td>IN201911049029</td>
<td>Lovely Professional University</td>
<td>20.12.2019</td>
<td>[125]</td>
</tr>
<tr>
<td>Topical ophthalmic peptide formulation</td>
<td>NZ600627</td>
<td>BCN Peptides S.A.</td>
<td>29.08.2014</td>
<td>[126]</td>
</tr>
<tr>
<td>Formulations comprising a compound that activates tie-2 and their use in treating ocular diseases</td>
<td>GB2540638</td>
<td>Aerpio Therapeutics Inc</td>
<td>25.01.2017</td>
<td>[128]</td>
</tr>
</tbody>
</table>
8. Conclusions

Diabetic retinopathy is a worldwide rising chronic microvascular disorder commonly causes vision loss in affected individuals. The identified risk factors for DR include long-term DM, and high arterial blood pressure. The four major biochemical pathways for DR have been identified: increased polyol pathway fluxes, advanced glycation end product growth, protein kinase C isoform activation, and increased hexosamine pathway flux. The surgical treatment strategies for DR include laser treatment, panretinal photocoagulation, focal laser photocoagulation and vitrectomy surgery. Furthermore, the systemic treatment approaches include management of glycemic, blood pressure, and hyperlipidemia. Nowadays, the remarkable alternatives for the treatment of DR are based on nano-based formulations like nanoparticles, polymeric nanomicelles, and nanocarrier composite. Based on investigations by several researchers summarized in this review, it has been conclusively established that DR can be treated better with nanotechnology-based approaches.

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Conflict of Interest

The authors declare no conflict of interest.
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117. Toragall, V.B.; Baskarn, V. Chitosan-sodium alginate-fatty acid nanocarrier composite: lutein bioavailability, absorption pharmacokinetics in diabetic rat and protection of retinal cells against H2O2 induced oxidative stress in vitro. *2020, 254, 117409, https://doi.org/10.21203/rs.3.rs.51890/v1.*


