CURRENT MEASURES AGAINST OPHTHALMIC COMPLICATIONS OF DIABETES MELLITUS-A SHORT REVIEW

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder, whose prevalence is predicted to rise shortly. The present review focuses on the various ocular complications associated with DM, and the various ophthalmic formulation approaches developed to treat the same. Diabetic macular edema (DME), diabetic retinopathy, cataracts, and glaucoma are some of the major vision-threatening complications linked to DM. The ocular route of drug delivery has undergone several advancements in recent decades, the introduction of various novel drug delivery systems (DDS), various modifications in the existing formulation approaches, development of custom-designed personalized medications, being some of the major developments introduced in the field of ocular drug delivery. Due to the application of state-of-the-art technologies in the field of innovations related to ocular DDS, patients have been immensely benefited by the current modes of ocular treatment imparting fewer side effects, enhanced penetration, sustained drug effect, and so on. The present review includes and emphasizes the gradual development that has occurred from the conventional ophthalmic dosage forms to the currently reported novel ocular drug delivery approaches along with the related clinical research works.

Keywords: Ophthalmic formulations, Diabetes mellitus, Ocular complications, Cataracts, Glaucoma, Diabetic retinopathy, Macular edema

INTRODUCTION

Diabetes has affected approximately 285 million people around the world to date. According to the International Diabetes Federation, this number is predicted to rise to 439 million by 2030 [1]. In 1997, the American Diabetes Association (ADA) has reported the prevalence of DM in the US has been reported during the last few decades. They are as follows:

- **Open-angle glaucoma (OAG)**: Diabetes mellitus has been linked to an increased risk of OAG in various studies. The risk factors associated with DM causing OAG include the development of high intraocular pressure (IOP), vascular abnormalities, such as malformed optic nerve vessels, and oxidative damages to the eye. It has been reported that the probability of developing OAG increases with the uncontrolled prolongation of type 2 DM. The disease has been reported to be painless, persistent, and asymptomatic at its early stages of development. In the advanced stages of the disease, the resistance imparted by the developed trabecular meshwork to the aqueous outflow within the eye, gradually increases, resulting in a gradual increase in IOP [10].

- **Closed-angle glaucoma (CAG)**: In CAG, the access to the drainage route from the eye is obstructed, resulting in the development of severe local pain, redness of the eye, nausea, and hike in IOP [10, 11].

- **Neovascular glaucoma (NVG)**: This type of glaucoma is associated with the development of new blood vessels in the eye, obstructing the normal flow of ophthalmic fluid, thereby causing a rise in intraocular fluid pressure [12]. It is quite difficult to treat this type of condition of the eye by usual treatment with medicines, thus categorizing NVG as an uncommon kind of glaucoma [10].

**Diabetic complications associated with DM**

**Diabetic cataracts**

This disease is the most prevalent cause of blindness in the world, as it arises when the natural lens of the eyes becomes obscured, and hence, light does not move clearly through the latter, with the development of cataracts, finally resulting in loss of vision, if not treated at the early stage of its development. The lens clouding and development of cataracts are caused by unwanted protein aggregation on the lens due to prolonged, and uncontrolled persistence of DM [6, 7]. The diabetics are reported to be five times more prone to get cataracts, especially at a young age. As the duration of diabetes increases, the chance of the development of diabetic cataracts also increases [8].

**Glaucoma**

The term glaucoma refers to a group of eye illnesses that affects the optic nerves. Diabetic patients are twice as likely to develop glaucoma, which can cause loss of vision, and the development of blindness, if not treated early [9]. Various types of glaucoma have been reported during the last few decades. They are as follows:

- **Open-angle glaucoma (OAG)**: Diabetics are reported to be five times more prone to get cataracts, especially at a young age. As the duration of diabetes increases, the chance of the development of diabetic cataracts also increases [8].

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Diabetic retinopathy

It is a common condition with diabetics, in which the blood vessels in the retina swell up, leak, or become completely obstructed due to impaired blood sugar regulation. There may also be the development of new ophthalmic blood vessels growing gradually on the surface of the retina [13].

Diabetic macular edema

Diabetic macular edema (DME) occurs when fluid accumulates on the retina, causing local swelling and distorted vision, ultimately resulting in permanent loss of vision. Diabetes-related vision loss can be averted in around 90% of instances, according to the Centres for Disease Control and Prevention (CDC) [4].

Thus, DM and its associated long-term ophthalmic complications have been the primary reasons for blindness for the last few decades, and surgical removal has been the only treatment available for the removal of diabetic cataracts [13, 14]. Recently, the development of various novel and targeted drug delivery approaches and custom-designed personalized medications has made it possible to delay and retard the process of development of various types of ocular complications resulting from DM [15].

Pathogenesis of ocular complications

Pathogenesis of diabetic cataracts

During prolonged DM, the enzymes aldose reductase, and sorbitol dehydrogenase, present in the ophthalmic lens, transform glucose into sorbitol, causing glutathione deficiency, resulting in the formation of cataracts [16]. The formation of AGE (advanced glycation end-products), and the activation of the polyol pathway help the ophthalmic cells to accumulate sorbitol [17]. Another mechanism of cataracts formation involves induction of lens protein oxidation, production of free radicals, and hydrogen peroxide [16].

It has been reported that three processes are involved in the formation of diabetic cataracts, viz, the polyol pathway, non-enzymatic glycation, and oxidation [18].

Polyol pathway

In the polyol pathway (Fig. 1), two enzymes are involved, viz, aldose reductase (AR), and sorbitol dehydrogenase (SDH). The former is responsible for the conversion of glucose to sorbitol, while the latter converts sorbitol to fructose. Osmotic, oxidative, glycation, and protein kinase-C (PKC) stresses are the principal cell-damaging effects of excessive intracellular glucose flux developed via the polyol pathway. The loss of NADPH, a co-factor in the reducing pathway, mediated by aldose reductase, is thought to produce oxidative stresses, resulting in a reduction in the antioxidant capacity of the cells [19]. Glycation of lens proteins is also caused by the increased glucose levels in the aqueous humor, which results in the generation of superoxide radicals (O2-) and advanced glycation end products (AGE) [20]. The advanced glycation end products then interact with the advanced glycation receptors and lens epithelial material [21]. The most prevalent antioxidant enzyme in the lens is superoxide dismutase (SOD), which breaks superoxide radicals (O2-) into H2O2 and O2 [22]. Another mechanism involved in the production of 3-deoxyglucose, a key precursor to the development of AGEs [23]. The sorbitol dehydrogenase enzyme enhances the elimination of dihydroxyacetone phosphate by increasing the NADH: NAD+ ratio, a precursor for conversion of diacylglycerol (DAG) to glycerol-3-phosphate, which can produce PKC stress [24, 25].

Non-enzymatic glycation

One of the well-known mechanisms implicated in diabetes cataracts with age, is non-enzymatic glycation, in which advanced glycation end products pile up, causing opacity of lens [26]. Advanced glycation is caused by a non-enzymatic interaction between excess glucose and proteins, which can result in the creation of superoxide radicals, and AGEs [27].

Oxidation

The effects of oxidative stress on diabetic lens fibers, generated by the free radicals, have been studied in several types of recent researches. There isn’t any proof, however, that the process of cataracts formation is initiated by these free radicals, but it rather accelerates and aggravates its growth. The aqueous humor of diabetics contains high levels of hydrogen peroxide (H2O2), which causes hydroxyl radicals (OH) to develop after entering the lens through a mechanism known as Fenton reactions [28]. Another component that is increasingly deposited on diabetic lenses, and aqueous humor, is the free radical nitric oxide (NO) Because of its oxidizing properties, it can cause an increase in the formation of peroxynitrite, which further causes cell damage [29].

Pathogenesis of glaucoma

The secretion of aqueous humor from the ciliary body, and drainage of the former through two distinct routes, the trabecular meshwork and the uveal scleral outflow pathway, regulate the intraocular pressure (the pressure inside the eye), the increase of which has been the key feature in the development of glaucoma. Diabetes mellitus also has been linked to a variety of glaucoma conditions, including open-angle glaucoma (OAG), angle-closure glaucoma (CAG), and neovascular glaucoma (NVG) [30, 31].

Several common links have been established and explained to contribute to the possible correlation between diabetes and glaucoma [32]. Diabetes or hyperglycemia is associated with lipid
glycation, and lipid metabolism disorders, which can lead to increased intraocular pressure (IOP), vascular dysfunction, oxidative damage, excitotoxic damage, and so on (fig. 2). The malfunction, and death of retinal ganglion cells (RGCs) in glaucomatous eyes, cause permanent loss of vision [33, 34]. Vascular dysregulation, as well as elevation of nitric oxide, a potent vasodilator, have been observed in both the disorders, diabetes eye disease, and glaucoma. Nitric oxide is not only a well-known regulator of vascular tone but also causes apoptosis [35]. Furthermore, it has been reported that reactive nitrogen species play a significant role in inflammatory reactions through oxidative stresses, resulting in the damage of optic nerves [36]. The elevation of protein kinase C may also be linked to matrix metalloprotease trabecular meshwork abnormalities, which may result in impaired aqueous outflow and higher IOP [32]. Furthermore, overexpression of the metalloprotease-9 matrix has been linked to structural abnormalities in the optic nerve head in diabetic individuals, suggesting yet another probable link between diabetes, and glaucoma [37, 38].

Pathogenesis of diabetic retinopathy and diabetic macular edema

As described in (fig. 3), hyperglycemia leads to the generation of free radicals (oxidative stress), activation of protein kinase C, and formation of advanced glycation end products (AGEs), which may trigger the development of DR, and maculopathy [39]. Disruption of the blood-retinal barrier (BRB) is important in the pathogenesis of diabetic macular edema; the altered vitreomacular interface may also play a role in the progression of macular edema. Other factors connected to the progression of DME, include hypoxia, reduced blood flow, retinal ischemia, and associated inflammation [40]. Inflammatory processes are upregulated within the diabetic retinal vasculature, such as increase in the vascular endothelial growth factor (VEGF) levels, endothelial dysfunction, leukocyte adhesion, decrease in the levels of pigment epithelium-derived factor (PDF), and increased development of protein kinase C, causing BRB breakdown, and increased vascular permeability [40-42]. Historically, DR has been thought to be caused by retinal capillary microvascular injury. However, there is mounting evidence that retinal neural failure occurs before vascular problems [43]. Neurodegeneration, neuroinflammation, and activation of RAS (renin-angiotensin system) have been identified as the important factors responsible for the development of DR [44]. Furthermore, both the stress in the endoplasmic reticulum (ER) and the abnormal production of mitochondria-derived reactive oxygen species play an important role in the development of DR [45]. As the unfolded protein response is unable to reduce ER stress, it contributes to increased oxidative damage, inflammation, and apoptosis in the ER lumen. All these are likely to play a significant role in the development of a variety of neuronal diseases in the brain, and retina, thereby aggravating DR from its early stage [46].
Prevention and treatment of ocular complications

Prevention and treatment of diabetic cataracts

The following categories of dietary phytochemicals and synthetic compounds are generally used to obtain the desired therapeutic effects against diabetic cataracts. These compounds are used as low-cost, non-surgical cataract preventive measures, which are the need of the day (fig. 4) [47]. The conventional and novel drugs available for ocular complications have been depicted in tables 1 and 2, respectively.

**Fig. 4: Treatment available for diabetic cataracts [7, 49, 51]**

**Aldose reductase inhibitors (ARIs)**

Some promising ARIs with significant potential for the treatment of diabetic cataracts have been discovered in recent decades [48, 49]. The ongoing researches in the field of natural products have revealed evidence confirming that certain bioactive compounds can help to slow or stop diabetic problems from getting worse. These compounds also have significant in vitro as well as in vivo inhibitory effects on aldose reductase, the enzyme responsible for the conversion of glucose to sorbitol, resulting in the deposition of diabetic cataracts.

The ARIs derived from natural sources include a range of structurally distinct compounds mostly belonging to the flavonoid category [50, 51]. Quercetin and genistein are two examples of such flavonoid compounds that slow the progression of the development of diabetic cataracts [51, 52]. Extracts from various indigenous herbs, often known as Indian Herbal Diabecona, such as Ocimum sanctum, Withania somnifera, Curcuma longa, and Azadirachta indica, have shown to support the ARIs role in preventing and delaying the progression of cataracts [53, 54]. Moreover, some synthetic ARIs, viz., alrestatin, imprestat, ponalrestat, epalrestat, zenerstat, and lidorestat have also been reported for their positive effects on the prevention of diabetic cataracts [55]. Amongst these, only epalrestat has been introduced into the market for the treatment of diabetic neuropathy [56]. These findings offer the basis for the possible potential prophylactic as well as therapeutic use of ARIs against diabetic cataracts [57].

**Antioxidant drugs and ROS scavengers**

Antioxidant drugs and ROS scavengers may be useful since oxidative damage occurs indirectly as a result of polyol accumulation during the formation of diabetic cataracts. A variety of antioxidants have been found to delay cataracts formation in diabetic mice [58]. These include alpha-lipoic acid, ascorbic acid, vitamin E, and carotenoids, all of which have been evaluated, and confirmed to protect against diabetic cataracts [58, 59]. The most commonly used antioxidant enzymes include superoxide dismutase (SOD), and glutathione peroxidase to be used in the ophthalmic lens. These enzymes break down the superoxide radicals into H2O2 and oxygen (O2) [61]. In several in vitro, and in vivo studies, SOD has been shown to protect against cataracts formation during DM [62].

Inhibitors of lens epithelial cell apoptosis

Apoptosis is a normal process of cell death that provides a physiological foundation for cataracts initiation and progression [63]. Depending on the nature of many apoptotic stimuli, the mechanisms involved in cell apoptosis are classified as intrinsic or extrinsic pathways. Oxidative stress, and mitochondrial damage, and dysfunction have been identified as important mediators of apoptosis in the epithelial cells of an ophthalmic lens, and they play a key role in the pathogenesis of cataracts [63, 64]. Grape seed extracts, resveratrol, and coenzyme Q10 (ubiquinone) are few examples of the reported inhibitors of epithelial cell apoptosis, all of which being operating as free radical scavengers, thereby reducing the development of ROS, increasing the defense against oxidative stress, and avoiding light-induced apoptosis of the epithelial cells [59, 65-68].

**Antiglycation agents**

Advanced glycation occurs in diabetic patients, but to a larger extent than that in normal aging, leading to the development of lens opacity [69]. The clinically used antiglycation agents also serve as potential antiacataract agents, such as the naturally bioactive molecules like the polyphenols, phenolics, flavonoids, terpenes, carotenoids, polyunsaturated fatty acids, and synthetic compounds like aspirin, ibuprofen, aminoguanidine, and pyruvate [70-72]. The most prevalent component of green tea (Camellia Sinensis) is epigallocatechin gallate (EGCG), which has strong antioxidant capabilities and also reduces the generation of H2O2 [7].

**Prevention and treatment of glaucoma**

**Adrenergic agonists**

Adrenergic agonists (norepinephrine), the primary neurotransmitters of the adrenergic system, produced by activation of the alpha, and/or beta receptors, have the potential for the treatment of glaucoma [73]. At the moment, the most well-known example is brimonidine, a selective alpha-2 receptor agonist that has been reported for its use in the treatment of glaucoma [74-76].

**β-receptor antagonists**

By lowering intracellular cAMP levels, antagonists of β-receptors, which are found in the eye, inhibit the production of aqueous humor in the ciliary body [77]. Timolol has been the first anti-glaucoma drug to receive FDA approval, and it has been the most popular drug treating glaucoma for many years. Betaxolol, carteolol, metipranolol, and levobetaxolol have been amongst the first β-receptor antagonists to hit the market, each with slightly distinct pharmacological features [78].
Carbonic anhydrase inhibitors

Topical carbonic anhydrase inhibitors prevent the formation of aqueous humor, thereby preventing the increase in IOP [79]. Brinzolamide and dorzolamide are two such drugs that have been used for lowering IOP. Acetazolamide, a systemic carbonic anhydrase inhibitor, is one of the most effective IOP-lowering medications now available on the market [80].

Parasympathomimetics

By extending the trabecular meshwork, and Schlemm’s canal, the body to contract, enhancing the outflow of aqueous humor [78]. The most well-known member of this class of antiglaucoma medications that can lower IOP is pilocarpine [81].

Prostaglandin analogs

Prostaglandin analogs connect to the prostaglandin F (FP) receptors, thereby increasing the uveoscleral outflow. As a result, the ciliary muscle expands and the tissue-filled spaces along the ciliary muscle bundles are decompressed, releasing the IOP. Bimatoprost, latanoprost, taluprost, and travoprost are some of the currently available prostaglandin analog drugs considered for first-line treatment of glaucoma [82].

Prevention and treatment of diabetic retinopathy and diabetic macular edema

Corticosteroids have been shown to have anti-inflammatory and anti-angiogenic properties via modulating pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and VEGF [83]. The levels of these mediators increase, as the disease progresses. For DME and DR, corticosteroid medication is a popular treatment option [84]. In the treatment of DME, and DR systemic corticosteroid therapy may be an effective adjunct to laser photocoagulation. Intravitreal triamcinolone acetone (IVTA) has been shown to have anti-inflammatory properties and can aid in the treatment of DME. Because of its potent antiangiogenic effects, IVTA can also help to reduce PDR [84, 85].

Corticosteroid therapy with the sustained delivery system

Triamcinolone acetone (TA) implant is one of these delivery mechanisms for DME [85]. Fluocinolone acetone nonbiodegradable intravitreal insert is another sustained drug delivery mechanism that attempts to release fluocinolone over three years. This approach is usually thin and allows for direct injection into the back of the eye through a self-sealing opening, which is under processing of FDA approval for future commercialization [83]. Ozurdex (allergen), a sustained-release biodegradable, intravitreal implant, and used for the treatment of macular edema, has also been authorized by the FDA. In phase I clinical trial with several open-label and dose-escalation scenarios, NOVA63035 (intravitreal injection of dexamethasone palmitate) is now being examined in patients with DME to determine its safety, and tolerability [86]. Clinical experiments for the sustained-release delivery of TA, are presently using Verisome technology (IBI-20089) [83, 87].

Other non-steroidal anti-inflammatory agents

Other nonsteroidal anti-inflammatory drugs (NSAIDs) have been licensed by the FDA for the treatment of DR, and DME. Nepafenac, a topical nonsteroidal medication that is beneficial in the treatment of DME, is one of them [88]. Clinical studies for nepafenac are presently underway. Anatomic and functional improvements were seen after systemic treatment of DME with intravitreal infliximab injection [89].

Antiangiogenic agents

In addition to corticosteroids, antiangiogenic drugs are beneficial in the treatment of PDR, and DME. The vascular endothelial growth factor (VEGF) subfamily protein, which has been linked to the development of DR, and age-related macular edema degeneration (AMD) [83], is the primary target of these antiangiogenic agents. Bevacizumab is a humanized full-length antibody that targets all kinds of VEGF [90]. Exudative AMD is treated with ranibizumab, the FDA approved a recombinant humanized antibody fragment that targets VEGF-A in 2006 [91, 92]. JSM6427 (α5β1-fibronectin), a German biopharmaceutical company’s developed antiangiogenic compound, has shown promising results in reducing DR. JSM6427 is now undergoing a phase I clinical trial [93]. Glauxsmithline developed Pazopanib, an antiangiogenic drug that is taken orally. VEGF receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and tyrosine-protein kinase (c-kit) are all targets for this drug. It is now being investigated for safety, efficacy, and tolerability in phase III clinical trials [94].

Vitreous agents

Vitrase is the first, and only ovine hyaluronidase that is free of preservatives and thimerosal. Its application as a spreading agent has been authorized by the FDA. A phase III clinical trial is underway to see if it can treat PDR-induced ocular hemorrhage [95]. Micropalamin is another vitreous agent that is injected intravitreally. It has been suggested that generating posterior vitreous detachment can be employed to treat DME, and PDR. For example, ThromboGenics NV [96].

The potential use of systemic agents to treat diabetic retinopathy

Many drugs used to treat dyslipidemia, and hypertension in diabetic individuals have been shown to decrease the advancement of DR [90].

Hypoglycemic agent-Insulin therapy, Thiazolidine

Hypolipidemic agent-Fibrates (fenofibrate)

Statin-Atorvastatin

Antiplatelets-Dipyridamole, Aspirin

Potential plant-based drugs

Plant-based therapies have also been shown to be useful in the treatment of DR. Because of their efficacy, ability to generate hypoglycemic effects, and renoprotective qualities, plant-based medicines are utilized to treat DR illness. One of the metabolic processes that contribute to DR development is the activation of the polyol pathway [97, 98].

This route is responsible for metabolizing excess glucose in diabetics. Ocimum sanctum, Tinospora cordifolia, Azadirachta indica, Ganoderma lucidum, and other plants contain AR inhibitors. Ocimum sanctum protects against DR when combined with vitamin E [97]. Tinospora cordifolia protects against DR by reducing oxidative stress in the retina caused by increased levels of proangiogenic, and proinflammatory mediators [98]. The fungus Ganoderma lucidum protects the retina against oxidative damage [99]. Curcumin is a plant-derived medication that has been shown to diminish DR progression in a rat model by suppressing retinal VEGF overexpression [100]. Curcumin, through antioxidant, and anti-inflammatory mechanisms, reduced the thickness of the basement membrane in the retina of treated rats [101]. Hesperetin has also been shown to aid in the prevention of DR transmission [102]. Other antioxidant-rich compounds, including quercetin, and rosmarinic acid, have been shown to decrease angiogenesis and so diminish DR [103, 104].

Antioxidants as a potential therapeutic agent

It has been discovered that N-acetylcysteine (NAC) vitamin C, and lipoic acid are involved in reducing diabetic complications [105, 106]. Calcium dobesilate has been demonstrated to lower retinal permeability and VEGF expression. Caffeic acid is an antiangiogenic medication that inhibits the development of reactive oxygen species (ROS), and the production of VEGF in retinal cells [107]. Lipoic acid suppresses apoptosis while also reducing nitrotyrosine buildup and NF-B activation [108]. Rosmarinic acid, Benfotiamine, Pycnogenol, Curcumin, Taurine, and green tea have all been shown to have free radical scavenging properties and have all been used to treat DR [109-111].

The medications tested in clinical trials to treat an eye problem associated with diabetes have been enlisted in tables 3.
Table 1: Conventional drugs available for diabetic ocular complications

| Disease | Formulation | Plant/Drug                          | Reference(s) |
|---------|-------------|-------------------------------------|--------------|
| Cataracts | Eye drop | Boerhaavia diffusa root | [112] |
| Cataracts | Eye drop | Calcium dobesilate | [113] |
| Cataracts | Eye drop | Cinnamomum zeylanicum, Curcuma longa, Trigonella foenum graecum, Azadirachta indica, Piper nigrum | [114] |
| Cataracts | In situ gel | Boerhaavia diffusa root | [112] |
| Macular edema | Eye drop | Dexamethasone | [115] |
| Macular edema | Tablet | Curcumin | [116] |
| Cataracts | Eye drop | Naproxen | [116] |
| Diabetes retinopathy (DR), diabetic macular edema (DME) and diabetic cataracts (DC) | Injection | Ranibizumab | [117] |
| Cataracts | Eye drop | Abruus precatorius | [118] |
| Cataracts | Eye drop | Aloe vera | [119] |
| Cataracts | Paste | Byttneria herbacea | [120] |
| Cataracts | Eye drop | Microglossa purpura | [121] |
| Glaucoma | Eye drop suspension | Acetazolamide | [122] |
| Macular edema | Injection | Ranibizumab | [123] |
| Macular edema | Eye drop | Epafenac | [124] |
| Macular edema | Eye drop | Ketorolac | [125] |
| Glaucoma | In-situ gel | Dorzolamide | [126] |
| Glaucoma | Mini-tablet | Timolol maleate | [127] |

Table 2: Novel formulations available for the treatment of diabetic ocular complications

| Disease | Drug | Novel approach | Description | Reference(s) |
|---------|------|----------------|-------------|--------------|
| Glaucoma | Brimonidine | Cubosomes | Ex-vivo corneal permeation tests revealed that the improved formulation had higher corneal permeability than the consumer product. | [128] |
| Glaucoma | Timolol maleate, Brimonidine | Hydrogel | Because they may localize, and sustain pharmacological activity at the site of action for prolonged periods, they have an additive effect on IOP reduction. As a result, long-term activity is possible. | [129] |
| Glaucoma | Brimonidine | Cubosomes | By preparing or extending the mean residence time of BRT-loaded cubosomes, improves the ocular bioavailability of BRT, and prolongs its intraocular pressure-lowering action. | [128] |
| Cataracts | Epalrestat | Hydrogel | This promises the aggregation, and diffusion of drugs across the cornea and central foveal thickness. | [130] |
| Glaucoma | Ketorolac | Cubosomes | High transcorneal permeation, and corneal retention were observed with cubosomal formulation corresponding to ketorolac solution and high transcorneal permeation, and retention, showing a biphasic release profile. | [121] |
| Glaucoma | Timolol maleate | Cubosomes | For traditional eye drops, Cubogel may be a successful option, since it maintained the release of the medication for a longer time, and could also minimize the number of drug applications. | [132] |
| Macular edema | Triamcinolone-acetonide | Liposomes | Patients with refractory macular edema were able to tolerate the treatment and see an improvement in their best-corrected visual acuity, and central foveal thickness. | [133] |
| Glaucoma | Latanoprost | Liposomes | Best-corrected visual acuity is well-tolerated, enhanced, and sustained in vitro release of central fovea (60%) was achieved over 14 d. For 90 d, a subconjunctival liposome injection reduced IOP in rabbit eyes (4.8 ± 1.5 mm Hg) compared to topical daily latanoprost treatment (2.5 ± 0.9 mm Hg) without causing ocular discomfort. | [134] |
| Glaucoma | Brinzolamide | Liposomes | With a lipid/cholesterol ratio of 7:4, and a lipid/drug ratio of 10:1, optimal liposomes had an EE of 98.32 ± 1.61% and a diameter of 84 ± 3.20 nm. Liposomes (1 mg/ml) demonstrated a 6.2-fold increase in the coefficient of cornal permeability and a more continuous and effective decrease of IOP in rabbits’ eyes (5-10 mm Hg). | [135] |
| Glaucoma | Dorzolamide hydrochloride | In situ gelling polymeric nanoparticles | Optimized nanoparticles (164 nm, 98.1 percent entrapment efficacy) showed sustained in vitro release and slower corneal penetration (35.5%) as compared to commercial eye drops (86.34%). Nanoparticles were mucadhesive, non-irritating, and remained in rabbit eyes for a long time. | [136] |
| Glaucoma | Dorzolamide hydrochloride | Polymeric nanoparticles | When compared to Trusopt®, nanoparticles showed a 1.8-2.5 fold improvement in corneal penetration and a greater drug concentration in the aqueous humor (1.5-2.3 fold). Vitamin E TPGS was found to be a safer and more efficient emulsifier than PVA. It functions as an inhibitor of P-glycoprotein (prominent eye tissue efflux transporters) and has induced a substantial increase in the efficacy of trapping and corneal permeation. | [137] |
| Glaucoma | Betaxolol hydrochloride | Polymeric nanoparticle | A biphasic release pattern was found in optimized (1:2) polymer: drug ratio nanoparticles, with an early burst followed by a persistent release lasting up to 12 h. Nanoparticles demonstrated excellent ocular tolerability and a considerable decline in IOP, with a high of 9.90 ± 5.5 mm Hg compared to control after 5 h. | [138] |
| Disease       | Drug                          | Novel approach                  | Description                                                                                                                                                                                                 | Reference(s) |
|---------------|-------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Glaucoma      | Brimonidine                   | Polymeric nanoparticles in preformed gel | Due to adhesion to the negatively charged cornea, and conjunctiva, optimized chitosan nanoparticles combined in prepared gel showed greater sustained release over SA nanoparticles. Compared to eye drops, cytotoxicity tests reported non-toxic formulations with a sustained reduction of IOP (>25 h). | [139]        |
| Glaucoma      | Methazolamide                 | SLNs                             | The Box-Behnken model was used to optimize SLNs with a size of 197.8 ± 4.9 nm, 68.39 percent drug trapped, continuous-release following the Peppas model, and a considerable extended reduction in IOP compared to AZOPT® without any signs of ocular discomfort. | [140]        |
| Glaucoma      | Brimonidine                   | SLNs; NLCs                       | After autoclaving at 121 °C for 15 min, both SLNs, and NLCs were physically stable, yielding particles below 500 nm that were non-irritant to the ocular mucosa, and had higher ZP, and brimonidine concentrations collected than non-autoclaved ones. | [141]        |
| Glaucoma      | Melatonin                     | Cationic SLNs                    | As a positive charge imposter, didecylmethylammonium bromide was employed to create cationic SLNs that demonstrated high mucoadhesion, extended ocular retention time, good tolerability, and was very successful for 24 hour IOP reduction (maximum IOP reduction of 7 mm Hg). | [142]        |
| Glaucoma      | Methazolamide                 | Surface modified SLNs by chitosan | In terms of particle stability (4 μo at 4 ° C), size (199.4 ± 2.8 nm), in vitro release, and ocular penetration, chitosan-modified SLNs beat non-modified SLNs. The peak reduction in IOP was better than both unmodified SLNs and AZOPT® eye drops without any signs of ocular discomfort. | [143]        |
| Glaucoma      | Latanoprost                   | Liposomal gels                   | The best liposomes had a 7:3 lipid: cholesterol ratio and a 1:1 drug: lipid ratio, with a trap performance of 98 percent. Latanoprost’s interaction with liposome excipients improved drug encapsulation. Vesicles are incorporated into the Pluronic® F127 gel’s continuous medication release system (45 percent discharged in 2 d). Liposomal gels did not irritate the eyes of rabbits. | [144]        |
| Glaucoma      | Brinzolamide                  | Liposomes                        | With a lipid/cholesterol ratio of 7:4, and a lipid/drg ratio of 10:1, optimal liposomes had an EE of 98.32% and 84.33%, respectively, and a diameter of 1.61 and 2.02 nm, respectively. In comparison to the commercial solution (10 mg/ml), liposomes (1 mg/ml) showed a 6.2 fold improvement in corneal permeability and a more consistent, and stable lowering of IOP in rabbit eyes (5-10 mm Hg). | [135]        |
| Glaucoma      | Diltiazem HCl                 | Unilamellar vesicles             | The vesicles rigidified with cholesterol were the most stable at a 1:1 molar ratio. The addition of cholesterol improved the efficacy of the percent trap while reducing the rate of drug release. Compared to the solution, an improved IOP lowering operation was obtained in rabbit eyes. | [145]        |
| Glaucoma      | Timolol maleate               | Liposome in ion-sensitive in-situ gel | Liposomes having a diameter of 136 nm, a trapping efficiency of 4.7 percent, and a corneal penetration augmentation of 1.93 times were found to be the most effective. When compared to eye drops, in situ gel liposomes beat commercial eye drops, and liposomes in terms of corneal retention time were non-irritant to ocular tissues and show a rapid reduction in IOP. Besides, the formulation was able to sustain the IOP for up to 72 h. | [146]        |
| Glaucoma      | Timolol maleate, Dorzolamide hydrochloride | Nano-fiber patches              | Nano-fiber patches                                                                                                                            | [147]        |
| Glaucoma      | Brimonidine                   | Inserts                          | Ocular implants containing 7% PVP, and 1.5% SA with or without an ethylcellulose layer were used to maintain brimonidine release in vitro (99% at 6 h). When injected into the eyes of albino rabbits, their therapeutic efficiency in lowering IOP was found to be more long-lasting than that of the brimonidine solution. There was a larger IOP lowering effect with the two-sided coated ocular insert than with the one-sided coated ocular insert. | [148]        |
| Glaucoma      | Timolol maleate               | Film                             | The drug was ready in four weeks (85% released over the first 2 w). During 10 w, the film’s drug release, on the other hand, reduced in vivo IOP levels. Between rabbits given a 0.5 percent commercial ophthalmic solution, and those treated with films, there was no significant difference in IOP reduction (P<0.05). There was no sign of anxiety or ocular problems. | [144]        |
| Glaucoma      | Latanoprost                   | Nanosheet                        | Nanosheets containing latanoprost (2.5 mg/cm) were given to rats for 1 w, with no evidence of local side effects, and a 20 percent reduction in IOP. | [150]        |
| Glaucoma      | Latanoprost                   | Contact Lenses                   | According to the in vivo animal study, contact lenses with 40-45 mm thick polymer-drug films (latanoprost) produced an initial burst of latanoprost in aqueous humor, followed by a steady-state concentration comparable to the average hourly concentration of latanoprost induced by a decrease in commercially available latanoprost. | [133]        |
| Glaucoma      | Acetazolamide, Ethoxzolamide | Contact Lenses                   | Biomimetic networks can load more drugs than conventionally synthesized pHEMA hydrogels, and monitor better drug release. The biomimetic hydrogels were incredibly cytocompatible, making them excellent for application as medicated soft contact lenses or oxygen-permeable inserts. | [151]        |
| Cataracts     | Naproxen sodium               | Eye drop                         | Due to poor AR inhibitory activity, naproxen has been reported to postpone cataracts in diabetic rats.                                                                                                        | [152]        |
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All the authors have contributed equally.

### CONFLICTS OF INTERESTS

The authors have reported no conflicts of interest.

### TABLE 3: Medication tested in clinical trials to treat an eye problem associated with diabetes

| Disease             | Drug          | Approach | Reference(s)          |
|---------------------|---------------|----------|-----------------------|
| Cataract            | Ketorolac     | Ophthalmic solution 0.4% | [15] |
| Diabetic Retinopathy| Nevanac, Ilevro| Suspension | [14] |
| Diabetic Retinopathy| Somatostatin  | Eye drop   | [15] |
| Glaucoma            | Citicoline    | Eye drop   | [15] |

### CONCLUSION

Diabetes mellitus and associated ocular consequences continue to be a leading cause of blindness. As a result, our understanding of these ocular issues has improved, as has our ability to detect effective treatment. With early diagnosis and treatment, all diabetic ocular complications can be avoided. The pathophysiological aspect, treatment, and formulation strategy to diabetic cataracts, glaucoma, diabetic retinopathy, and macular edema are all addressed in this analysis.

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### ABBREVIATION

DM: Diabetic Mellitus, DME: Diabetic Macular Edema, FDA: Food and Drug Administration, DR: Diabetic Retinopathy, AR: Aldose Reductase Inhibitor, AGE: Advanced Glycation End-Product, IOP: Intraocular Pressure, PKC: Protein Kinase C, CAG: Closed Angle Glaucoma

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