Drug, delivery and devices for diabetic retinopathy (3Ds in DR)

Natarajan, Jayaganesh V.; Laude, Augustinus; Lim, Tock Han; Venkatraman, Subbu S.; Agrawal, Rupesh; Nirmal, Jayabalan; Radhakrishnan, Krishna; Moreno, Miguel

2016

Nirmal, J., Radhakrishnan, K., Moreno, M., Natarajan, J. V., Laude, A., Lim, T. H., et al. (2016). Drug, delivery and devices for diabetic retinopathy (3Ds in DR). *Expert Opinion on Drug Delivery*, 13(11), 1625-1637.

<https://hdl.handle.net/10356/84621>

<https://doi.org/10.1080/17425247.2016.1188800>

© 2016 Informa UK Limited. This is the author created version of a work that has been peer reviewed and accepted for publication in *Expert Opinion on Drug Delivery*, published by Taylor & Francis on behalf of Informa UK Limited. It incorporates referee's comments but changes resulting from the publishing process, such as copyediting, structural formatting, may not be reflected in this document. The published version is available at: [<http://dx.doi.org/10.1080/17425247.2016.1188800>].

Downloaded on 26 Apr 2023 18:09:44 SGT

Publisher: Taylor & Francis

Journal: *Expert Opinion on Drug Delivery*

DOI: 10.1080/17425247.2016.1188800

Drug, delivery and devices for diabetic retinopathy (3Ds in DR)

Nirmal Jayabalan^{1*}

Krishna Radhakrishnan¹

Miguel Moreno¹

Jayaganesh V Natarajan¹

Augustinus Laude²

Tock Han Lim^{1,2}

Subbu Venkatraman¹

Rupesh Agrawal^{1, 2*}

¹NTU-Northwestern Institute for Nanomedicine (NTU), School of Material Science & Engineering (MSE), Nanyang Technological University

²National Healthcare Group Eye Institute, Tan Tock Seng Hospital

Corresponding authors: (* Joint corresponding authors)

Dr Rupesh Agrawal, MD (Res)

Consultant,

National healthcare Group Eye Institute,

Tan Tock Seng Hospital,

Singapore

Email: Rupesh_agrawal@ttsh.com.sg

Dr Nirmal Jayabalan, PhD

Post-doctorate fellow.

School of MSE,

Nanyang Technological University

Singapore

njayabalan@ntu.edu.sg

Abstract

Introduction: Diabetic Retinopathy (DR) is one of the most common causes of blindness among the working population worldwide. Clearly, there is an unmet clinical need to find better treatment options for DR. **Areas covered:** The literature search was conducted on PubMed with no limitation on language or year of publication. The review focuses on the clinically used drugs/proteins along with a brief background on the pathophysiology of DR. The major focus of this review revolves around three treatment approaches involving drugs/proteins, drug delivery formulations and drug delivery devices. In each category, major advances are discussed along with the possible solutions. We have also discussed the various modes of administration that are currently being evaluated in the clinic. An attempt has been made to address the potential targeted site of action for DR drug delivery, and also to understand the role of Blood Retinal Barrier (BRB). **Expert Opinion:** In the current scenario, although there have been some advances in the drug delivery devices for delivering drugs/proteins, there are still challenges to be overcome with regard to the particulate systems. For long-term success of DR therapeutics, research options should consider taking into account the 3Ds (drug, delivery and devices).

Keywords:

Diabetic retinopathy; Anti-VEGF; Drugs; Delivery systems; Delivery devices

1. Introduction

Diabetic retinopathy (DR) with or without diabetic maculopathy is a diabetes induced microvascular complication leading to blindness amongst population aged 20–64 years in developed countries.[1] Normally, the tight junctions prevent the retinal microvessels from leaking. But in the case of diabetes, excess glucose accumulation damages the tight junctions present in the retinal blood vessels. The retinal blood vessels (microvascular damage) becomes leaky which allows the intravascular fluid to escape into the retina. In non-proliferative diabetic retinopathy (NPDR), increased retinal vascular permeability is considered as the critical step for its progression. [2] The obstructed retinal capillaries upregulate pro-angiogenic growth factors, leading to abnormal vessel growth development in retina resulting in proliferative diabetic retinopathy (PDR). If untreated, PDR can potentially lead to retinal detachment and blindness. [3, 4] Another important vision-threatening complication of diabetes is Diabetic Macular Edema (DME), which involves retinal thickening and build-up of fluid (edema) in the macula. [3, 5] In DR, especially in NPDR, DME is the major cause of vision loss [2]

Various important clinical trials including the Diabetes Control and Complications Trial (DCCT) Research Group, 1993, and the United Kingdom Prospective Diabetes Study (UKPDS) Group, 1998, concluded that hyperglycemia is an important risk factor for the diabetic microvascular and macrovascular complications.[6, 7] In this article, we will review the pathophysiology, related drug therapeutics and drug delivery aspects for DR.

1.1. Pathophysiology and role of VEGF and inflammation in DR

The blood retinal barrier (BRB) is formed by tight junctional complexes between retinal pigment epithelial (RPE, outer BRB) and vascular endothelial cells (inner BRB). Breakdown of BRB in diabetes may involve the inner BRB, the outer BRB, or both. BRB provides biological and mechanical barrier for transport of solutes among cells. There is extracellular fluid accumulation within the inner layers in DME, which displaces tissues of the outer layers. Basic research has shown several overlapping interrelated pathways leading to BRB alteration and dysfunction, which results in DR and DME.[8]

The damage of the inner BRB is caused by dilation of capillaries, loss of retinal capillary pericytes and endothelial cells as well as endothelial tight-junctions disruption; and is considered the most important factor in DME.[9] However, dysfunction of the retinal pigment epithelium (RPE) can also contribute to DME.[10] In addition, there are cytokines and vascular endothelial growth factor (VEGF), which play an important role in the breakdown of BRB and DME. Furthermore, some alterations in leukocyte functions, secondary to chronic hyperglycemia, increases the release of placental growth factor (PlGF)[11] and VEGF [12]. Two key observations were noted with regards to VEGF: microvascular changes in primate model associated with DR after VEGF injections[13] and increase in intraocular VEGF levels in patients suffering from DME.[14, 15] Following this work, it is strongly believed that VEGF plays an important role in DR, increasing the vascular hyperpermeability. Within the retina, VEGF is produced and secreted in RPE, endothelial, glial, pericytes, Muller and ganglion cells (**Figure 1**).[16] VEGF stimulates angiogenesis, increases vasodilation and vascular permeability, and induces recruitment of inflammatory cells; these events are accompanied by vascular leakage.[17] At present, VEGF is recognized as an important target for developing therapeutics to treat DR. Hence, many VEGF inhibitors (anti-VEGF) are being developed and are also, currently, in clinical use.

Hyperglycemia results in various molecular events including Advanced Glycation End product (AGE) and reactive oxygen species formation, which lead to nitric oxide synthase dysregulation. This, in turn, activates Nuclear Factor- κ B (NF- κ B) followed by an increase in cytokines (IL-1, IL-6, TNF α), chemokines, such as CCL-2, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Furthermore, this activates endothelial cells, recruitment of inflammatory cells and increases the level of VEGF. NF- κ B activation leads to the synthesis of many pro-inflammatory molecules[18]. From the reported literature, it seems well accepted that inflammation also has a critical role in aetiopathogenesis of DR (**Figure 2**). Moreover, many anti-inflammatory therapies were found to significantly inhibit development of different aspects of DR in animal models and in humans[18], thus underpinning the role of inflammation in DR. As a result, drugs targeting inflammatory pathways represent a new approach, and the hypothesis gained considerable attention for the treatment of DR [18, 19]. Although other mechanisms have been proposed for DR, there are no related interventions which have been developed to counter these mechanisms in the clinic as of today.

1.2. Current treatment options for DR

The advanced stages of DR can be treated using laser, anti-VEGF therapies, intravitreal (IVT) steroid and vitrectomy in severe cases.[20] Laser may help to reduce the risk of vision loss from DR if used in a timely manner, however, laser therapy is destructive in nature. [21] The favorable effects of IVT steroids seems to be temporary, as problems like cataract formation and steroid-induced glaucoma have developed after IVT steroids.[18] The intraocular delivery of anti-VEGF agent is now widely used to treat advanced DR. The hypothesis about the involvement of VEGF and inflammation was established based on the success of anti-VEGF agents and steroids in the treatment of DR, however the exact mechanisms are not clearly known. [2]

1.3. Various ocular routes of administration for DR therapeutics

To achieve therapeutic success for various ocular diseases, delivery options are also being evaluated for maximum effect. However, the selection of administration route is governed by the targeted site of action, as well as by convenience. Conventionally, topical, IVT, systemic (oral and intravenous) and, recently, periocular routes have been used. Topical route is the preferred option for anterior segment, whereas for the posterior segment, both intravitreal and periocular routes have been proposed.[22]

1.3.1. Topical

The oldest and perhaps the most patient-friendly mode of delivery is the topical route. However, the major limitation to this administration mode is the low bioavailability of drug, primarily due to the limited contact time, and limited trans-corneal penetration, even to the anterior segment. For the posterior segment, bioavailability is even lesser, as there are additional static and dynamic barriers that need to be overcome.[23] In spite of these limitations, studies have explored using nepafenac (small molecule) topical drops to reach the retina for treating early developmental stages of DR. The study reported the significant inhibition of most of the abnormalities in DR within 2 months of nepafenac topical drops treatment (four times/day) in diabetic rats. This report shows the feasibility of topical drops to reach sufficient concentration in the retina. It also suggests the localized inhibition of inflammatory pathways in the posterior eye segment for DR.[24] The co-administration of topical anti-inflammatory drugs also showed a reduction in frequency of anti-IVT injections.[25] In another study, it was shown that topical eye drop instillation of ranibizumab could reach retina possibly through the transcleral route. Even though the low concentration of ranibizumab in the vitreous is able to inhibit VEGF[26], the higher frequency of administration and resultant high cost may not be able to compete with IVT administration of the macromolecules.[27]

1.3.2. Intravitreal

Intravitreal injections are the current gold standard for intraocular administration of anti-VEGF and non-anti-VEGF therapeutics. The advantage of IVT technique is that it can circumvent the blood ocular barrier to achieve high drug concentrations in the vitreous, as well as to avoid the adverse effects resulting from systemic administration. However, many drugs are rapidly cleared from vitreous humor; therefore, to achieve and to maintain effective therapy, repeated administrations are necessary but this has various adverse effects. Therefore, better DDS with sustained release capabilities have been designed to treat chronic ocular diseases using IVT administration. Among them, intraocular implants for prolonged release of glucocorticoids have already demonstrated their effectiveness in various ocular disorders, including diabetic macular edema.[28] In spite of the current standard use of anti-VEGF agents, clinical studies show variable results, which is largely due to the multifactorial nature of DR. The anti-VEGF injections also cause a heavy economic burden on both the patient and the health services, which could be reduced if future studies support the use of inexpensive and easier-to-administer injections.

1.3.3. Periocular

The large surface area of the sclera could offer a good option for periocular drug delivery to reach the retina; the administration could be done through subconjunctival, sub-tenon, peribulbar, posterior juxtasclera and retrobulbar spaces.[29] The periocular route takes a relatively longer route as it has to overcome episclera, sclera, choroid, Bruch's membrane (static and dynamic barriers), to reach vitreous humor or retina. However, studies have shown that both small and macro molecules could reach retina after subconjunctival injection as discussed below.

In one study, it was found that a single subconjunctival dose of 1.25 mg/ 0.05 ml of bevacizumab led to the retina/choroid ($C_{\max}$) of 295 ± 48 ng/g one week after administration in pigmented rabbits. The $t_{1/2}$ in retina/choroid was 2.85 weeks. Also, detectable levels of drug were observed in retina/choroid even after 12 weeks of administration. The detectable levels were close to the *in vitro* inhibitory concentration required for 50% VEGF inhibition (11–27 ng/ml) at 12 weeks[26, 30]. Another study used subconjunctival injection of ranibizumab to determine if it could reach the posterior segment. The study showed that ranibizumab could reach the retina after a single subconjunctival injection and could be detected in the retina for 8 weeks in rabbits.[31] This shows that compared to bevacizumab, ranibizumab is shorter-lived in the posterior segment, primarily due to its smaller size and lack of binding to neonatal Fc (FcRn) receptor [30-32] In summary, these studies did show that macromolecular therapeutic proteins could reach the retina after subconjunctival injection.

It is well-documented that the BRB is compromised in DR, and it is important to consider dose while extrapolating pharmacokinetics data derived from animal models with intact BRB to periocular DDS in disease model. A clinical study showed significantly higher levels of subtenon triamcinolone acetonide (TA) in the vitreous humor of DR patients than in patients with idiopathic macular hole, macular epiretinal membrane, rhegmatogenous (caused by a retinal “tear”) retinal detachment (RRD) and RRD accompanying choroidal detachment [33]. However, detailed studies are required to understand the pharmacokinetics of the periocular delivery from various regions of periocular spaces. Novel DDS could improve or sustain the periocular therapeutics. Considering these studies with minimally invasive routes as compared to IVT, periocular route could potentially be adopted for delivering DR therapeutics.

2. Drugs and targets for DR

2.1. Anti-VEGF proteins

Even though the exact mechanism of DR pathogenesis is not clearly known, currently both VEGF and inflammatory cells are recognized as major causative factors. The aim of intraocular anti-VEGF therapies is to block the activity of elevated concentrations of VEGF. For the treatment of DME, anti-VEGF proteins have been approved for IVT injection. At present, the most commonly used anti-VEGF protein for DME is bevacizumab, marketed by Genentech, which was originally approved by the Food and Drug Administration (FDA) as an immunosuppressive drug, but is used off-label for DR and AMD. The off-label use of repackaged bevacizumab (**Table 1**) by IVT administration is controversial, with only some clinicians approving its usage[34], while others objecting to potential repackaging issues due to its storage stability in individual 1 ml single-use syringes. This repackaging leads to variable protein concentration and aggregation as well as contamination by silicone oil microdroplets.[35, 36] Bevacizumab (149 kDa) contains recombinant humanized monoclonal immunoglobulin G1 antibody (expressed by Chinese Hamster Ovary cells (CHO) cells), where 93% of its sequence is human and the remaining 7% is murine. It binds with high affinity to the three biologically active isoforms of VEGF-A: VEGF₁₆₅, VEGF₁₂₁ and VEGF₁₁₀ [37].

In 2012, ranibizumab was the first FDA approved anti-VEGF protein for the treatment of DME, marketed by Genentech. Ranibizumab is a recombinant humanized monoclonal antibody fragment of 48 kDa produced in *E. coli*. It is formed by light-chain murine anti-VEGF-A complementary-determining regions linked by a disulfide bond to heavy-chain human IgG1 (Immunoglobulin G). Ranibizumab binds with the same affinity as bevacizumab, to the same three VEGF-A isoforms.

The approval of ranibizumab for DME was based on three results of phase II clinical trials (RISE and RIDE), where 2 doses of ranibizumab were compared to sham injections, with rescue laser available 3 months after randomization [38]. The results, after 24 months from the initial injections, revealed that 39.2% of the patients who received monthly injections of 0.3 mg of Ranibizumab, and 42.5% of those who received the 0.5 mg dose, gained at least 15 letters in corrected visual acuity on a standard eye chart, compared to 15.2% of the patients who received sham injections. Recently, at the beginning of 2015, Genentech announced the FDA approval of the extension of ranibizumab use for the treatment of DR in patients with DME. As per protocol S, (Writing Committee for the Diabetic Retinopathy Clinical Research Network (DRCR.net)), ranibizumab was shown to be non-inferior to pan retinal photocoagulation (PRP) with regard to visual acuity outcome and visual field changes in patients with PDR. At 2 years, visual acuity improved by 2.8 letters from baseline in the ranibizumab arm as against only 0.2 letters improvement from baseline in PRP group. There was significant visual field loss in the PRP group and more vitrectomies were required in the PRP group. [39]

Two years after the approval of ranibizumab, another anti-VEGF drug, aflibercept developed by Regeneron Pharmaceuticals was also approved by FDA for DME. The approval of aflibercept was based on 1-year data from two studies, comparing intra-vitreous injections of 2 mg of aflibercept administered either monthly or every 2 months (after 5 initial monthly injections) with laser photocoagulation treatment[40]. Aflibercept is a recombinant fusion protein of 96.9 kDa expressed in CHO cells, which contain around 15% of glycosylation having a final MW of 115 kDa. It is a chimeric protein that contains the second Ig domain of the human VEGFR1 fused with the third Ig domain of human VEGFR2, and both the domains in turn fuse to the constant region of human IgG1. Aflibercept binds to all VEGF-A isoforms, other isoforms of the VEGF family (B, C and D), and also to placental growth factor (PLGF) [41]. The binding of aflibercept to VEGF-A has almost one order of magnitude higher

affinity than that in the case of bevacizumab and ranibizumab.[42] Recent clinical trials carried out by the DRCR.net proved that IVT aflibercept, ranibizumab or bevacizumab improved eye vision in patients with DME; however, the relative outcome was based on baseline visual acuity. Interestingly, aflibercept was more efficient in improving the vision when the initial visual acuity was worse [43].

Another anti-VEGF molecule, Conbercept, developed by the Chinese company Chengdu Kanghong, is under phase III clinical trial for DME[44]. It is a recombinant fusion protein composed of the second immunoglobulin (Ig) domain of VEGFR1 and the third and fourth Ig domains of VEGFR2 to the Fc of human IgG1[45], with properties similar to aflibercept. Another novel, single-chain antibody fragment with smaller molecular weight than the other anti-VEGF proteins, called RTH258 (formerly ESBA1008) developed by Novartis AG is currently in phase III trials, demonstrating more promising visual acuity than aflibercept. RTH258 (26 kDa) has the potential to penetrate and distribute easily through ocular tissues, exhibiting better retinal penetration than larger proteins. VGX-300 (OPT-302) is a soluble receptor from VEGFR-3 that traps VEGF-C and D, and inhibits their biological activity. It would be a complementary therapy in combination with ranibizumab or bevacizumab, which target VEGF-A isoforms. Ocular distribution and pharmacokinetics studies have been carried out in rabbits [46]. Allergan developed a drug called abicipar pegol which is a novel highly potent anti-VEGF-A based on the DARPIn (designed ankyrin repeat proteins) technology that may increase the potency and improve the delivery of anti-VEGF agents [47]. DARPIn's are derived from natural ankyrin proteins and have 3–5 repeat motifs which can be genetically engineered to achieve high-affinity target protein binding [48]. Abicipar pegol has successfully passed stage 3 of the phase II study, entering recently into phase III.

A potential alternative to the aforementioned anti-VEGF proteins, where their systematic use can induce hypertension because of vascular contraction[49], may be the endogenous semaphoring 3A (sema3A).[50] In fact, this protein is implicated in neural cell migration, tumor metastasis, and vascular

genesis.[51, 52] Recently, an extensive investigation of its anti-angiogenic effects and possible mechanism in retinal neovascularization may enable a new therapeutic strategy for the treatment of retinal neovascularization.[50]

2.2. Non-anti-VEGF agents

Basic research shows a critical role of inflammation in DR pathogenesis. Anti-inflammatory agents have the potential to inhibit progress of various aspects of DR in experimental animal models and humans[18] underpinning the role of inflammation in DR. As a result, continuous research is going on to establish anti-inflammatory drugs to treat DR. However, whether anti-inflammatories will be useful in treating early phase or late phase of DR needs to be validated.[18, 19]

Non-steroidal Anti-Inflammatory Drugs (NSAIDs) inhibit prostaglandin G/H synthase, or cyclooxygenase. NSAIDs are known to inhibit the expression of cell adhesion molecules, which target circulating cells to inflammatory sites and also inhibit neutrophils activation and function [53]. Corticosteroids are reported to inhibit prostaglandins, leukotrienes [54], VEGF expression, and hence reduces angiogenesis.[55] It also down regulates the pro-inflammatory cytokine (platelet derived growth factor), which induces the VEGF gene expression.[56]

2.2.1. Steroids

Corticosteroids could be administered IVT, subtenon or periocularly, or topically for the DME treatment. The IVT triamcinolone acetonide (TA) is well accepted for its use in DR and it is commercially available as a suspension.[28] TA was approved by the US FDA for ocular inflammatory conditions, but is being used off label for DR (**Table 1**).[57] Intra-vitreous TA is associated with increased risk of glaucoma and cataract formation [58]. The single dose for TA ranges from 4 to 20 mg, with multiple injections at 4 monthly intervals over two years.[59-61] The improvement in the visual

acuity was shown to decline after month following a single IVT injection of TA; however, the effect was maintained after multiple injections, and this could be due to the clearance of TA from the vitreous cavity. [61] Unlike laser photocoagulation, TA did not show long-term benefits in DME. Also, TA shows a dose dependent effect, on DR progression. [62] The IVT TA use has not been established still for DME. The combination therapy of TA with anti-VEGF agents could be considered carefully in selected cases.[28]

Dexamethasone (DEX) is reported to be more potent than TA, but could be associated with more side effects than TA. The FDA approval and the success of anti-VEGF and corticosteroid-incorporated implant devices is a real game changer and the details of these devices are discussed in Section 5. Also DR being a multifactorial disease, many other agents targeting various other pathways are in the pipeline, but still under investigation. Therefore, even today there is no gold standard treatment available for treating DR successfully. The current scenario suggests that the corticosteroids could be a viable option for the patients who failed to respond to the laser and anti-VEGF treatments. Also, the combination therapy of corticosteroids with anti-VEGF agents needs further systematic studies in a large number of patients.

3. Drug Delivery Systems (DDS)

The delivery of therapeutic doses of DR therapeutics to the posterior segment tissues remains a significant challenge. In the pursuit to overcome these challenges, carefully designed DDS have been developed that can increase the transportation of the drugs to the posterior eye, improving their residence time at the target site and eliminating the need for repeated invasive administration. Ideally, an effective drug delivery system to posterior segment of the eye would meet the following criteria: (1) Safe and minimally invasive; (2) Target-specific with minimal drug loss, resulting in lower dose requirement; (3) Sustained delivery to avoid frequent administration; (4) Self-administration.

3.1. Particulate DDS

Particulate DDS consists of both microparticles (MPs) and nanoparticles (NPs) loaded with drug molecules. While MPs are mostly useful as sustained release depots, NPs bring additional advantages such as increased permeation through various ocular barriers.[63] Depending on their composition and structure, particulate systems may be classified as polymeric particles, liposomes, micelles and emulsions (**Figure 3; Table 2**).

3.1.1. Polymeric particles

Nanoparticles and microparticles are usually composed of one or more polymers. Particulate polymeric systems may be broadly classified as spheres and capsules based on their structure. Spheres typically consist of a continuous matrix of polymers with the drug molecules embedded within the matrix, whereas in the case of nanocapsules, the drug is encapsulated inside an inner liquid (or solid) core surrounded by a polymeric membrane.

One of the most-widely studied polymers is the poly (lactic-co-glycolic acid) (PLGA) particle, which have been used in several FDA-approved drug products. PLGA (and its degradation products) are known to be highly biocompatible and safe for human use. So these polymers have been studied extensively for ocular delivery. For example, DEX-loaded PLGA NPs with an average size of around 250 nm, prepared by the emulsification/solvent evaporation method, were able to release the drug at a constant rate for as long as 40 days. *In-vivo* studies with this system showed that the system was capable of maintaining a therapeutically effective range of DEX in the vitreous, and of inhibiting inflammatory response for more than 56 days after IVT injections.[64] In a similar study, PLGA NPs loaded with DEX were prepared by the dialysis and oil/water (O/W) emulsion/solvent evaporation method. The

optimized lactide glycolide ratio for this formulation was 65:35 to achieve the best sustained release and particle size distribution. In order to further reduce the burst release, the study employed a PLGA-Polyethylene Glycol (PEG)-PLGA thermosensitive gel into which the drug loaded particles were embedded. This strategy was useful in sustaining the release for nearly 100 hours as opposed to the 40 hours release from the free PLGA NPs. The study (using *ex-vivo* model) also suggests that encapsulation of drug releasing NPs within hydrogels can help in localization of these NPs at the target site.[65]

In a human trial, PLGA microspheres loaded with triamcinolone acetamide (TA microspheres) were tested in patients with diffuse DME. TA microspheres administered by direct IVT injections showed a marked decrease of retinal thickness as well as improvement of visual acuity for 12 months as compared to free TA. TA microspheres were also found to be well tolerated and safe. A phase I/II study showed that 3 months after TA microspheres injections, there was a considerable reduction in central macular edema in comparison to the baseline by as much as 59% as observed from Optical Coherence Tomography (OCT) measurement.[66]

PLGA particles have also been used to load bevacizumab.[67, 68] Pan et al. studied the effect of PLGA encapsulated bevacizumab and PEGylated bevacizumab in reducing the extent of experimentally induced Choroidal Neovascularization (CNV) in rat eyes. The study divided the experimental rats into 4 groups wherein each group was given a specific treatment regimen consisting of injections at varying time points in laser induced CNV rats. Within each group there were four subgroups which were given injections of either free bevacizumab, PEGylated bevacizumab, PLGA encapsulated bevacizumab or saline control. They found out that there was significant decrease in CNV area compared to the saline control, but there was no significant difference between the subgroups consisting of free bevacizumab, PEGylated bevacizumab and PLGA encapsulated bevacizumab. [67]

In another study, bevacizumab loaded in nanoparticles made from PLGA, showed sustained invitro release for approximately 90 days.[68] Although it was shown that proteins loaded in PLGA particles can be released in a sustained manner, but the drugs may undergo inactivation and aggregation due to the extreme conditions employed during fabrication. Also, the highly acidic pH generated during the degradation of the PLGA particles could adversely affect the activity of protein drugs. Recently, some groups have come up with strategies to overcome this, for instance, Varshochian et al. reported that the drug activity was considerably improved when bevacizumab loaded PLGA particles was prepared with albumin as a stabilizer. *Ex vivo* release studies carried out using this system demonstrated their ability to sustain the release of active drug for as long as 6 weeks, during which 49% of the drug was released.[69]

Other polymeric particles include polypeptide or polysaccharide or oligosaccharide-based MPs and NPs. For example, DEX-loaded polyglutamic acid NPs conjugated with l-phenylalanine was shown to suppress the expression of TNF $\pm$ and MCP-1 in cultured macrophages or microglia, thereby suppressing the activity of inflammatory cells in the retina.[70]

3.1.2. Cyclodextrins

Cyclodextrins are oligosaccharides that are amphiphilic with a water soluble outer surface and a lipid soluble inner cavity. This facilitates loading of lipophilic drugs in the core, thereby converting them into water soluble complexes. Due to this capability and because of the mucoadhesive properties of cyclodextrin, eye drop formulations have been made using cyclodextrin MPs and NPs.[71-73]

In the rabbit preclinical studies, the eye drop suspension of cyclodextrin MPs encapsulated dexamethasone could reach vitreous and retina 2 hours after single topical application at the concentrations which could be comparable with the levels maintained after 1 month intravitreal administration of dexamethasone. The formulation was well tolerated and chemically stable during 7

months storage period. Also the drug levels reached the systemic circulation was low hence could reduce side effects; this indicates the site specific (vitreous and retina) capability of the cyclodextrin eye drops as compare to the conventional one. [75] In the pilot clinical study, it showed that the eye drops are well tolerated by DME patients with decrease in central macular thickness and improve visual acuity. [71] This system proceeded to Phase II/III clinical trials to investigate its efficacy in human subjects in treating DME.[74]

3.1.3. Liposomes

Liposomes are vesicular in structure and are formed by spontaneous assembly of lipids into an aqueous core and a concentric bilayer of lipids. The aqueous core is utilized to load hydrophilic drugs, whereas the hydrophobic bilayers offer suitable environment for hydrophobic drug encapsulation. Their fabrication methods offer flexibility to synthesize systems with sizes ranging from nanometers to micrometers, with considerable control over surface-charge lipid composition and bilayer fluidity. Liposomes were among the few nanoparticle DDS that have been commercialized. In ophthalmic applications, liposomal formulation of verteporfin has reached the clinic for treatment of CNV.[76]

Liposomal drug formulations have been shown to increase the half-life of several DR therapeutics. For example, loading fluocinolone acetonide (FA) into liposomes increased the half-life of the drug by a factor of 7.[77] Bevacizumab concentration in the eyes treated with intravitreal liposomal bevacizumab was 2 and 5 times higher than the free drug at Days 28 and 42, respectively.[78] Liposomes have also been shown to increase the transport of topically applied drugs to the retina. Liposomes decorated with a phospholipid binding protein, Annexin A5 was shown to increase posterior eye concentration of bevacizumab following topical eye drop application. [79]

Although liposomes have several advantages for delivering drugs to the posterior segment via IVT injections, one of the main challenges lies in the aggregation of the vesicles in the vitreous environment, leading to blurring of vision.[80] One alternate way could be to deliver drugs via the periocular route. If we are able to design DDS that overcome scleral and choroidal barriers, these systems could potentially be a safer method of administration resulting in an overall improved patient compliance with minimal side effects.

3.1.4. Emulsions

Similar to liposomes, emulsions are useful for encapsulating hydrophobic drug molecules. A tissue activated dexamethasone prodrug, dexamethasone palmitate was formulated as oil-in-water emulsion to treat DME. A single IVT injection of this formulation was capable of sustaining the retinal and choroidal drug levels of 1,179.6 and 577.7 ng/g with a half-life of 189 and 103 days, respectively, and thereby was capable of inhibiting vascular hyper-permeability for months.[81] A phospholipid emulsion, of the same prodrug has reached the Phase I trials for DME. A single injection of this drug has been capable of sustaining the release for over 6–9 months.[82]

3.1.5. Micelles

Micelles are very similar to liposomes except for the fact that the amphiphilic species in micelles are arranged in monolayers around the hydrophobic core. Polymeric micelles have been used to carry dexamethasone. Micelles based on copolymers of polyhydroxyethylaspartamide encapsulating dexamethasone displayed enhanced drug permeation across ocular epithelia compared to free DEX. This system also improved the bioavailability of dexamethasone by 40%.[83] In another study, a micellar system made up of polyoxyethylated nonionic surfactant Pluronic® F127 and cationic polyelectrolyte chitosan were synthesized to load dexamethasone. Bioavailability of dexamethasone encapsulated

within this micellar system was enhanced by a factor of 2.4 when administered as an eye drop.[84] In another study, polymeric micelles made from N-isopropylacrylamide, vinyl pyrrolidone (VP), and methacrylate (MAA) by cyclic polymerization was used to deliver dexamethasone topically. The study reported a higher anti-inflammatory activity for a longer duration than in the case of aqueous suspension of the drug.[85]

3.1.6. Hydrogels

Hydrogels are polymeric biomaterials that have the ability to swell in the presence of water. The drugs are usually immobilized within the cross-linked gel and the release is modulated by controlling degree of cross-linking between the polymeric network chains.

Xu et al. used oxidized alginate and chitosan hydrogel to encapsulate bevacizumab. The 3D structured hydrogel forms spontaneously through dynamic covalent Schiff-base linkages between the amino group on chitosan and the aldehyde group on oxidized alginate. Bevacizumab was added during the gel formation and gets entrapped within the gel as it cross-links. The authors observed an initial burst release of bevacizumab followed by a sustained release regimen for 3 days. [86] Yu et al. reported the fabrication of a hyaluronan-based hydrogel system by catalyst-free click chemistry. The system that gelled in physiological conditions demonstrated a long release time of greater than 3 months for bevacizumab.[87]

One of the most interesting categories of hydrogels is *in situ* gelling hydrogel systems, which remain liquid during administration and hence can be injected easily. When the gel comes in contact with the physiological milieu, it utilizes the surrounding stimuli, such as ion concentration, temperature, pH, etc., and undergoes a phase change to form a gel. One such system was developed by Derwent et al. where a thermoresponsive hydrogel was prepared from poly (N-isopropylacrylamide), cross-linked with poly

(ethylene glycol) diacrylate (PEG-DA) that remains liquid at room temperature and turns into a solid gel at body temperature. The study showed successful loading of bevacizumab and ranibizumab into these hydrogels. However, the release profiles of these drugs and their *in vivo* efficacy still needs to be evaluated. [88] In a similar study, a triblock copolymer of poly (2-ethyl-2-oxazoline)-b-poly (μ -caprolactone)-b-poly (2-ethyl-2-oxazoline) was used to fabricate thermo-responsive hydrogels for loading bevacizumab. The system was able to sustain the release of bevacizumab for as long as 18 days *in vitro*. [89]

Tyagi et al. fabricated a light responsive hydrogel based on polycaprolactone dimethacrylate and hydroxyethyl methacrylate for sustained release of bevacizumab. The *in vivo* studies using this gel showed that it was able to sustain the release of bevacizumab for as long as 60 days in the suprachoroidal space in rat eyes. [90]

4. Drug Delivery Devices

The advancements made in surgical insertion into the posterior eye segment, has given an edge to the development of various drug delivery devices, which can replace IVT injections. (Figure 3; Table 3). [91]

4.1. Implants

The introduction of injectable implant technology has revolutionized the IVT drug delivery. Nowadays, much research is concentrated on drug delivery using implants. The implants can be classified as biodegradable or non-biodegradable based on the polymer used in the implant. The non-biodegradable polymer offer great advantage in controlling the release of drug over a long period of time as compared to biodegradable polymer. The biodegradable implant undergoes degradation in the eye and hence does not require surgical removal, whereas the non-biodegradable implant needs removal after treatment

duration, as otherwise successive implants may start to obscure vision. Both biodegradable and non-biodegradable implants provide an advantage in principle, of removal if found to be toxic or causes side effects, although the removal of IVT implant could be challenging as compared to scleral implants.[92-94] The success stories of approved implants also provides impetus for extended use as a vehicle for DR therapeutics [92]. The IVT and periocular routes are the potential routes for implants to deliver sufficient drug to the retina for treating DR/DME.

4.1.1. IVT Implants

Intravitreal FA is a better drug for development into a sustained release implantable system for DME, due to its characteristics, such as solubility and lipophilicity. The injectable IVT FA non-biodegradable insert (Iluvien™) was developed by Alimera Sciences, Inc., GA, USA. The tiny cylindrical implant consists of a polyimide tube and polyvinyl alcohol or silicone seal.[95] A 25-gauge proprietary inserter is used to inject the implant into the vitreous without any suture due to its small size of 3.5×0.37 mm cylinder. The release of FA was regulated by the PVA cap. The FA implant was clinically tested for DME treatment at the high dose of $0.5 \mu\text{g/day}$ and low dose of $0.2 \mu\text{g/day}$. The implant was developed to release FA over a period of 18–24 months for high dose and for 24–30 months period for low dose. [96] A multi-centered trial [Flucinolone Acetonide in Diabetic Macular Edema (FAME)] studied the percentage of patients with improvement from baseline best-corrected visual acuity (BCVA) with a letter score of 15 or more after 24 months. The group with implants were positive for resolution of DME but required more cataract and glaucoma surgery than those of the sham group. At 24 months, 28.7 and 28.6% (for low and high dose) of patients showed improvement from baseline. The low dose implant provided a superior risk-to-benefit ratio and interestingly the implant can be given as an outpatient injection, which provides benefit over 2 years for DME.[97, 98] The FA implant was suggested for the

patients with recurrent or persistent DME[28] The FAME study suggests visual benefit for 3 years in patients with DME.[99]

Another non-degradable implant (RetisertTM; Bausch and Lomb Inc, Rochester, NY, USA) was studied in a multi-center trial for their efficacy and safety in patients with persistent or recurrent DME. The implant needs to be surgically implanted and can release the drug over 3 years. The implant is made up of a tiny tablet packed inside an elastomer cup of silicone which contains an orifice to release the drug and polyvinyl alcohol membrane in between the orifice and the tablet. When the vitreous environment hydrates the implant, some drug turns into a solution then slowly release through the orifice in a linear fashion.[95] In the clinic, patients were treated with FA 0.59 mg implant or standard of care (SOC) **additional** laser therapy or observation. The implant showed a significant reduction in DME along with improvement in the visual outcome (VA) and Diabetic Retinopathy Severity Score (DRSS). However, the IOP and cataract risks were found to be the most common adverse effects after implantation [100].

Could biodegradable implants overcome some of the issues associated with biostable implants? In two randomized, multicenter masked, sham controlled phase III clinical trials, patients with DME were treated with dexamethasone IVT biodegradable implant (0.7 mg, 0.35 mg; OzurdexTM, Allergan, CA, USA) and sham implants. The preservative-free implant contains micronized dexamethasone and a polymer matrix of PLGA which slowly degrades into water and carbon dioxide, hence requiring no surgical removal. The ratio of lactide and glycolide in the polymer can be altered to regulate the release of drug. However, achieving zero order release is quite challenging [95, 101, 102]. The dexamethasone 0.7 mg (22.2%), dexamethasone 0.35 mg (18.4%) and sham (12%)- treated patients showed improvement in BCVA from baseline at end of the study and also a reduction in average central retinal thickness from baseline. Unfortunately, in phakic eyes, the rate of cataract related adverse events was

found to be 67.9% (Dexamethasone 0.7 mg) and 64.1% (Dexamethasone 0.35 mg) as compared to 20.4% in sham group. In conclusion, the dexamethasone implant could meet the primary efficacy endpoint for BCVA improvement with the acceptable safety profile.[103] In 2014, the dexamethasone implant (0.7 mg) was approved by FDA for treating DME.[104]

The Verisome technology (injectable biodegradable delivery system) to deliver TA is being tested adjunctively with ranibizumab for treating neovascular age related macular degeneration, but its use in DR is not known (Table. 3).[105]

4.1.2. Periocular Implants

Biodegradable periocular implants could be manufactured in various shapes, such as pellets, rods, disks, plugs and sheets, and a small incision is sufficient for the implantation. The drug can be conjugated to various polymers, like PLGA, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(methylene malonate) and poly(caprolactone).[92] An intrascleral biodegradable TA 6.4 mg implant (1 mm thick × 3mm diameter) was made of PLA (poly[D,L-lactide]) of molecular weight 125,000). Interestingly, to provide a unidirectional TA absorption in the sclera, the implant was coated on one side with a high molecular weight (300,000) PLA film barrier: this barrier allows the TA to be released towards the sclera, and presumably avoids TA absorption by conjunctiva vessels and lymphatics. When the implant was used in a preliminary efficacy study in 20 rabbits, significant levels of TA reached the retina-choroid for up to 8 weeks and the aqueous humor for 4 weeks post-implantation. Also, the TA was detected in the vitreous for the entire 12 weeks of the study. However, further studies are required to evaluate its usage in humans.[106, 107]

A refillable ranibizumab loaded pre-programmed micro-pump implant was recently tested in a first-in-man (FIM) study for DME. The device can deliver the drug in form of controlled nanoliter droplets. It is

a subconjunctival implant refilled through a needle tubing kit in clinics.[108, 109] The device demonstrated improvements in visual acuity in 7 out of 11 enrolled patients.[110] Another ranibizumab-loaded, refillable non-biodegradable subconjunctival implant, was also reported using a port delivery system technology; however, the implant's application for DR has not been tested yet.[111] Many research groups are also currently attempting to develop sustained-release implants to deliver anti-VEGF protein therapeutics for DR.

5. Conclusion

Molecular understanding of the pathology of DR has paved the way for newer molecules, while understanding of pharmacokinetics and pharmacodynamics of different agents have led to newer routes of drug delivery. In the case of DR, which is the current focus of this review, various novel anti-VEGF protein therapeutics are being developed and this class of molecules remains the mainstay of the treatment options for DR. In the clinic, IVT is considered the gold standard for administration even though the side effects associated with this mode of administration are many. For DDS, some of the challenges lie in the preparation strategies of particulate systems, such as the stability of the bioactive material to the process used, and the inability to control the release of the drugs over a long period of time. In addition, the transport barriers are substantial and challenging if non-IVT routes are considered. In this regard, it is safe to say that topical administration of anti-VEGF molecules for DR will not make it to the clinic in the foreseeable future whereas other modes of administration have better chances.

6. Expert opinion

From this review, it should be evident that intra-vitreous delivery of agents to treat DR has been commercialized with some degree of success. For small drugs, such as TA and dexamethasone, the duration of delivery is quite long, up to 36 months in one case, and hence the invasive procedure with its

side effects is justifiable. However for larger molecules such as anti-VEGF agents, IVT remains problematic in terms of cost-to-benefit ratio; the “cost” here is defined in terms of actual cost of the drug as well as associated side effects of the procedure, such as retinal detachment. For these drugs, there is a crying need for a minimally-invasive approach, or to prolong the duration of action of intra-vitreally administered drug.

Thus, the search for an ideal drug delivery system continues, with efforts concentrated on designing a long-lasting, stable and easy-to-administer therapy with minimal side-effects. With extensive research carried out at major pharmaceutical companies and by retinal scientists on newer drugs and drug delivery systems for the back of the eye, the invention of such an ideal system is not a distant dream. In our opinion, with the advent of novel drug molecules and drug delivery approaches, there has been a considerable shift in the treatment paradigm for back of the eye diseases, including DR. The results are encouraging from preclinical studies; however, there is a huge lacuna in translating preclinical results into the clinic. Very few human studies have borne out the promise from animal studies: there are various reasons for this lack of translation, but a key factor is the BRB: how to traverse this barrier and deliver the drug to the retina is a major hurdle that has not been satisfactorily overcome. However, in the last decade, there has been a concerted effort to overcome these pitfalls and effective strategies are being implemented.

There is also considerable interest in developing alternative small molecular weight drugs to treat DR, which have better chances of being successful in the future. Nevertheless, the successful use of small molecular weight drugs in the clinic still needs to be demonstrated. In our opinion, there needs to be a shift in research focus towards periocular drug delivery systems and devices; as we believe these could be a safer and a better alternative than IVT because of the procedure is inherently less risky, with minimal side effects such as endophthalmitis, increase in IOP, retinal hemorrhage, tear, or detachment.

However, a better understanding and challenges to overcome physiological and anatomical barriers are profound in periocular drug delivery. Periocular implants that can sustain the release of the drug over a long period (months to years) are being developed and are in the market already. Periocular implants could be used to deliver both large molecular weight proteins, such as aflibercept and ranibizumab, and small molecular weight drugs, such as fluocinolone acetonide.

Considering the size of the protein therapeutics and stability, it is even more challenging to load these into microparticle/nanoparticle carrier systems. There are very few published articles that examine the factors affecting loading and release of drugs/proteins for sustained release applications. More research effort is required in this area of DDS, possibly with the use of newer naturally inspired biomaterials.

Although intra-vitreous drugs will continue to play a role in the treatment options for DR, patient acceptance demands less invasive procedures, and so the efforts continue to find the right combination of drug, carrier and mode of administration. For that purpose, research needs to be more focused taking into consideration all the factors involved in 3Ds (drug, delivery and devices).

Declaration of Interest

The project is funded by National Thematic Research Grant, Ageing Research Grant and Nanyang Technological University – National Healthcare Group Metabolic disease grant administered by National Healthcare Group, Singapore. J Nirmal is a post doctorate fellow working under National Thematic Research Grant, R Agrawal is the clinical Principal investigator and Prof Subbu Venkatraman is the technical Principal investigator. The authors have no other relevant affiliations or financial

involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed

7. References

1. Aiello LM. Perspectives on diabetic retinopathy. *Am J Ophthalmol* 2003 Jul;136(1):122-135.
2. Klaassen I, Van Noorden CJ, Schlingemann RO. Molecular basis of the inner blood-retinal barrier and its breakdown in diabetic macular edema and other pathological conditions. *Prog Retin Eye Res* 2013 May;34:19-48.
3. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care* 2003 Sep;26(9):2653-2664.
4. Kern TS. Contributions of inflammatory processes to the development of the early stages of diabetic retinopathy. *Exp Diabetes Res* 2007;2007:95103.
5. Meyer CH. Current treatment approaches in diabetic macular edema. *Ophthalmologica* 2007;221(2):118-131.
6. Villar G, Garcia Y, Goicolea I, et al. Determinants of development of microalbuminuria in normotensive patients with type 1 and type 2 diabetes. *Diabetes Metab* 1999 Sep;25(3):246-254.
7. Reaven PD, Emanuele N, Moritz T, et al. Proliferative diabetic retinopathy in type 2 diabetes is related to coronary artery calcium in the Veterans Affairs Diabetes Trial (VADT). *Diabetes Care* 2008 May;31(5):952-957.
8. Kleinman ME, Baffi JZ, Ambati J. The multifactorial nature of retinal vascular disease. *Ophthalmologica* 2010;224 Suppl 1:16-24.
9. Antcliff RJ, Marshall J. The pathogenesis of edema in diabetic maculopathy. *Semin Ophthalmol* 1999 Dec;14(4):223-232.
10. Dahrouj M, Desjardins DM, Liu Y, et al. Receptor mediated disruption of retinal pigment epithelium function in acute glycated-albumin exposure. *Exp Eye Res* 2015 Aug;137:50-56.
11. Miyamoto N, de Kozak Y, Jeanny JC, et al. Placental growth factor-1 and epithelial haemato-retinal barrier breakdown: potential implication in the pathogenesis of diabetic retinopathy, 2007.
12. Shams N, Ianchulev T. Role of vascular endothelial growth factor in ocular angiogenesis. *Ophthalmol Clin North Am* 2006 Sep;19(3):335-344.
13. Tolentino MJ, Miller JW, Gragoudas ES, et al. Intravitreal injections of vascular endothelial growth factor produce retinal ischemia and microangiopathy in an adult primate. *Ophthalmology* 1996 Nov;103(11):1820-1828.
14. Funatsu H, Yamashita H, Noma H, et al. Increased levels of vascular endothelial growth factor and interleukin-6 in the aqueous humor of diabetics with macular edema. *Am J Ophthalmol* 2002 Jan;133(1):70-77.
15. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med* 1994 Dec 1;331(22):1480-1487.
16. Campochiaro PA. Retinal and choroidal neovascularization. *J Cell Physiol* 2000 Sep;184(3):301-310.

17. Dejana E, Spagnuolo R, Bazzoni G. Interendothelial junctions and their role in the control of angiogenesis, vascular permeability and leukocyte transmigration. *Thromb Haemost* 2001 Jul;86(1):308-315.
18. Tang J, Kern TS. Inflammation in diabetic retinopathy. *Prog Retin Eye Res* 2011 Sep;30(5):343-358.
19. Russo A, Costagliola C, Delcassi L, et al. Topical nonsteroidal anti-inflammatory drugs for macular edema. *Mediators Inflamm* 2013;2013:476525.
20. Rechtman E, Harris A, Garzosi HJ, et al. Pharmacologic therapies for diabetic retinopathy and diabetic macular edema. *Clin Ophthalmol* 2007 Dec;1(4):383-391.
21. Singh R, Ramasamy K, Abraham C, et al. Diabetic retinopathy: an update. *Indian J Ophthalmol* 2008 May-Jun;56(3):178-188.
22. Urtti A. Challenges and obstacles of ocular pharmacokinetics and drug delivery. *Adv Drug Deliv Rev* 2006 Nov 15;58(11):1131-1135.
23. Hughes PM, Olejnik O, Chang-Lin JE, et al. Topical and systemic drug delivery to the posterior segments. *Adv Drug Deliv Rev* 2005 Dec 13;57(14):2010-2032.
24. Kern TS, Miller CM, Du Y, et al. Topical administration of nepafenac inhibits diabetes-induced retinal microvascular disease and underlying abnormalities of retinal metabolism and physiology. *Diabetes* 2007 Feb;56(2):373-379.
25. Shimura M, Yasuda K. Topical bromfenac reduces the frequency of intravitreal bevacizumab in patients with branch retinal vein occlusion. *Br J Ophthalmol* 2015 Feb;99(2):215-219.
26. Klettner A, Roider J. Comparison of bevacizumab, ranibizumab, and pegaptanib in vitro: efficiency and possible additional pathways. *Invest Ophthalmol Vis Sci* 2008 Oct;49(10):4523-4527.
27. Chen JJ, Ebmeier SE, Sutherland WM, et al. Potential penetration of topical ranibizumab (Lucentis) in the rabbit eye. *Eye (Lond)* 2011 Nov;25(11):1504-1511.
28. Bandello F, Preziosa C, Querques G, et al. Update of intravitreal steroids for the treatment of diabetic macular edema. *Ophthalmic Res* 2014;52(2):89-96.
29. Ranta VP, Urtti A. Transscleral drug delivery to the posterior eye: prospects of pharmacokinetic modeling. *Adv Drug Deliv Rev* 2006 Nov 15;58(11):1164-1181.
30. Nomoto H, Shiraga F, Kuno N, et al. Pharmacokinetics of bevacizumab after topical, subconjunctival, and intravitreal administration in rabbits. *Invest Ophthalmol Vis Sci* 2009 Oct;50(10):4807-4813.
31. Zhao Y, Lei W. [Retina penetration of subconjunctival ranibizumab injection in the rabbit eye]. *Zhonghua Yan Ke Za Zhi* 2015 May;51(5):356-359.
32. Ferrara N, Damico L, Shams N, et al. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina* 2006 Oct;26(8):859-870.
33. Shen L, Mao J, Chen Y, et al. Transscleral permeation of subtenon triamcinolone in different vitreoretinal diseases. *Ophthalmology* 2015 Mar;122(3):649-651.
34. Paul M, Vieillard V, Roumi E, et al. Long-term stability of bevacizumab repackaged in 1mL polypropylene syringes for intravitreal administration. *Ann Pharm Fr* 2012 May;70(3):139-154.
35. Signorello L, Pucciarelli S, Bonacucina G, et al. Quantification, microbial contamination, physico-chemical stability of repackaged bevacizumab stored under different conditions. *Curr Pharm Biotechnol* 2014;15(2):113-119.
36. Yannuzzi NA, Klufas MA, Quach L, et al. Evaluation of compounded bevacizumab prepared for intravitreal injection. *JAMA Ophthalmol* 2015 Jan;133(1):32-39.
37. Wang Y, Fei D, Vanderlaan M, et al. Biological activity of bevacizumab, a humanized anti-VEGF antibody in vitro. *Angiogenesis* 2004;7(4):335-345.
38. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012 Apr;119(4):789-801.

39. Writing Committee for the Diabetic Retinopathy Clinical Research N, Gross JG, Glassman AR, et al. Panretinal Photocoagulation vs Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. *JAMA* 2015 Nov 24;314(20):2137-2146.
40. Do DV, Schmidt-Erfurth U, Gonzalez VH, et al. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. *Ophthalmology* 2011 Sep;118(9):1819-1826.
41. Weidle UH, Schneider B, Georges G, et al. Genetically engineered fusion proteins for treatment of cancer. *Cancer Genomics Proteomics* 2012 Nov;9(6):357-372.
42. Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis* 2012 Jun;15(2):171-185.
43. Diabetic Retinopathy Clinical Research N, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 2015 Mar 26;372(13):1193-1203.
44. NCT02194634. Safety and Efficacy Study of Conbercept in Diabetic Macular Edema (DME) (Sailing). [cited [Last accessed 1 December 2015]]; Available from: <https://clinicaltrials.gov/ct2/show/NCT02194634>
45. Wu Z, Zhou P, Li X, et al. Structural characterization of a recombinant fusion protein by instrumental analysis and molecular modeling. *PLoS One* 2013;8(3):e57642.
46. Struble C, Tester A, Gerometta M, et al. Ocular distribution and pharmacokinetics of 125I-OPT302 and 125I-Aflibercept (EYLEA) following intravitreal administration to pigmented rabbits. *Acta Ophthalmologica* 2014;92:0-0.
47. Stahl A, Stumpp MT, Schlegel A, et al. Highly potent VEGF-A-antagonistic DARPins as anti-angiogenic agents for topical and intravitreal applications. *Angiogenesis* 2013 Jan;16(1):101-111.
48. Binz HK, Amstutz P, Kohl A, et al. High-affinity binders selected from designed ankyrin repeat protein libraries. *Nat Biotechnol* 2004 May;22(5):575-582.
49. Gariano RF, Gardner TW. Retinal angiogenesis in development and disease. *Nature* 2005 Dec 15;438(7070):960-966.
50. Yu W, Bai Y, Han N, et al. Inhibition of pathological retinal neovascularization by semaphorin 3A. *Mol Vis* 2013;19:1397-1405.
51. Eichmann A, Le Noble F, Autiero M, et al. Guidance of vascular and neural network formation. *Curr Opin Neurobiol* 2005 Feb;15(1):108-115.
52. Melani M, Weinstein BM. Common factors regulating patterning of the nervous and vascular systems. *Annu Rev Cell Dev Biol* 2010;26:639-665.
53. Agrawal NK, Kant S. Targeting inflammation in diabetes: Newer therapeutic options. *World J Diabetes* 2014 Oct 15;5(5):697-710.
54. Dedania VS, Bakri SJ. Novel pharmacotherapies in diabetic retinopathy. *Middle East Afr J Ophthalmol* 2015 Apr-Jun;22(2):164-173.
55. Nauck M, Roth M, Tamm M, et al. Induction of vascular endothelial growth factor by platelet-activating factor and platelet-derived growth factor is downregulated by corticosteroids. *Am J Respir Cell Mol Biol* 1997 Apr;16(4):398-406.
56. Nauck M, Karakiulakis G, Perruchoud AP, et al. Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. *Eur J Pharmacol* 1998 Jan 12;341(2-3):309-315.
57. Schwartz SG, Flynn HW, Jr., Scott IU. Emerging drugs for diabetic macular edema. *Expert Opin Emerg Drugs* 2014 Sep;19(3):397-405.
58. Diabetic Retinopathy Clinical Research N, Beck RW, Edwards AR, et al. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Arch Ophthalmol* 2009 Mar;127(3):245-251.
59. Audren F, Erginay A, Haouchine B, et al. Intravitreal triamcinolone acetate for diffuse diabetic macular oedema: 6-month results of a prospective controlled trial. *Acta Ophthalmol Scand* 2006 Oct;84(5):624-630.

60. Massin P, Audren F, Haouchine B, et al. Intravitreal triamcinolone acetonide for diabetic diffuse macular edema: preliminary results of a prospective controlled trial. *Ophthalmology* 2004 Feb;111(2):218-224; discussion 224-215.
61. Sutter FK, Simpson JM, Gillies MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. *Ophthalmology* 2004 Nov;111(11):2044-2049.
62. Diabetic Retinopathy Clinical Research N, Googe J, Brucker AJ, et al. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. *Retina* 2011 Jun;31(6):1009-1027.
63. Aukunuru JV, Sunkara G, Ayalasomayajula SP, et al. A biodegradable injectable implant sustains systemic and ocular delivery of an aldose reductase inhibitor and ameliorates biochemical changes in a galactose-fed rat model for diabetic complications. *Pharm Res* 2002 Mar;19(3):278-285.
64. Xu J, Wang Y, Li Y, et al. Inhibitory efficacy of intravitreal dexamethasone acetate-loaded PLGA nanoparticles on choroidal neovascularization in a laser-induced rat model. *J Ocul Pharmacol Ther* 2007 Dec;23(6):527-540.
65. Boddu SH, Jwala J, Vaishya R, et al. Novel nanoparticulate gel formulations of steroids for the treatment of macular edema. *J Ocul Pharmacol Ther* Feb;26(1):37-48.
66. Cardillo JA, Souza-Filho AA, Oliveira AG. Intravitreal Bioerudivel sustained-release triamcinolone microspheres system (RETAAC). Preliminary report of its potential usefulness for the treatment of diabetic macular edema. *Arch Soc Esp Oftalmol* 2006 Dec;81(12):675-677, 679-681.
67. Pan CK, Durairaj C, Kompella UB, et al. Comparison of long-acting bevacizumab formulations in the treatment of choroidal neovascularization in a rat model. *J Ocul Pharmacol Ther* 2011 Jun;27(3):219-224.
68. Li F, Hurley B, Liu Y, et al. Controlled release of bevacizumab through nanospheres for extended treatment of age-related macular degeneration. *Open Ophthalmol J* 2012;6:54-58.
69. Varshochian R, Jeddi-Tehrani M, Mahmoudi AR, et al. The protective effect of albumin on bevacizumab activity and stability in PLGA nanoparticles intended for retinal and choroidal neovascularization treatments. *Eur J Pharm Sci* 2013 Nov 20;50(3-4):341-352.
70. Ryu M, Nakazawa T, Akagi T, et al. Suppression of phagocytic cells in retinal disorders using amphiphilic poly(gamma-glutamic acid) nanoparticles containing dexamethasone. *J Control Release* 2011 Apr 10;151(1):65-73.
71. Tanito M, Hara K, Takai Y, et al. Topical dexamethasone-cyclodextrin microparticle eye drops for diabetic macular edema. *Invest Ophthalmol Vis Sci* 2011;52(11):7944-7948.
72. Johannesson G, Moya-Ortega MD, Asgrimsdottir GM, et al. Kinetics of gamma-cyclodextrin nanoparticle suspension eye drops in tear fluid. *Acta Ophthalmol* 2014 Sep;92(6):550-556.
73. Ohira A, Hara K, Johannesson G, et al. Topical dexamethasone gamma-cyclodextrin nanoparticle eye drops increase visual acuity and decrease macular thickness in diabetic macular oedema. *Acta Ophthalmol* 2015 Nov;93(7):610-615.
74. NCT01523314. Topical Dexamethasone - Cyclodextrin Microparticle Eye Drops for Diabetic Macular Edema. [cited [Last accessed 1 December 2015]]; Available from: <https://clinicaltrials.gov/ct2/results?term=NCT01523314&Search=Search>
75. Loftsson T, Hreinsdottir D, Stefansson E. Cyclodextrin microparticles for drug delivery to the posterior segment of the eye: aqueous dexamethasone eye drops. *J Pharm Pharmacol* 2007 May;59(5):629-635.
76. Ruiz-Moreno JM, Montero JA, Arias L, et al. Photodynamic therapy in subfoveal and juxtafoveal idiopathic and postinflammatory choroidal neovascularization. *Acta Ophthalmol Scand* 2006 Dec;84(6):743-748.
77. Gupta SK, Velpandian T, Dhingra N, et al. Intravitreal pharmacokinetics of plain and liposome-entrapped fluconazole in rabbit eyes. *J Ocul Pharmacol Ther* 2000 Dec;16(6):511-518.

78. Abrishami M, Zarei-Ghanavati S, Soroush D, et al. Preparation, characterization, and in vivo evaluation of nanoliposomes-encapsulated bevacizumab (avastin) for intravitreal administration. *Retina* 2009 May;29(5):699-703.
79. Davis BM, Normando EM, Guo L, et al. Topical delivery of Avastin to the posterior segment of the eye in vivo using annexin A5-associated liposomes. *Small* 2014 Apr 24;10(8):1575-1584.
80. Bochot A, Fattal E. Liposomes for intravitreal drug delivery: a state of the art. *J Control Release* 2012 Jul 20;161(2):628-634.
81. Daull P, Paterson CA, Kuppermann BD, et al. A preliminary evaluation of dexamethasone palmitate emulsion: a novel intravitreal sustained delivery of corticosteroid for treatment of macular edema. *J Ocul Pharmacol Ther* 2013 Mar;29(2):258-269.
82. Noriyuki F, Shinobu, F. Recent Advances in Ocular Drug Delivery Systems. *Polymers* 2011;3((1)):193-221.
83. Civiale C, Licciardi M, Cavallaro G, et al. Polyhydroxyethylaspartamide-based micelles for ocular drug delivery. *Int J Pharm* 2009 Aug 13;378(1-2):177-186.
84. Pepic I, Hafner A, Lovric J, et al. A nonionic surfactant/chitosan micelle system in an innovative eye drop formulation. *J Pharm Sci* 2010 Oct;99(10):4317-4325.
85. Rafie F, Javadzadeh Y, Javadzadeh AR, et al. In vivo evaluation of novel nanoparticles containing dexamethasone for ocular drug delivery on rabbit eye. *Curr Eye Res* 2010 Dec;35(12):1081-1089.
86. Xu X, Weng Y, Xu L, et al. Sustained release of Avastin(R) from polysaccharides cross-linked hydrogels for ocular drug delivery. *Int J Biol Macromol* 2013 Sep;60:272-276.
87. Yu Y, Ying, C. Development of injectable hydrogel based on catalyst-free click chemistry for controlled release of macromolecules - a formulation study for Avastin. *ARVO* 2014.
88. Kang Derwent JJ, Mieler WF. Thermoresponsive hydrogels as a new ocular drug delivery platform to the posterior segment of the eye. *Trans Am Ophthalmol Soc* 2008;106:206-213; discussion 213-204.
89. Wang CH, Hwang YS, Chiang PR, et al. Extended release of bevacizumab by thermosensitive biodegradable and biocompatible hydrogel. *Biomacromolecules* 2012 Jan 9;13(1):40-48.
90. Tyagi P, Barros M, Stansbury JW, et al. Light-activated, in situ forming gel for sustained suprachoroidal delivery of bevacizumab. *Mol Pharm* 2013 Aug 5;10(8):2858-2867.
91. Yilmaz T, Cordero-Coma M, Lavaque AJ, et al. Triamcinolone and intraocular sustained-release delivery systems in diabetic retinopathy. *Curr Pharm Biotechnol* 2011 Mar 1;12(3):337-346.
92. Shah SS, Denham LV, Elison JR, et al. Drug delivery to the posterior segment of the eye for pharmacologic therapy. *Expert Rev Ophthalmol* 2010 Feb 1;5(1):75-93.
93. Khurana RN. How to Manage a Migrating Dexamethasone Intravitreal Implant Review of Ophthalmology 2015 [cited [Last accessed 31 March 2016]]; Available from: <http://www.retina-specialist.com/article/how-to-manage-a-migrating-dexamethasone-intravitreal-implant>
94. Implantation and Removal Procedures. *Retinal Physician* 2011 [cited [Last accessed 31 March 2016]]; Available from: <http://www.retinalphysician.com/articleviewer.aspx?articleID=105433>
95. Haghjou N, Soheilian M, Abdekhodaie MJ. Sustained release intraocular drug delivery devices for treatment of uveitis. *J Ophthalmic Vis Res* 2011 Oct;6(4):317-329.
96. Kane FE, Burdan J, Cutino A, et al. Iluvien: a new sustained delivery technology for posterior eye disease. *Expert Opin Drug Deliv* 2008 Sep;5(9):1039-1046.
97. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology* 2011 Apr;118(4):626-635 e622.
98. Campochiaro PA, Hafiz G, Shah SM, et al. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. *Ophthalmology* 2011 Jul;117(7):1393-1399 e1393.
99. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology* 2012 Oct;119(10):2125-2132.

100. Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. *Ophthalmology* 2011 Aug;118(8):1580-1587.
101. Kompella UB, Kadam RS, Lee VH. Recent advances in ophthalmic drug delivery. *Ther Deliv* 2010 Sep;1(3):435-456.
102. Dugel PU, Bandello F, Loewenstein A. Dexamethasone intravitreal implant in the treatment of diabetic macular edema. *Clin Ophthalmol* 2015;9:1321-1335.
103. Boyer DS, Yoon YH, Belfort R, Jr., et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology* 2014 Oct;121(10):1904-1914.
104. Ozurdex Approval History. . 2014 [cited Last accessed 30 November 2015]; Available from: <http://www.drugs.com/history/ozurdex.html>
105. NCT01175395. 20089 TA+Lucentis Combo Intravitreal Injections for Treatment of Neovascular Age-related Macular Degeneration (AMD) (20089/Combo). [cited; Available from: <https://clinicaltrials.gov/ct2/show/NCT01175395?term=NCT01175395&rank=1>
106. Kim S, Kim JH, Jeon O, et al. Engineered polymers for advanced drug delivery. *Eur J Pharm Biopharm* 2009 Mar;71(3):420-430.
107. Kim YM, Lim JO, Kim HK, et al. A novel design of one-side coated biodegradable intrascleral implant for the sustained release of triamcinolone acetonide. *Eur J Pharm Biopharm* 2008 Sep;70(1):179-186.
108. Chen H. Recent developments in ocular drug delivery. *J Drug Target* 2015 Aug;23(7-8):597-604.
109. Avery RL, Saati S, Journey M, et al. A novel implantable, refillable pump for intraocular drug delivery. . *ARVO*. Fort Lauderdale, Florida 2010.
110. Drug-delivery micropump for chronic retina disorders. 2014 [cited 2 December 2015]; Available from: <http://ophthalmologytimes.modernmedicine.com/ophthalmologytimes/news/drug-delivery-micropump-chronic-retina-disorders?page=full>
111. Good early results seen with anti-VEGF refillable port delivery system. 2013 [cited 4 December 2015]; Available from: <http://www.healio.com/ophthalmology/retina-vitreous/news/print/osn-retina/%7B4df622f8-54f7-4895-a182-a1fbb6902b4%7D/good-early-results-seen-with-anti-vegf-refillable-port-delivery-system>
112. Struble C TA, Gerometta M, Kreuger M, Prusakiewicz J, Baldwin M. Ocular distribution and pharmacokinetics of 125I-OPT302 and 125I-Aflibercept (EYLEA) following intravitreal administration to pigmented rabbits. . *Acta Ophthalmologica* 2014;92.
113. Kern TS, Engerman RL. Pharmacological inhibition of diabetic retinopathy: aminoguanidine and aspirin. *Diabetes* 2001 Jul;50(7):1636-1642.
114. Stitt A, Gardiner TA, Alderson NL, et al. The AGE inhibitor pyridoxamine inhibits development of retinopathy in experimental diabetes. *Diabetes* 2002 Sep;51(9):2826-2832.
115. Dawson DW, Volpert OV, Gillis P, et al. Pigment epithelium-derived factor: a potent inhibitor of angiogenesis. *Science* 1999 Jul 9;285(5425):245-248.
116. Bhatwadekar A, Glenn JV, Figarola JL, et al. A new advanced glycation inhibitor, LR-90, prevents experimental diabetic retinopathy in rats. *Br J Ophthalmol* 2008 Apr;92(4):545-547.
117. A randomized trial of sorbinil, an aldose reductase inhibitor, in diabetic retinopathy. Sorbinil Retinopathy Trial Research Group. *Arch Ophthalmol* 1990 Sep;108(9):1234-1244.
118. Sun W, Oates PJ, Coutcher JB, et al. A selective aldose reductase inhibitor of a new structural class prevents or reverses early retinal abnormalities in experimental diabetic retinopathy. *Diabetes* 2006 Oct;55(10):2757-2762.
119. Galvez MI. Rubosixtaurin and other PKC inhibitors in diabetic retinopathy and macular edema. Review. *Curr Diabetes Rev* 2009 Feb;5(1):14-17.
120. Campochiaro PA, Group CPS. Reduction of diabetic macular edema by oral administration of the kinase inhibitor PKC412. *Invest Ophthalmol Vis Sci* 2004 Mar;45(3):922-931.
121. Gupta N, Mansoor S, Sharma A, et al. Diabetic retinopathy and VEGF. *Open Ophthalmol J* 2013;7:4-10.

122. Iluvien Approval History. 2014 [cited Last accessed 30 November 2015]; Available from: <http://www.drugs.com/history/iluvien.html>
123. NCT00692614. A Study of MK0140 in Diabetic Patients With Macular Edema (0140-001) A Study of MK0140 in Diabetic Patients With Macular Edema (0140-001) [cited [Last accessed 1 December 2015]]; Available from: <https://clinicaltrials.gov/ct2/results?term=NCT00692614&Search=Search>
124. NCT02510794. Study of the Efficacy and Safety of the Ranibizumab Port Delivery System for Sustained Delivery of Ranibizumab in Participants With Subfoveal Neovascular Age-Related Macular Degeneration (LADDER). [cited [Last accessed 31 March 2016]]; Available from: <https://clinicaltrials.gov/ct2/show/NCT02510794?term=NCT02510794&rank=1>

ACCEPTED MANUSCRIPT

TABLES

Table 1: Drugs for diabetic retinopathy (DR)

Drug class	Drugs	Current status (Indication)	References
VEGF inhibitors	Bevacizumab	Off label use	[34, 37]
	Ranibizumab	FDA approved (DME)	[38]
	Aflibercept	FDA approved (DME)	[40, 41]
	RTH258	Phase III	[112]
	Abicipar Pegol	Phase II/III	[49]
Corticosteroids	Triamcinolone	Off label use (DME)	[28]
	acetonide		
	Flucinolone	Off label use (DME)	[28]
	acetonide	Off label use (DME)	[28]
Advanced Glycation End Product Inhibitors	Dexamethasone		
	Aminoguanidine	Experimental	[113]
	Pyridoxamine	Experimental	[114]
	PEDF	Experimental	[115]
	LR-90	Experimental	[116]

Aldose reductase inhibitors	Sorbinol	Phase III completed	[117]
	ARI-809	Experimental	[118]
PKC Inhibitor	Roboxistaurin mesylate	Phase III completed (Not approved)	[119]
	Midostaurin (PKC 412)	Phase I (Terminated)	[120, 121]

DME: Diabetic macular edema; ARI: Aldose reductase inhibitor; PKC: Protein kinase C; PEDF:

Pigment Epithelium Derived Factor

Table 2: Drug delivery system (DDS) that has been explored for clinically used drugs in DR

Drug delivery system	Type of particles	Drugs	References
Polymeric systems	PLGA NPs prepared by emulsification/solvent evaporation	Dexamethasone	[86]
	PLGA microparticles called as RETAAC system	Triamcinolone acetonide	[66]
	PLGA microparticles	Bevacizumab	[67-69]
	Poly glutamic acid NPs	Dexamethasone	[70]
	Cyclodextrin based NPs	Dexamethasone	[71-73]
	Cyclodextrin microparticles		[74]
Liposomes	Submicron sized liposome	Fluocinolone	[77]
	Nano-liposomes	Bevacizumab	[78]

	Annexin A5 decorated liposomes	Bevacizumab	[79]
Emulsions	Nova63035 (Cortiject®)	DEX Palmitate	[82]
	Oil in water emulsion	DEX Palmitate	[81]
Micelles	Polyhydroxyethyl aspartamide based Micelles	Dexamethasone	[83]
	Chitosan and Pluronic F127 micelles	Dexamethasone	[84]
	N-isopropylacrylamide, vinyl pyrrolidone and methacrylate	Dexamethasone	[85]
Hydrogels	Alginate and chitosan hydrogel	Bevacizumab	[86]
	Hyaluronan based hydrogel	Bevacizumab	[87]
	Thermoresponsive poly (N-isopropylacrylamide and polyethylene glycol hydrogel	Bevacizumab and Ranibizumab	[88]
	Poly (2-ethyl-2-oxazoline)-b-poly (μ -	Bevacizumab	[89]

	caprolactone)-b-poly (2-ethyl-2-oxazoline)		
	Polycaprolactone dimethacrylate and hydroxyethyl methacrylate hydrogel	Bevacizumab	[90]

NPs: PLGA: poly (lactic-co-glycolic acid); Nanoparticles; VEGF: Vascular endothelial growth factor

Table 3: Drug delivery devices for DR

Device	Drug candidate	Status	References
Intravitreal implant (Iluvien™)	Fluocinolone acetonide	FDA approved (DME); Approved in some European countries (DME)	[98, 122]
Intravitreal implant (I-vation™)	Triamcinolone acetonide	Phase II terminated	[123]
Intravitreal implant (Ozurdex™)	Dexamethasone	FDA Approved (DME)	[104]
Intravitreal implant (Verisome™)	Triamcinolone acetonide	Phase II *	[105]
Subconjunctival implant (Posterior	Ranibizumab	Phase I	[108-110]

micro pump system)			
Subconju nctival implant (Port delivery system)	Ranibiz umab	Phase II *	[111, 124]

* Being tested for Age related macular degeneration

FDA: Food and drug administration; DME: Diabetic macular edema; DEX: Dexamethasone

Figure 1: Interpretation of a histological section of retinal neovascularization (VEGF: Vascular endothelial growth factor)

Figure 2: Various molecular events and signalling pathways in diabetic retinopathy (AGE: Advanced glycation end products; VEGF: Vascular endothelial growth factor)

Figure 3: A comparison of various drug delivery routes and an illustration of various drug delivery systems that has been designed to overcome limitations associated with these routes.

Topical route

- Less than 5% of the drug reach the target
- Poor permeation through ocular barriers
- Less residence time
- Tear fluid enabled lacrimal drainage
- Pre corneal clearance
- Poor bioavailability

Polymeric spheres

Polymeric capsules

Liposomes

Micelles

Intravitreal route

- Frequent administration
- Retinal detachment & tears
- Hemorrhage & traumatic cataract
- Endophthalmitis
- Maximum bioavailability

Implants

Hydrogels

Drug delivery systems

- Improved bioavailability
- Sustained release – less frequent administration
- Enhanced permeability through ocular barriers

Periocular route

- Minimal injection risk
- Conjunctival & choriocapillaries clearance of drugs
- Long transport route
- Subconjunctival hemorrhage
- Intermediate bioavailability

Article highlight box:

- The plethora of drugs, drug delivery systems and drug delivery devices (3D's) which are developed and under development are summarized
- The readers will get an insight about how VEGF and inflammation plays a role in the progression of diabetic retinopathy.
- The current treatment options for DR in clinics and its routes of delivery and potential alternative routes for future therapeutics have been discussed
- Advantages and disadvantages of topical, intravitreal and periocular routes for DR therapeutics are demonstrated.
- Various particulate drug delivery systems for anti-vegf and nonanti-vegf agents which are under development are reviewed
- The current status of devices (implants) for DR therapeutics is covered.