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RECENT ADVANCES FOR THE TREATMENT OF DIABETIC RETINOPATHY

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ABSTRACT

Innovative drug administration methods are revolutionizing various scientific disciplines, including medicine, by addressing challenges related to drug delivery. The primary objective is to transport therapeutic compounds in adequate amounts to specific areas, such as melignacy and damaged muscles, while reducing toxicity and adverse effects. Diabetic retinopathy is a major concern for pharmaceutical researchers, and the evolution of an ocular drug delivery system (ODDS) is challenging due to outdated ocular solution, ointment, and suspension dosage formulas. Novel intraocular drug delivery methods based on biodegradable carriers must be developed to overcome these constraints. Ophthalmic formulations, such as eye drops and ointments, require sustained drug interaction with ocular tissue, good cornea penetration, ease of use, superior rheological characteristics, and a unirritating variation. ODDS offers benefits such as improved dosage accuracy, steady distribution, longer corneal contact duration, safety precautions, patient comfort, efficient delivery systems, quick absorption, and improved patient compliance. Due to the significant effect that diabetic retinopathy (DR) has on public health, the difficulties that come with the current therapeutic approaches, and the encouraging developments in drug delivery technology, the planned review paper on " RECENT ADVANCES FOR THE TREATMENT OF DIABETIC RETINOPATHY" is justified. A comprehensive review would address the need for consolidated knowledge, guide future research, inform clinical practice, and serve as a valuable educational resource. This evaluation would be current and beneficial to the field given the rapid improvements and the need for new knowledge.

KEYWORDS: Diabetic retinopathy, neovascularization, vitreous bleeding, intravitreal injection, subconjunctival inection., vulnerability.

INTRODUCTION

Innovative drug delivery methods have improved various scientific disciplines, including medicine, by overcoming distribution obstacles. These methods aim to deliver medications in adequate quantities to target specific regions, such as malignancy and damaged cells, while reducing cytotoxicity and adverse reactions.

Hyperglycemia, an elevated blood glucose level in diabetes patients, affects 7% of Americans, with 14.6 million diagnosed, compared to 20.8 million adults and adolescents.[1]

The ODDS method is crucial for pharmaceutical professionals, but developing an updated, sterile, isotonic, and buffered formulation for eye care is a challenging task. This unique system addresses the outdated dosage formulas for modern pathogenic diseases, ensuring effective medication delivery to the eyes.[2]

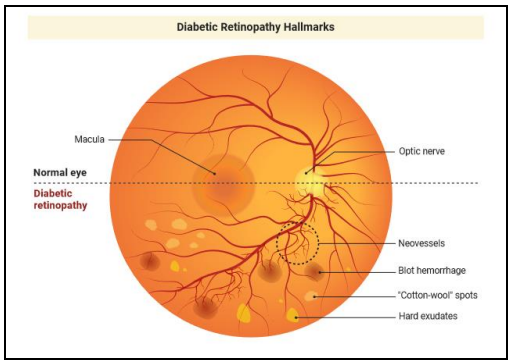

Figure 1: Normal eye and Diabetic retinopathy eye.

Non-proliferative diabetic retinopathy (NPDR) can progress to PDR (Proliferative Diabetic Retinopathy), which is defined by retinal angiogenesis. n. and vitreous bleeding. This disease damages the blood-retinal barrier (BRB) and increases capillary permeability, which results in outflow and diabetic macular edema (DME).[3]

Increased accessibility of a blood vessel, which worsens capillary blokage, is the cause of retinal ischemia and escalated of vascular endothelial growth factor (VEGF).[4]

VEGF inhibitors like Bevacizumab, ranibizumab, and pegaptanib sodium show promise in preventing ocular neovascularization, but face challenges like short half-lives, poor solubility, high dosage effectiveness, and degradation susceptibility.[6] There has only been a small range of technology accessible to treat illnesses and abnormalities of the eyes.

Traditional delivery methods like topical eye drops, intravitreal injection, and subconjunctival injection face physiological and biological challenges, including safety concerns due to immunogenicity, tissue tropism, and genomic insertional mutagenesis.[7] Novel intraocular drug delivery methods using biodegradable carriers are needed to improve stability and efficacy in the intraocular milieu, including various devices like solid lipid nanoparticles, micelles, hydrogels, implants, and emulsions.[6] Formulators face challenges in bypassing eye defenses without damaging tissue, potentially impacting drug bioavailability. Ocular drugs have low bioavailability due to eye defenses, including blinking, baseline, reflex lachrymation, and drainage, which can cause blindness.[7]

Opthalmic formulations, categorized into conventional and non-conventional systems, include eye drops and ointments, accounting for 70% of the market's opthalmic dosages.[8]

Over the past two decades, there's been a focus on developing a controlled, sustained medicine delivery system to maximize therapeutic impact and avoid dose frequency, based on localization at the mechanism of action and eye anatomy and physiology.[9] Understanding drug ingredients and distribution constraints is crucial for effective eye medicine delivery. Two types include sustained drug delivery and optimizing corneal absorption, aiming to increase therapeutic impact and absorption.[10]

Benefits of the ocular drugs delivery method[11]

1. To improve dosage accuracy in order to mitigate the adverse consequences of dose pulsation caused by the traditional method.
2. To distribute drugs in a steady and regulated manner.
3. To lengthen the corneal contact duration in order to boost the drug's ocular absorption. The corneal contact duration might be lengthened to accomplish this. Effective adhesion to the corneal surface can accomplish this.
4. To stop the loss of other ocular tissues, these ocular drug delivery systems (ODDS) offer aiming inside the bulbus oculi.
5. While doing so, get around safety precautions like drainage.
6. To make the patient more comfortable, increase patient compliance, and enhance the medication's therapeutic effect.
7. To offer a housing delivery system that is more efficient.
8. They often absorb quickly and have fewer systemic and ocular adverse effects.
9. The patient can readily administer them on his own.
10. There is improved patient compliance with this ocular medication administration device.[11]

Ocular drugs delivery method drawbacks[12,13]

1. The medication solution only briefly remains on the surface of the eye.
2. They could obstruct one's view.
3. It can demonstrate the drug's fragility after dissolution.
4. The application of preservatives is required.
5. They should often take their medications frequently since the medicine is eliminated from their bodies quickly through eye blinking and tear flow, which shortens the time that the therapeutic impact lasts.
6. The majority of the dosage that is delivered generates undesirable systemic side effects by draining into the lacrimal duct.
7. The cornea's restricted permeability, which results in a reduced absorption of ophthalmic medication formulation, is the physiological restriction.[12,13]

Traditional drug formulations face challenges like short half-lives, poor solubility, high dosage effectiveness, and degradation susceptibility. Traditional eye delivery techniques face physiological and biological obstacles, safety concerns, and immunogenicity issues in clinical trials.[15]

Novel intraocular drug delivery methods using biodegradable carriers are needed to improve stability and efficacy in the intraocular milieu, using various devices like solid lipid nanoparticles, micelles, hydrogels, implants, nanoliposomes, emulsions, and implants.

Nanocarriers face challenges like complex production, immunogenic reactions, toxicity, manufacturing difficulties for medical use, and varying body clearance based on nanoparticle size and characteristics.[17]

This study analyzes new intraocular medicine delivery methods for treating depression, focusing on tonicity, a crucial factor in maintaining ocular tissues' structural integrity. Common tonicity modifiers include Sodium acid posphate buffer and 1.9% boric acid.[18,19]

When treating DR, sterile medication delivery methods are essential for reducing the risk of infection and guaranteeing patient safety. Microbiological contamination might have serious implications due to its direct interaction with delicate eye tissues. Production procedures must thus be carried out in a sterile setting.

You can use sterilization methods like autoclaving, gamma irradiation, or filtering to get rid of any microbiological contamination that are already there. In addition, aseptic packaging and temperature control are necessary for maintaining the sterility of drug delivery systems until they are administered.

ANATOMY OF HUMAN EYE

Given that humans possess binocular vision, the eyes are among the body's most vital organs. Clear vision is essential for daily living and the enjoyment of life, and it is a sign of a healthy set of eyes. eyes merge to form a single picture. An picture is produced by optical components, and the brain uses these connections to see and interpret the image. The entire apparatus operates in a very complex way.

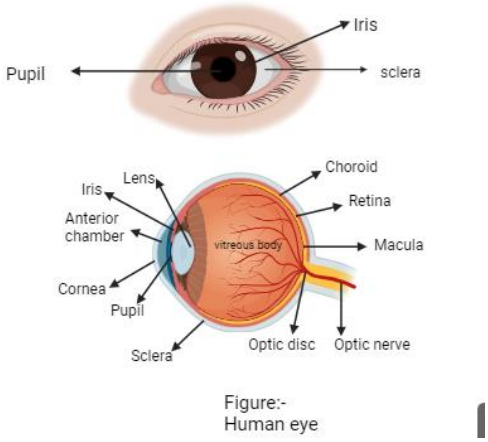

Figure 2: Human Eye.

STRUCTURAL COMPONENTS OF THE EYE

External Components

The eye's outer protective layer is the eyelid, which acts as a barrier against the outside world. Eyelashes cover the eyelids' edges. The cornea, the cornea's circular façade, filters incoming light before it reaches the retina and lens. The iris, pigmented and determining eye color, has a spherical pupil that manages light flow. The pupil dilates and constricts in dark situations, causing temporary blindness when exposed to bright light.

Internal Components

The lens, attached to the eyeball by two muscles, maintains focus for images and changes brightness in response to outside light. It refracts light to concentrate it at the retina. The retinal membrane, the deepest layer, is the focal point of light entering the eye. It consists of photosensitive retinal ganglion cells and tissue components, with cones crucial for sharp contrasted images.

OCULAR DRUG DELIVERY ROUTES

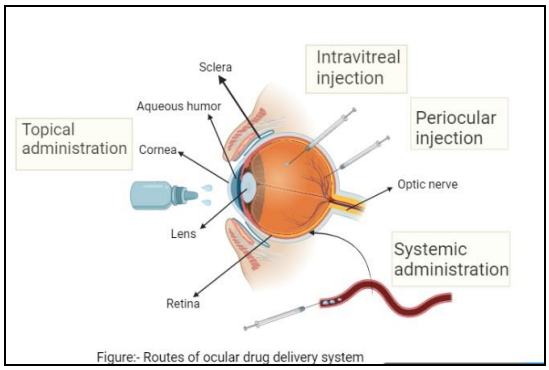

Figure 3: Routes of ODDS.

1. Intravitreal: This method of administering a medicine or other chemical involves injecting it into the vitreous fluid of the eye, where it is absorbed into the eye. Various conditions are treated with this intravitreal mode of administration.[20]

2. Intracameral: This method of administering the medication inside a alcove, such the eye's dorsal and ventral alcove, is known as intracameral administration. Example: During surgery, an anesthetic drug is often injected into the ventral chamber of the eye.

3. Peril ophthalmic: By injecting the steroid in close proximity to the eyes, this particular sort of injection relieves intraocular inflammation or swelling.[21]

4. Supera choroidal: The gap allying the choroid and the sclera is known as the suprachoroidal space. These are the methods for administering the medication to the eye's suprachoroidal area.

Table 1: Devices for ocular implants.[22]

Sr.no	Name	Description
1.	Inserts for soluble ocular drugs	A tiny obovate wafer made of soluble copolymers—acrylamide and ethyl acetate—softens upon implantation.
2.	Collagen shields	Porcine sclera collagen cross-links make up the erodible disc.
3.	Ocuserts	A two-layer, flat, flexible, elliptical insoluble device that surrounds a reservoir and is used in the pharmaceutical industry to distribute pilocarpine for seven days.
4.	Minidisc or ocular therapeutic system	curved hydrophilic or hydrophobic disk with a diameter of 4-5 mm.
5.	Lacrisert	A rose-shaped device composed of hydroxyl propyl cellulose is used as a substitute to tears for treating eye syndrome.
6.	Dry drop	On the point of a smooth hauler, a preservative-free hydrophilic polymer solution freeze-dries and instantly hydrates in a tear strip.

7.	Gel-foam	The medication and cetyl ester wax combination was infused into the gel foam slab using chloroform.
8.	Novel medication delivery method for the eyes	Solid polyvinyl alcohol flag with medication attached, enclosed in a paper handle. When this happens, the medication is released when the flag progressively dissolves and becomes detached.
9.	Bio-adhesive ophthalmic eye inserts	The foundation of adhesive rods is a combination of polyacrylic acid cellulose phthalate, hydroxyl propyl cellulose, and ethylcellulose.

5. Subconjunctiva: The mucosa that enfold the bare area of the eyeball and the inside iris is where the medication is administered using the subconjunctiva method.[23]

6. Topical: To treat anterior segment illnesses, they are mostly available as driblet, liniment, clabber, or emulsions. Because of its low cost and ease of administration, this approach is the most popular one.

7. Systemic: The main barriers for the anterior and posterior segments of the ODDS are typically the blood-aqueous barrier and the blood-retinal barrier.

Physical methods that resemble the typical ocular dose form

1. Enhanced viscosity agents: Numerous Ophthalmic medication formulations use polymers like PVA, methylated cellulose, PVP, natrosol, HPMC, HPC, xanthum gum, veegum, and HA to increase viscosity and improve bioavailability, with minimal human impact.[24,25]

2. Ointments for the eyes: Ointments with a blend of hydrocarbon and semi-solid ingredients, primarily in a micronized powder, are non-irritant, liquefaction point ointments that disintegrate into tiny drops for enhanced bioavailability.[26,27]

3. Enhancers of penetration: Lowering the permeability of the cornea's epithelial membrane, known as a accessible ameliorate, temporarily improves corneal accessibility, increasing the bioavailability of ophthalmic drugs.[28]

4. Prodrug: The primary objective of a prodrug is increase the drug's accessibility by altering either its lipophilicity or hydrophilicity. In addition to having a high partition coefficient and improved lipophilicity, the perfect prodrug also has to be highly susceptible to enzymes.[29]

An obstacle to the system of ocular medication delivery

The primary drawback of systemic administration of ocular medicines is that only 1 to 2% of the prescribed dosage reaches the anterior region due to limited ocular bioavailability. Because of this, the preferred method of medication administration in these clinical settings for ocular illnesses allied to the anterior segment of the eye—which includes the cornea, conjunctiva, sclera, anterior uvea, etc.—has been topical distribution. To get to the intended location of action, this route of administration needs to go past a few physicochemical, metabolic, and biological obstacles.[30] The ocular medication delivery method involves the following obstacles.

1. Physical constraints on the ocular medication delivery system
2. Drug dispersion from the surface of the eyes
3. Obstacles caused by lacrimal fluid
4. Ocular blood barriers
5. Barriers in the ocular wall
6. Barriers in the retina

1. ODDS physiological barriers

The drug's diffusion and absorption in the corneal and precorneal regions are limited by physiological barriers. These include lacrimation, tear turnover, dilute, solution outflux, and conjunctival absorption. The drug's contact time with the cornea is shortened, reducing its bioavailability.[31]

2. Drug dispersal from the surface of the eye

After lacrimal fluid injection, materials are extracted from the eye's surface, interacting with the cornea and conjunctiva. The ocular surface is designed to prevent substances from penetrating. However, the drug's effectiveness is due to systemic absorption rather than ocular absorption. The cornea makes up only 5% of the total ocular surface, while the conjunctiva makes up 95%. Drug absorption lowers agglomeration in lacrimal fluid, leading to local systemic assimilation and a 10% ocular bioavailability.[31]

3. Eye barriers caused by lacrimal fluid

Lacrimal fluid-eye barriers are linked to corneal epithelial restrictions on medication absorption. The permeability of drug's corneal cells is often ten times greater than hydrophilic medications. As epithelial cells mature, a corneal barrier forms, primarily entering the aqueous humor through transcorneal permeation. The bulbar conjunctiva's permeability to hydrophilic substances has led to increased attention to drug absorption.

4. Ocular-blood barrier

Blood-ocular barriers protect the eye from xenobiotics in blood steam. They consist of two sections: the ventral blood aqueous barrier and the dorsal blood retina barrier. The anterior blood-ocular barriers, made up of uvea endothelial cells, inhibit drug ingress and plasma albumin entry. The dorsal barrier, made up of retinal pigment epithelium and retinal capillaries, separates

circulation from the eye. Inflammation can compromise this barrier, limiting drug dosage.

5. Barriers to the ocular wall

The eye globe's skeleton consists of a stiff scleral collagenous shell, lining the ocular wall barriers. The posterior wall covers 80% of the sclera, with the cornea overlapping the ventral portion. The scleral stroma, avascular, allows arteries and nerves to flow through sizable canals.[32]

6. Barriers to the Retina: Typically, there are ten layers in it.

1.1 The epithelium of retinal pigment.
1.2 External segments of photoreceptors.
1.3 The membrane that limits outside.
1.4 The outer layer of the nuclear structure.
1.5 The innermost nuclear layer.
1.6 Inner layer of plexiform
1.7 The layer outside the plexiform structure.
1.8 Ganglion Cells (M-cells)
1.9 stratum opticum.
1.10 Limiting membrane within.

PATHOPHYSIOLOGY

As Per UKPDS and DCCT, the primary causative agent in diabetic ketoacidosis (DR) is believed to be persistent hyperglycemia.[33,34] The polyol pathway is one of the alternative glucose metabolism mechanisms that become active in response to hyperglycemia. Advanced glycation endproducts (AGEs) are caused by oxidative stress, millard reaction, and cAMP dependent protein kinase. These alternate routes cause capillary endothelial dysfunction, growth factors, and cytokine activation, which ultimately results in increased vascular permeability and microvascular occlusion. Intraretinal macrovascular occlusion (IRMA) is formed as a result of microvascular occlusion induced retinal ischemia microvascular abnormalities and neovascularization.

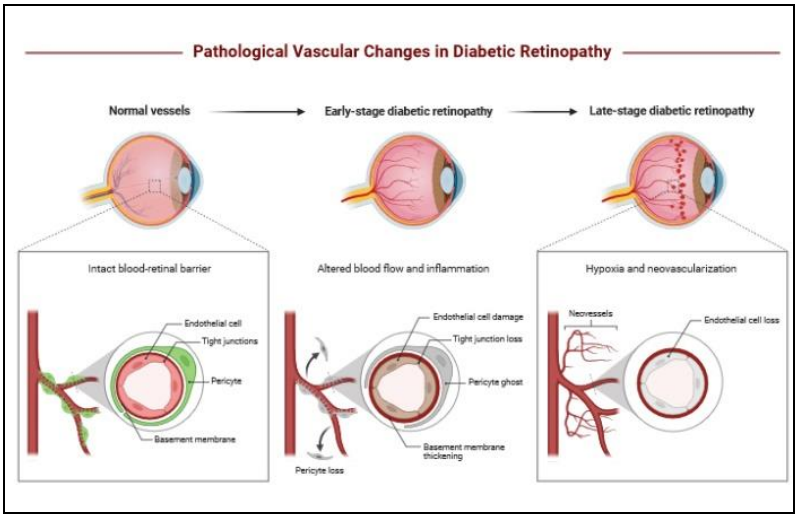

Figure 4: Pathological vascular changes in DR.

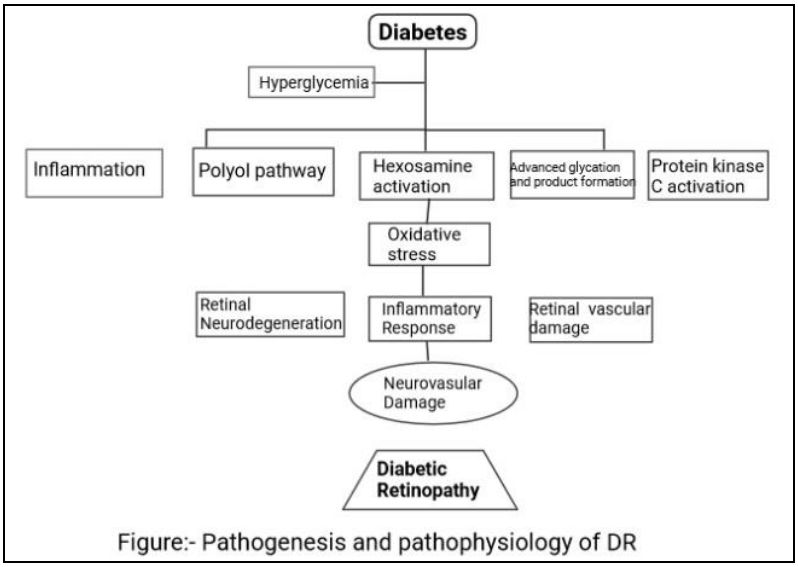

Figure 5: Pathogenesis and pathophysiology of DR.

The enzyme aldose reductase via the metabolic poloyl pathway. Because sorbitol is negotiable, it accumulates in each retinal cells, resulting in osmotic vandalism. Furthermore, the utilization of NADPH (reduced nicotinamide adenine dinucleotide phosphate) during the reduction citation results in increased oxidative damage. Increased susceptible oxygen species (ROS) lead to redox stress, which harms cells and tissues.

Signal transmission involves protein kinase C. Its activation results in vascular and basement membrane modifications, including capillary blockage, angiogenic growth factor release, vascular stasis, and enhanced vascular permeability.

Advanced glycation endproducts (AGEs) are created when aldoses sugar combines with the free amino acids of proteins, lipids, and nucleic acids through a process known as non-enzymatic protein glycation. These AGEs subsequently alter the structure and function of extracellular matrix proteins, potentially impacting cellular signaling and tissue integrity.

The small retinal capillaries in diabetic retinal illness exhibit structural changes that include early pericyte loss, thickening of the basement membrane, loss of endothelial cells, increased vascular permeability, platelet aggregation, leukostasis, and capillary dropout.

In diabetic retinal illness, a variety of structural changes are observed in the small retinal capillaries. These changes include the early loss of pericytes, which are crucial for blood vessel stability, and the thickening of the basement membrane, which affects the permeability and function of the capillaries. Additionally, there is a noticeable loss of endothelial cells that line the blood vessels, leading to increased vascular permeability. This further contributes to the aggregation of platelets and leukostasis, where white blood cells adhere to the capillary walls. Ultimately, these processes result in capillary dropout, where the capillaries become non-functional and cease to carry blood.[37,38]

Diabetic retinopathy impacts both the microvessels and the primary glial cells of the retina, referred to as Müller cells. They are responsible for preserving the retina's structural integrity, controlling blood flow to and from the retina, regulating the blood-retinal barrier, recycling different neurotransmitters, retinoic acid compounds, and ions (like potassium), controlling metabolism, and supplying the retina with nutrients.[39]

Because of the attenuation of the Kir 4.1 channel in diabetes, there is persistent potassium absorption, which causes Müller cell enlargement and ultimately results in Muller cell malfunction.[40] DME is brought on by fluid buildup inside the Muller cells.[41,40] In preclinical and early clinical DR, early involvement of Müller cells and inner retinal neurons may be seen.[42] In DR, glial fibrillary acidic protein (GFAP) overexpression and Müller cell activation are seen.[39]

TREATMENT AND FUTURE PERSPECTIVE

There are several pharmaceutical approaches for treating diabetic retinopathy. Significant alterations in cellular metabolism brought on by high blood glucose levels include endothelial dysfunction, which initiates the etymological process of DR.[49] DR affects a large number of diabetic patients and can cause many critical diseases that need to be treated with laser photocoagulation in addition to blood pressure and glucose management.[50] Pharmacologically, a number of drug classes are now being developed that have the potential to considerably mitigate, if not always repair, the metabolic damage brought on by persistent hyperglycemia. Thus, strict glycemic control combined with an efficient ophthalmologic identification and pursue program is essential for preventing diabetic patients' DR from developing or worsening. It has been demonstrated that antiplatelet medications delay the progression of diabetic retinopathy in its initial stages, resulting in a reduced degree of microaneurysms, indicating a potential role for endothelial dysfunction. Nonetheless, a unique approach that primarily makes use of VEGF inhibitors to control endothelial dysfunction seems promising. These medications may be very helpful in the management of PDR. Antioxidant medications and those that prevent the development.

Positive results have also been observed with glycation end-products.[49] In addition to having serious financial and societal repercussions, DR has psychological effects on sufferers. In light of this, researchers are putting a lot of effort into creating DR therapies. Numerous treatment trials have also been escorted to evaluate the potency of various medicines. The polyol pathway, oxidative stress, latest glycation end products, and protein kinase C have all been connected to the expansion of DR. According to recent findings, DR exhibits characteristics of both neurological and chronic inflammatory diseases, which raises the prospect of pharmacological treatment.[49]

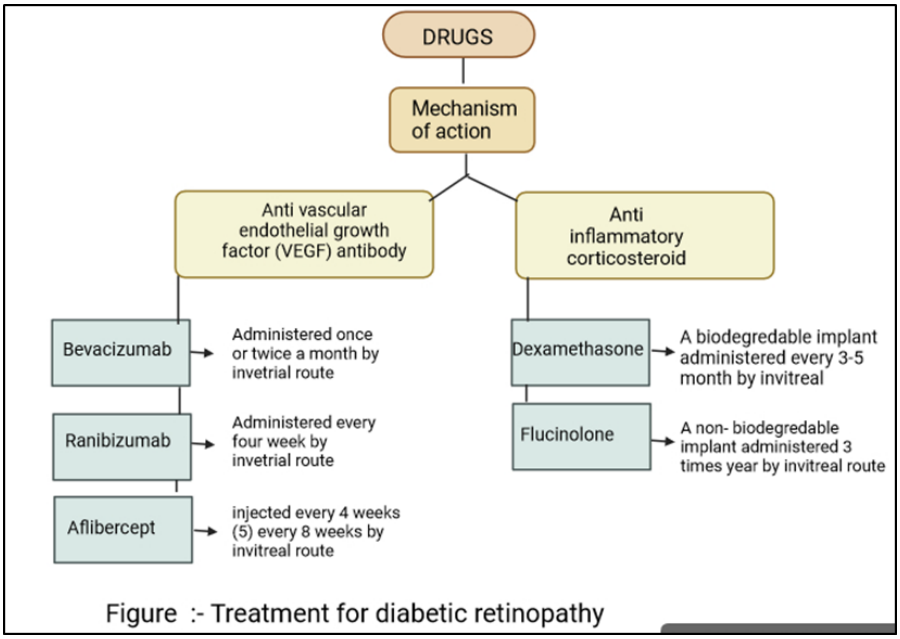

Figure 6: Drugs used in Diabetic Retinopathy.

RESULT

As a result of its complex ocular makeup, DR is a multifactorial disorder. The primary treatment obstacle is to discover a drug that aims many pathways involved in the development of DR. DR is classified as mitochondrial dysfunction and vascular degeneration of the retina. One effective treatment approach for controlling disease onset is the homogenisation of vascular degeneration also return of mitochondrial function. New discoveries on the prevention and management of DR will undoubtedly result from ongoing research in this field.[51]

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