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Recent advances in ocular drug delivery systems and targeting VEGF receptors for management of ocular angiogenesis: A comprehensive review

Soumya Narayana[1], Mohammed Gulzar Ahmed[1*], B. H. Jaswanth Gowda[1], Pallavi K. Shetty[1], Arfa Nasrine[1], M. Thriveni[1], Nadira Noushida[2] and A. Sanjana[1]

Abstract

Background: Angiogenic ocular diseases address the main source of vision impairment or irreversible vision loss. The angiogenesis process depends on the balance between the pro-angiogenic and anti-angiogenic factors. An imbalance between these factors leads to pathological conditions in the body. The vascular endothelial growth factor is the main cause of pathological conditions in the ocular region. Intravitreal injections of anti-angiogenic drugs are selective, safe, specific and revolutionized treatment for ocular angiogenesis. But intravitreal injections are invasive techniques with other severe complications. The area of targeting vascular endothelial growth factor receptors progresses with novel approaches and therapeutically based hope for best clinical outcomes for patients through the developments in anti-angiogenic therapy.

Main text: The present review article gathers prior knowledge about the vascular endothelial growth factor and associated receptors with other angiogenic and anti-angiogenic factors involved in ocular angiogenesis. A focus on the brief mechanism of vascular endothelial growth factor inhibitors in the treatment of ocular angiogenesis is elaborated. The review also covers various recent novel approaches available for ocular drug delivery by comprising a substantial amount of research works. Besides this, we have also discussed in detail the adoption of nanotechnology-based drug delivery systems in ocular angiogenesis by comprising literature having recent advancements. The clinical applications of nanotechnology in terms of ocular drug delivery, risk analysis and future perspectives relating to the treatment approaches for ocular angiogenesis have also been presented.

Conclusion: The novel ocular drug delivery systems involving nanotechnologies are of great importance in the ophthalmological sector to overcome traditional treatments with many drawbacks. This article gives a detailed insight into the various approaches that are currently available to be a road map for future research in the field of ocular angiogenesis disease management.

Keywords: Ocular drug delivery, Ocular angiogenesis, Nanotechnology, Vascular endothelial growth factor, Photothermal therapy

Background

Visual impairment has become a major threat to all age category people globally. According to the reports, almost 246 million people are affected by subnormal vision, 285 million people with vision disabilities and 39

*Correspondence: mohammedgulzar1@gmail.com
[1] Department of Pharmaceutics, Yenepoya Pharmacy College and Research Centre, Yenepoya (Deemed to be University), Mangalore 575018, India
Full list of author information is available at the end of the article

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million people with blindness [1, 2]. In India, more than 30 percent of people become blind before they cross 17 years of age and most of them are of less than 5 years [3]. Impairment in vision is also widespread among elderly individuals in various other forms [4]. According to a study conducted in Al-Madinah Al-Munawarah, Saudi Arabia, among diabetic patients ($n=690$), 36.1% were found to be suffering from diabetic retinopathy (DR) of which 6.4% had proliferative disease [5]. An additional cross-sectional study conducted in Al Ain, United Arab Emirates reported DR in 19% of diabetic patients ($n=513$). Almost all the patients were completely unaware of the condition of their retina [6, 7]. Approximately 8.7% of worldwide blindness is occurred due to age-related macular degeneration (AMD) especially in aged patients [8]. Angiogenesis accounts for the formation of new blood vessels from the existing vasculature. The physiological angiogenesis process in the human body is the balance between anti-angiogenic and pro-angiogenic factors [9]. Disturbance of such balance leads to a pathological condition in the human body. During the conditions such as wound healing and peripheral arterial disease ischemic heart disease, the stimulation of angiogenesis will cure the disease. Wherein case of diseases such as rheumatoid arthritis, cancer and ophthalmic conditions, the inhibition of angiogenesis is the cure [10]. Global ocular morbidity is the main reason behind severe ocular angiogenesis. In ocular angiogenesis conditions, the angiogenic switch must be turned "on" for neovascularization progression [11]. It may lead to diseases like retinal vein occlusions, diabetic retinopathy, corneal neovascularization, age-related macular degeneration, retinopathy of prematurity, choroidal and retinal neovascularization, etc. Pro-angiogenic growth factors implicated in the development of pathological vessels in ocular diseases include endothelial growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), etc. [12]. The present review gives clear-cut knowledge on VEGF and their respective receptors with various regulations, affecting factors and available treatments with recent literature. It majorly focuses on numerous novel nanotechnology-based approaches in ocular drug delivery to treat many ocular conditions specifically angiogenesis to overcome traditional injection treatments that affect bioavailability and patient compliance.

Main text

Regulation of angiogenesis

In the human body, angiogenesis is involved in various processes [13]. In healthy adults, angiogenesis is a rare phenomenon, involved only locally and transiently under distinctive physiological and pathological conditions in the body. Angiogenesis is regulated by endogenous pro-angiogenic and anti-angiogenic factors (Table 1) [12, 14–16]. Among all angiogenic and anti-angiogenic factors, VEGF is marked to be a highly critical regulator of ocular angiogenesis. Regulation of angiogenesis involved five steps, initially, angiogenic factors bind to endothelial cells leading to the degradation of basement membrane with the proliferation of endothelial cell, further, migration and also tube formation, elongation finally vessel stabilization (Fig. 1).

Vascular endothelial growth factor (VEGF)

VEGF is a signal protein also known as vascular permeability factor. The VEGF family includes various members, i.e., VEGF-A, VEGF-B, VEGF-C, VEGF-D, placenta growth factor (PGF) and the viral VEGF homologue VEGF-E. VEGFs bind selectively with receptors namely VEGF receptor-1 (VEGFR-1), VEGFR-2, VEGFR-3, neuropilin-1 (NRP-1) and NRP-2 [34].

VEGF-A

VEGF-A is one of the well characterized and highly investigated of the VEGF family members. Mainly it enhances the endothelium's permeability by forming the intercellular gaps and fenestrations. Hence, it was originally known as a vascular permeability factor (VPF). Most commonly VEGF-A isoforms have been identified from six transcripts: $VEGF_{111}$, $VEGF_{121}$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{189}$ and $VEGF_{206}$ [19].

VEGF-B

VEGF-B is mainly present in various tissues of the body, as well as the retina but it is greatly available in the region of skeletal and heart muscle. VEGF-B also contains two isoforms, $VEGF\text{-}B_{167}$ and $VEGF\text{-}B_{186}$ by alternative splicing, which signal through VEGFR-1 and NRP-1. Genetic studies showed the absence of VEGF-B in experimental mice is healthy, fertile and not affected with any vascular diseases. This concludes that VEGF-B is not responsible for angiogenesis [20].

PGF

It is expressed mainly in the region of the lungs, placenta and heart that further binds to the VEGFR-1 and NRP-1. The complex formation between VEGFR-1 and VEGFR-2 is due to the attachment of PGF to VEGFR-1 that in turn leads to the signaling of VEGF-A and stimulation of angiogenesis [19, 35].

VEGF-C, VEGF-D and Viral VEGF homologue VEGF-E

Both VEGF-C and VEGF-D bind to VEGFR-2 and with lower affinity, it binds to VEGFR-3. It also stimulates the proliferation of endothelial cells and also migration both

Table 1 Pro-angiogenic and anti-angiogenic factors involved in the angiogenesis process

Factor	Type	Function	Properties	References
VEGF	Angiogenic	Stimulator of angiogenesis	Produced in the eye by retinal pigment epithelial cells Upregulated by hypoxic condition Contains 5 ligands {VEGF-A, B, C, D and placental growth factor (PGF)} Consists of three protein-tyrosine kinases {(VEGFR-1, Flt-1), (VEGFR-2, Flk-1/KDR), (VEGFR-3)} Two non-protein kinase co-receptors: neuropilin-1 and neuropilin-2	[17–20]
EGF & TGF	Angiogenic	Associated with signaling pathway in cancer & enhances cell proliferation process, leads to metastasis besides decreased apoptosis	Binds to VEGF receptors Mitogens for endothelial cells in vitro, in vivo	[21, 22]
Angiopoietins	Angiogenic	Promotes angiogenesis in the uterus or embryonic vascular development	Paracrine growth factor Contains 4 ligands Angiopoietin 1, 2, 3, 4 (Ang-1, 2, 3, 4) Two corresponding tyrosine-kinase receptors (Tie-1 and Tie-2)	[23–25]
FGF	Angiogenic	Stimulates angiogenesis	FGF contains mainly FGF-1 and FGF-2 and it is also called acidic and basic FGF FGF-1 (acidic FGF) and FGF-2 (basic FGF)	[26]
MMP	Angiogenic	Degradation of the basement membrane	Belongs to the category of soluble and membrane tied proteolytic enzymes	[27]
PEDF	Anti-angiogenic	Promotes endothelial cell apoptosis	Also known as serpin F1 Secreted by retinal epithelial cells First factor is described for its neurotrophic properties in vitro	[28, 29]
Prolactin	Anti-angiogenic	Suppresses cell proliferation process also stimulates expression of plasminogen activator inhibitor	N-terminal 16-kDa fragment 16 K-PRL is a natural inhibitor of ocular angiogenesis	[30, 31]
Angiostatin	Anti-angiogenic	Inhibits ATP synthesis and that slows down migration of EC and proliferation	It is a fragment of protein plasminogen Plasminogen and angiostatin can be synthesized by corneal layers	[19]
Vaso inhibins	Anti-angiogenic	It blocks inducers of angiogenesis (VEGF, FGF, etc.) through in vitro and in vivo	It can be generated by various proteases (MMP's)	[32]
Endostatin	Anti-angiogenic	Suppresses migration and proliferation of endothelial cells and increases apoptosis	Derived from collagen XVIII	[19]
Thrombospondin	Anti-angiogenic	Assists in tumor death	First discovered in activated platelets Contains five multifunctional proteins that can bind extracellular calcium that is TSP-1 to TSP-5	[33]

VEGF vascular endothelial growth factor, *PGF* placental growth factor, *KDR* kinase-insert-domain receptor, *EGF* epidermal growth factor, *TGF* transforming growth factor, *FGF* fibroblast growth factor, *MMP* matrix metalloproteinase, *PEDF* pigment epithelium-derived factor, *EC* endothelial cells

in vitro and in vivo. VEGF-E is also a potent angiogenic. The binding of VEGF-E to VEGFR-2 with greater affinity results in angiogenesis stimulation and vascular permeability thus increasing in viral infection [20, 36].

VEGF receptors

VEGFs bind selectively with receptors namely VEGF receptor-1 (VEGFR-1), also called Flt-1; VEGFR-2, also called Flk-1; VEGFR-3, also called Flt-4; neuropilin-1 (NRP-1), and NRP-2. The VEGFRs belong to the family of the tyrosine-kinase receptor. The receptor dimerization is caused due to the binding of the ligand to an extracellular immunoglobulin-like domain. The angiogenic effect of VEGF-A was mediated by a vital receptor called VEGFR-2 [19].

VEGFR-1

Vascular endothelial growth factor receptor-1 (VEGFR-1) is also termed as fms-like tyrosine kinase-1 (Flt-1) which is having 180 kDa and is also seemingly linked to receptor tyrosine kinase (RTK). The VEGFR-2 and Flt-1 are majorly expressed on vascular endothelium, Even though some of the mRNA remains in the stroma of human placenta, monocytes and renal mesangial cells. With high affinity, VEGF-A_{165} binds to VEGFR1 when compared with VEGF-A_{121} [37, 38].

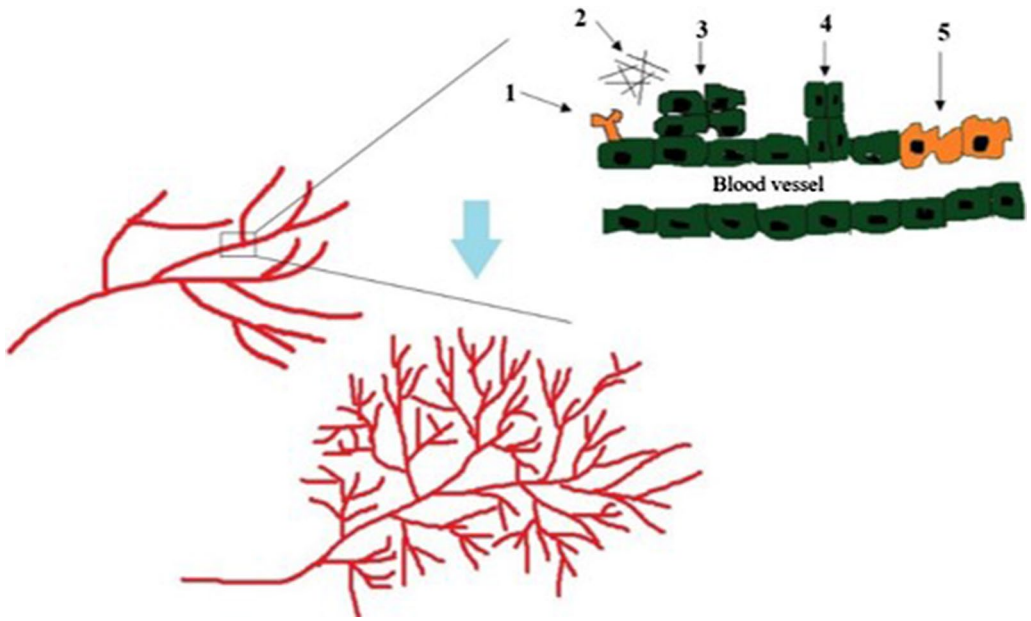

Fig. 1 Regulation of angiogenesis (Steps: 1. Angiogenic factors bind to endothelial cells, 2. Basement membrane degradation, 3. Endothelial cell proliferation and migration, 4. Tube formation, elongation and remodeling and 5. Vessel stabilization.) [13]

VEGFR-2

VEGFR-2 is the second VEGF tyrosine-kinase receptor that is present on chromosome 4q12. It is also called a kinase-insert-domain containing receptor (KDR). This KDR is majorly expressed in the region where endothelial cells are abundantly present and were also replicated from a human endothelial cell cDNA library. Due to the ligands of VEGF family, the VEGFR-1 and VEGFR-2 convert the signals for endothelial cells [39].

VEGFR-3

VEGFR-3 is also called fms insert-like tyrosine kinase 4 (Flt-4). They have got the extracellular domain which is almost 80% homologue to the other VEGFRs. The VEGF-C and VEGF-D that belong to the family of VEGF are also associated with VEGFR-3. The Flt-4 is majorly expressed in lymphatic endothelium specifically in adult tissues which are usually not seen for VEGFR-1 and VEGFR-2 [40].

Neuropilins

The neuropilin-1 (NRP-1) and neuropilin-2 (NRP-2) are expressed in endothelial cells just like VEGFR-1 and VEGFR-2. It is particularly with less affinity binds to the VEGF-A_{165}. The neuropilin-1 balances the development of blood vessels during the angiogenesis embryonic stage, conveying a major role for VEGFR-2 as a co-receptor [41].

Regulation of VEGF

VEGF is a crucial regulator of angiogenesis, in a condition of uncontrolled regulation of VEGF leads to pathological angiogenesis. As we have already discussed earlier, angiogenesis is a balance between the pro-angiogenic and anti-angiogenic factors if is there any imbalance between these factors that leads to pathological angiogenesis [42]. Although, many growth factors and cytokines are released in response to any damage in the tissue which leads to stimulation of angiogenesis either directly or indirectly through VEGF that is crucial in tissue repairing. The elevated pathological angiogenesis is occurred due to the stimulation of VEGF expression during pathophysiological conditions like diabetes mellitus and cancer. The literature data was supported this hypothesis by demonstrating suppression of neovascularization by the inhibition of VEGF or its effects. But, during the conditions like atherosclerosis, the elevated concentration of plasma VEGF might be an attempt to make up for the damage of tissue [43, 44]. In all these pathological conditions, angiogenesis is stimulated by local tissue hypoxia. The ocular cells like muller cells, astrocytes, retinal pigmented epithelium, endothelial cells (EC) and ganglion cells secret and produce VEGF. In vitro studies showed

that under hypoxic condition muller cells and astrocytes produces larger amounts of VEGF [45].

Effect of oxygen, nitric oxide, glucose and other growth factors on VEGF regulation

In various diseases like atherosclerosis, solid tumors, ocular diseases, etc., the stimulation of VEGF results in neovascularization and it is mainly due to the hypoxic condition. The major protein named hypoxia-inducible protein complex (HIPC) or hypoxia-inducible factor (HIF) is produced by hypoxia. The up-regulation of transcription of VEGF mRNA was occurred due to the activation of basic heteromeric helix–loop–helix transcriptional regulator. The production and stability of some VEGF isoforms are majorly due to the hypoxia condition. In terms of stability, the VEGF-A isoforms are highly sensitive to hypoxia, wherein the case of VEGF-B and VEGF-C mRNA has little or no effect on hypoxia [46, 47]. The vascular endothelium and endothelial cells can release nitric oxide (NO) in response to VEGF. Additionally, during the VEGF-induced angiogenesis, the production of nitric oxide synthase (NOS) is also increased. A demonstration showed the part of NO in VEGF-induced angiogenesis on NOS knock-out mice as well as after inhibition of NOS, leads to angiogenesis depletion [48, 49]. In the beginning, the increased expression of VEGF was believed to be from the hypoxic condition but it was the hypoglycemic condition. However, in later stages, it was reported that the cells exposed to hypoglycemia without HIF (hypoxia) elevated the expression and up-regulation of VEGF. The production of VEGF came back to the pre-experimental level in response to a balanced concentration of glucose suggesting the acute hypoglycemia is the sole responsible to activate angiogenesis mediated via VEGF. Also, pro-angiogenic growth factors such as fibroblast growth factor 4 (FGF 4), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), insulin-like growth factor I, PDGF, angiotensin-2, keratinocyte growth factor, interleukin 1 (IL-1) and IL-6 can alter the production of VEGF. It was also found that some of the anti-angiogenic growth factors such as the cytokines IL-10 and IL-13 can deduce the production of VEGF [50, 51].

Angiogenesis inhibitors or vascular endothelial growth factor inhibitors (anti-VEGF)

The inhibition of VEGF-VEGFRs protein factors unlocked new prospects in medicine since they are the sole ones responsible for many pathological conditions such as angiogenesis and ocular vascular diseases. In many ocular neovascularization conditions, the hindrance of VEGF activity plays a major role in treating such conditions. In recent years, research to develop anti-VEGF has transformed the treatment of ocular angiogenic conditions. These are the most considered treatments for many conditions such as vein occlusions, myopic neovascularization of the choroid, retinopathy of prematurity (ROP), diabetic macular edema and choroidal neovascularization [52, 53]. The FDA approved the ranibizumab for many treatments such as macular edema along with branch retinal vein occlusion (BRVO) and also for treating all angiographic subtypes of the subfoveal neovascularization of AMD [54, 55]. Many literatures indicated short-term effects of ranibizumab on foveal thickness (FT) and visual acuity for about 1 week and 1 month, respectively, after injecting the ranibizumab. The short-term effects ranging from few minutes to hours, after injection of anti-VEGF drugs for BRVO have also been evaluated [56]. Bevacizumab is a full-length humanized recombinant monoclonal Immunoglobulin-G (IgG) anti-VEGF-A antibody [57] that is approved to treat many tumors by hindering all the VEGF-A isoforms. Since this therapy is economical compared to other treatments, it is the most widely used anti-VEGF medicine in ophthalmology [58, 59]. Intravitreous bevacizumab, ranibizumab and aflibercept were potent and also safe in the treatment of diabetic macular edema that causes vision impairment. The mild loss of initial visual acuity was able to manage with help of all three agents with a slight difference between each other. Where, in case of severe loss of initial visual acuity, aflibercept played a better role in improving the vision [60]. In India, a high alert puts ophthalmologists in a legal and ethical dilemma. Commercial entities must not be allowed to dictate which drug should be used for which disorder. The safety of the patient must be the paramount concern and physicians and governmental agencies must ensure this by fair drug compounding practices. Strong leadership of national and international ophthalmological societies is needed to represent the scientific facts regarding bevacizumab to drug regulatory agencies globally [61]. The research initiatives continue at organizations and pharmaceutical companies globally to find a safe and effective medicine for AMD. The currently available anti-VEGF drugs in the market furnish a slight hope but the drawbacks associated with them are such as repeated intravitreal injections that lead to patient incompliance [62]. Many patients living in developing countries like India face an economic crisis due to these expensive treatments. Even though the bevacizumab is not officially approved to treat a wide range of ocular conditions, it has shown better results at a relatively low cost. Since extensive research is still going on. Thus, we may expect the many novel and potent drugs that can treat many ocular neovascular diseases (Table 2) [63, 64].

Table 2 Classification and application of anti-VEGF drugs

Class	Drug name	Mechanism of action	FDA approval	Application	References
Monoclonal antibody	Bevacizumab	Binds to circulating VEGF, thereby inhibiting binding to its cell surface receptors thus limits blood supply to tumor tissue	2004	Off label use in ophthalmology Colorectal cancer Non-squamous & non-small cell lung cancer	[65, 66]
Antibody derivative	Ranibizumab	Binds to receptor binding site on VEGF-A & blocks all isoforms of VEGF-A	2006	Age-related macular degeneration Macular edema Diabetic retinopathy	[67]
Aptamer	Pegaptanib	Binds to extracellular $VEGF_{165}$ thereby inhibits binding to the VEGF receptor	2004	Age-related macular degeneration	[68]
Oral small molecule (Inhibit tyrosine kinases)	Lapatinib	Inhibits intracellular tyrosine kinase domains of epidermal and human epidermal growth receptors	2007	Certain type of breast cancer	[69, 70]
	Sunitinib	Inhibits multiple receptor tyrosine kinase and also PDGFR and VEGFRs	2006	Certain types of cancer (kidney, pancreas and intestinal)	[71]
	Sorafenib	Interacts with multiple cell surface and multiple intracellular kinases. Therefore, inhibits transcription	2005	Used to treat kidney, liver and thyroid cancers	[72, 73]
Fusion proteins	Aflibercept	It functions as a decoy receptor for ligands	2011	Age-related macular degeneration Diabetic retinopathy	[74]
Miscellaneous	siRNA-Bevasiranib	It is a small interfering RNA (siRNA) drug that works by silencing the specific genes that induce VEGF	–	Age-related macular degeneration Diabetic retinopathy	[75]
	adPEDF	Rapidly increases intraocular levels ofadPEDF protein in the eye and hinders unusual development of blood vessel	–	In the treatment of macular degeneration	[76, 77]

Novel approaches in ocular drug delivery

The novel approach-based dosage forms in ophthalmic delivery may ray of hope for better therapies for the future, in the treatment of ocular angiogenesis (Table 3).

Ocular gene therapy

Gene therapy is a novel technique in the field of medicine which delivers the nucleic acids into the cells of a patient as the drug to treat diseases. It is the supplementation of an ineffective gene with a healthy working gene in defective target cells. Depending on the types of cells treated, the gene therapy can be divided into two types called germline and somatic gene therapy. Some of the techniques to achieve gene therapy are said to be inhibition gene therapy, gene augmentation therapy and scavenging specific cells. Ocular gene therapy is the introduction of an exogenous gene product into a host's cell. The delivery of drugs to the ocular region is a hurdle due to the presence of many cellular barriers. These techniques can clear all the hurdles and challenges. To target a tissue, further development in this field with novel strategies may necessary [78, 79].

Ocular inserts

Ocular inserts are tiny, thin, sterile, stratified solid pieces of a device placed into the conjunctival sac to deliver various drugs. Erodible and non-erodible are two types of ocular inserts. Ocular inserts also offer the advantages of increasing the contact time, better bioavailability of drugs and reducing the dosing frequency. Drug release profile from the ocular inserts depends on the following mechanism: diffusion, osmosis and bio-erosion. Within 24 h, the inserts can dissolve completely. The erosion of the inserts is majorly dependent on the type and concentration of polymer used. The pattern of drug release from the ocular inserts varies between individuals depending upon their physiological conditions. The non-erodible inserts consist of either matrix structure or reservoir that helps in sustaining the drug release [80, 81].

Ocular implants

Ocular implant is an artificial material that is surgically implanted in the position of the eye, to improve impaired vision. For the delivery of drugs into a posterior region, the implants are surgically inserted anteriorly to the retinal region and posteriorly to the lens. There are two types of ocular implants biodegradable and non-biodegradable.

Table 3 Potential novel approach-based strategies for ocular diagnostics

Novel technique	Author/Year/ Journal	Study	Conclusion	References
Ocular gene therapy	Testa et al., (2013), Ophthalmol	Conducted clinical trial for 3 years on 5 patients having Leber congenital amaurosis type 2 (LCA2) and the treatment was done with one unilateral injection of adeno-associated virus AAV2-hRPE65v2	They concluded retinal and visual function improvement to a greater extent	[145]
	Tamboli et al., (2011), Ther Deliv	Reviewed on polymeric vectors for ocular gene delivery	They summarized that polymers are considered as a vector for gene therapy due to their non-toxic and non-immunogenic nature	[146]
Ocular inserts	Mirzaeei et al., (2017), J Rep Pharm Sci	Designed soluble ocular insert for controlled release of chloramphenicol	They concluded that the prepared formulation shown sustained drug release and reduced frequency of administration	[147]
	Franca et al., (2014), PloS One	Prepared bimatoprost loaded ocular insert for glaucoma	They reported that bimatoprost loaded ocular insert reduced intraocular pressure and increased precorneal residence time	[148]
Implants	Catalu et al., (2018), Rom J Ophthalmol	Developed ocular implants-methods of ocular reconstruction following radical surgical interventions	They reported that use of integrated *hydroxyapatite* implant in enucleated patients for superior incorporation of ocular prosthesis resulting in better movement	[82]
	Gradinaru et al., (2015), J Med Life	Developed hydroxyapatite ocular implant and non-integrated implants in eviscerated patients	They reported that hydroxyapatite ocular implant caused larger rate of conjunctival dehiscence, where extrusion of implant and socket infection was seen for non-integrated ocular implants	[149]
Microneedle Technology	Takur et al., (2016), Drug Deliv and Transl Res	Prepared instantly dissolving polymeric microneedles for minimally invasive intraocular drug delivery	They reported that MN technology able to deliver high molecular weight drugs and dissolving MN possess greater applications in improving ocular delivery	[150]
	Prausnitz et al., (2007), Investig Ophthalmol Vis Sci	Developed ocular drug delivery using a microneedle	They concluded that no inflammatory responses and delivered the drug into the ocular region	[151]
Iontophoresis	Molokhia*et al*., (2020), Ocul Pharmacol Ther	Examined the transscleral iontophoresis of macromolecules effect in vitro and in vivo	They showed that transscleral iontophoresis successfully delivered macromolecules into cornea and sclera	[152]
	Sun et al., (2015), J Ophthalmol	Examined the use of reverse iontophoresis to extract iron from Rabbit anterior chamber	They concluded that reverse iontophoresis is a non-invasive and promising approach to treat ocular siderosis by iron extraction from the anterior chamber	[153]
In situ gel	Nagai et al., (2020), Front Bioeng Biotechnol	Developed methylcellulose and tranilast solid nanoparticles	They reported increased ocular surface residence time and absorption of the drug from nanoparticles	[154]
	Barse et al., (2017), Drug Dev Ind Pharm	Designed pH triggered brimonidine tartrate in situ gel to treat glaucoma	The developed in situ gelling system showed good results and can be a better ophthalmic formulation in reducing intraocular pressure	[155]

Table 3 (continued)

Novel technique	Author/Year/ Journal	Study	Conclusion	References
Contact lens	Qin et al., (2017), Biomaterials	Developed ciprofloxacin-loaded contact lenses using fluorous chemistry	They successfully constructed a drug delivery system that exhibits controlled drug release, high drug loading capacity and efficient biological activity	[156]
	Garhwal et al., (2012), Investig Ophthalmol Vis Sci	Developed antibiotic-loaded nanospheres to incorporate on conventional contact lenses that	They concluded that sustained and effective bactericidal activity using a novelapproach	[157]
Artificial intelligence (AI)	Hassanzadeh et al., (2019), Adv Drug Deliv Rev	Significance of AI in drug delivery system	They reported that artificial neural networks are helpful in the development of novel hypotheses and medical strategy	[103]
	Schmidt et al., (2018), Prog Retin Eye Res	Evaluated effect of AI in the retina	They concluded that AI in the retina will empower the quality of diagnosis/therapy to eradicate issues in current ophthalmology	[158]
Nanoemulsion	Zhang et al., (2018), Biomed Pharmacother	Developed and studied nanoencapsulation using PLGA on the anti-angiogenic activity of bevacizumab for ocular angiogenesis	They reported enhanced therapeutic efficiency of bevacizumab for ocular neovascularization	[159]
	Salimi et al., (2017), Asian J Pharm	Prepared celecoxib nanoemulsion for ocular delivery	They concluded celecoxib nanoemulsion showed enhanced permeability, prolonged release with better availability	[160]
Nanosuspension	Yadollahi et al., (2015), J Nanomater	Reviewed on nanosuspension technologies for delivering lipophilic drugs	They summarized that nanosuspension is a flexible technique and creating novel clinical approaches for treating various ocular diseases	[161]
	Jacob et al., (2020), Biomater Res	Reviewed on role of nanosuspensions in delivering various drugs	They reported that nanosuspension has the potential to eradicate challenges associated with many drug delivery systems	[162]
Nanoparticle	Khan et al., (2019), Arab J Chem	Reviewed on nanoparticles properties, application and toxicities	They summarized that due to nano-sized particles it is a suitable candidate for various techniques	[163]
	Bourges et al., (2003), Investig Ophthalmol Vis Sci	Examined the delivery of polylactide (PLA) nanoparticles to target retina and retinal pigment epithelium	They concluded that PLA nanoparticles remained in the retinal pigmental epithelial cells and continuous delivery of drugs achieved	[164]
Nanomicelles	Singh et al., (2018), Int J Pharm Sci Res	Reviewed on impact of nanomicelle for ocular drug delivery system	They summarized nanomicelles are the ocular drug delivery due to their exceptional biocompatibility, low toxicity, enhanced blood circulation time	[165]
	Xu et al., (2020), Carbohydr polym	Development of topical ocular delivery of dexamethasone from functionalized chitosan oligosaccharide nanomicelles	They reported that nanomicelles could be a prominent drug delivery system in various ocular conditions	[166]
Liposomes	Taha et al., (2013), Saudi Pharm J	Designed liposomal colloidal system of ciprofloxacin for ocular delivery	They concluded that liposomes enhanced drug bioavailability	[167]
	Lai et al., (2019), J Nanobiotechnol	Reviewed on liposomes for effective drug delivery to the ocular posterior chamber	They concluded that it is a potential way of technique to treat ocular diseases	[168]

Table 3 (continued)

Novel technique	Author/Year/ Journal	Study	Conclusion	References
Niosomes	Praveen et al., (2018), Int J App Pharm	Developed niosomal in situ gel containing prednisolone sodium phosphate for ocular drug delivery	They concluded that niosomal in situ gel of prednisolone sodium phosphate increased bioavailability in the ocular region	[169]
	Durak et al., (2020), Nanomaterials	Reviewed on niosomal drug delivery systems for ocular disease	They summarized various uses of niosomes in gene delivery to both the posterior and anterior region of the eye followed by enhanced permeation through cornea and greater ocular bioavailability	[170]
Dendrimers	Michael et al., (2017), Can J Chem	Reviewed on dendrimers for ocular delivery	They concluded that dendrimers hold tremendous potential as ocular drug delivery vehicles	[171]
	Yavuz et al., (2013), Sci World J	Reviewed on dendrimeric systems and application in ocular drug delivery	They described that even though the dendrimers are not involved clinically, they could be a better ocular delivery system in near future	[172]
Polymeric micelles	Safwat et al., (2020), Drug Deliv	Developed polymeric micelles for the ocular delivery of triamcinolone acetonide	They concluded that prepared polymeric micelles delivered drugs in sustained manner and corneal inflammation completely reduced	[173]
	Arafa et al., (2020), Int J Nanomed	Developed chitosan-coated PLGA nanoparticles for enhanced ocular anti-inflammatory efficacy of atorvastatin calcium	They concluded that prepared nanoparticle enhanced ocular anti-inflammatory effect of atorvastatin calcium	[174]
Biodegradable microspheres	Liu et al., (2019), Curr Eye Res	Prepared biodegradable microsphere-hydrogel ocular drug delivery system for controlled and extended release of bioactive aflibercept in vitro	They concluded that prepared microsphere hydrogel was safe and delivered aflibercept in controlled manner	[144]
	Liu et al., (2020), Transl Vis Sci Technol	Developed biodegradable aflibercept-loaded microsphere-hydrogel drug delivery system	They concluded that prepared aflibercept-loaded microspheres treated choroidal neovascularization lesions and the prepared formulation was safe and biocompatible	[175]
Photothermal therapy	Hatamie et al., (2020), Nanomaterials	Synergic effect of novel WS_2 carriers holding spherical cobalt ferrite @cubic Fe_3O_4 (WS_2/s-$CoFe_2O_4$@c-Fe_3O_4) nanocomposites in magnetic resonance imaging and photothermal therapy for ocular treatments and investigation of corneal endothelial cell migration	They concluded that for eye diseases designed nanocomposites have a synergic effect as photothermal therapy agents and also target drug delivery in an ocular drug delivery system using MRI	[176]
	Levin et al., (2019), Beilstein J Nanotechnol	Developed tungsten disulfide-based nanocomposites for photothermal therapy	They concluded that prepared nanocomposites are additional cancer therapy agents for achieving increased therapeutic activity	[177]

Drugs are encapsulated by using biodegradable polymers like polylactic acid (PLA) and polylactic-co-glycolic acid (PLGA) are in a particular system of nanoparticles or microparticles. The polymers are usually viscous materials that help in releasing the drug for a prolonged period. But, the nanoparticles or microparticles can distribute unusually in the ocular conditions upon injection via needles due to their compact size and composition [82].

Microneedle technology

These are micron-sized needle configurations, designed using microelectronics industry devices. Besides, microneedles were designed for the delivery of drugs for transdermal delivery. Glass microneedles are made of borosilicate material. Generally, the microneedles were made by using stainless steel called solid microneedles (75–1000 μm in length). It is a minimally invasive technology where it can deliver the drug into the posterior region and also overcomes complications associated with intraocular injections. Mainly, microneedle technology in ophthalmic delivery can provide localized and target delivery of drug into the posterior region [83, 84].

Iontophoresis

This is a novel technique to deliver various drugs to the target site of action. The drugs, specifically charged macromolecules can be delivered into the anterior and posterior segments. The delivery is mainly based on a basic principle of attraction/binding between opposite charges whereas repelling between same charges. The iontophoretic device consists of a continuous DC source with two electrodes. The mechanism of this device is placing of an ionized drug in the compartment of an electrode that bears the same charge and the ground electrode is placed at any region around the eye [85].

In situ gelling system

In situ gel is a novel approach to deliver the drug to the ocular region that is solution form before administration and converts into gel form to release the drug that is triggered by an external stimulus like pH, temperature, etc. [86]. Several mechanisms are involved in triggering the conversion of the solution to in situ gel such as a physical change in biomaterials such as exchange of solvent and cross-linking between solvent/swelling. Trigger due to physiological stimuli such as pH of body fluids and temperature of the body and chemical reactions. Trigger due to various chemical reactions such as photopolymerization, oxidation and reduction. In a temperature triggered system, when the temperature rises, the formulation converts into gel. The polymers like poloxamers are used to formulate these gels. In pH triggered in situ gel formation of gel is induced by a change in pH. Most of the anionic pH-sensitive polymers are based on polyacrylic acid (PAA) (carbopol, carbomer) or its derivatives. In the diffusion method, the solvent present in the solution of polymer will diffuse and enter the nearby tissue leading to the polymer precipitation. The ionic strength can also promote the formation of gel from the introduced polymeric solution. Gelrite is the best example of an ion-sensitive polymer. In the enzyme responsive process, gel formation can be occurred due to specific enzymes present in physiological conditions even in the absence of any chemicals like monomers and initiators. In photopolymerization process, the polymeric solution injected to the desired site will swell with help of a photo via fiber optic cables to sustain the drug release for a longer period [87, 88].

Contact lens

Contact lenses are a thin type of plastic-shaped twisted type of cover that protects the eye. The contact lens can deliver the drug efficiently when compared with eye drops. Due to the longer contact time, the dosage frequency can be lowered with less systematic toxicity. The topical drug delivery to the ocular region became a major hurdle for scientists due to the various barriers like corneal barriers, conjunctival barriers, blood-retinal barriers and blood-aqueous barriers. The fabrication of polymeric nanoparticle embedded contact lens may prolong the delivery of drug leading to reduced frequency of administration which will improve patient compliance [89, 90].

Photothermal therapy

Photothermal therapy (PTT) is a novel treatment of choice for various medical complications; it is a minimally invasive, local treatment with less toxicity [91]. The mechanism involves the activation of a photosensitizing agent by using electromagnetic radiation to convert energy into heat to kill cancerous cells [92]. PTT has several advantages when compared with radiotherapy or chemotherapy; it specifically targets the unhealthy cell by its deep penetrating power without affecting surrounded healthy cells or tissues [93]. In photothermal therapy, cell death occurs due to the denaturation of proteins, lysis of membrane and evaporation of cytosol [94]. The ideal photosensitizing agent should have several characteristics like low toxicity to the cells, high solubility in biocompatible solution and ease in functionalization. Phosphorous photothermal agents exist in three allotropic forms, i.e., white phosphorous, red phosphorous and black phosphorous (BP) [95]. Among three allotropes of phosphorus, BP is the most stable at high temperature and high pressure. The most interesting properties of BP are its photothermal property, narrow band gaps, large specific surface

area, high carrier mobility, good biodegradability and biocompatibility properties [96]. Studies have been shown that BP offers promising and better applications in the nano-field of technologies like bio-imaging, photothermal therapy and drug delivery fields. BP is a direct bandgap semiconductor in which band topology remains the same and also it has high carrier mobility [97]. Bulk silicon is another photothermal agent that has an indirect bandgap semiconductor, which means its valence band maximum and conduction band minimum have different momentum vectors. The photoluminescence effect of BP increases exponentially as the layer thickness decreases from 5 to 2 layers [97, 98]. In silicon nanocrystals, the wavelength of photoluminescence is dependent on the diameter of nanocrystals. The photothermal effect is mainly the conversion of optical energy to thermal energy. In ocular phototherapy, the laser is the source of light [99]. Ocular phototherapy has wide application in the treatment of ocular tumors [100]. The study has been conducted to assess the safety and clinical efficacy of non-damaging photothermal therapy for the treatment of the retina. The study included 16 patients suffering from persistent central serous retinopathy who were treated with the PASCAL streamline at 577 nm wavelength, using 200 mm retinal spot sizes. They concluded that photothermal therapy was safe and it was improved visual acuity and resolution of subretinal fluid in patients suffering from chronic central serous retinopathy [101]. Another study was conducted to evaluate the effect of near-infrared (NIR) on photothermal therapy agents by using Ag@Oxides nanoprisms for uveal melanoma therapy. Silver oxide nanoparticles were prepared by a simple sol–gel route and irradiated with an 808 nm NIR laser. They concluded that Ag@oxides nanoparticles were demonstrated to be an efficient photothermal therapy agent for solid cancers by local delivery [102].

Artificial intelligence

For the last two decades, pharmaceutical scientists are developing novel techniques for targeted drug delivery with maximum efficacy by minimizing the side effects. Artificial intelligence (AI) is the branch of computer science also and it is the intelligence demonstrated by machines. Generation of new information, automated working system and prediction, continuous performance, monitoring various diseases is the main advantage of AI. AI technique enables prediction of pharmacokinetic responses including quantitative structural activity relationships, in vivo responses, etc. So, the incorporation of AI technology into the ophthalmic sector may be a ray of hope for the ocular drug delivery system [103].

Nanotechnology in ophthalmic drug delivery

Many researchers are facing huge problems in the sector of ocular drug delivery. The bioavailability of a drug is not up to the mark due to several ocular barriers [104, 105]. Many literatures revealed that the particle size of the drug should be appropriate and narrow. It should also possess less irritation, more biocompatible and possess appropriate bioavailability to achieve ocular drug delivery [106]. Hence, the ideal ocular drug delivery system must be in the form of eye drops without inducing any irritation or blurred vision [107]. The topical delivery is the only efficient way to deliver the drug into the anterior segment of an eye but the only minute concentration of the drug will reach into the posterior segment of the eye. But the systemic administration will help to achieve a small quantity of drug in the target site of ocular tissues. However, the dose needed to obtain therapeutic efficacy may induce several drug-related side effects. Thus, the adoption of nanotechnology-based drug delivery such as liposomes, niosomes, solid lipid nanoparticles, nanosuspensions, nanoemulsions, nanomicelles and biodegradable microspheres could help in overcoming various toxicity and bioavailability issues of many drugs. The drugs that are intended to deliver to a specific target site for treating many ocular conditions could be achieved by surpassing the ocular barriers. These nanotechnology-based drug delivery systems can also help in sustaining the release of drugs by crossing several ocular barriers such as the blood-retinal barrier in the eye [108]. This can further improve the bioavailability of many drugs thereby increasing the therapeutic efficacy [109].

Nanoemulsions

They are fine dispersions of infinitesimal droplets of two immiscible liquids. They contain the dispersed phase, where the particles dispersed are in the nano- or submicron range. Generally, the nanoemulsions are made of one or more surfactants containing both hydrophilic and hydrophobic parts. The high-pressure homogenization is adapted to obtain the dispersed globules in a size range of below 100 nm with a translucent look. Since the nanoemulsions are globule-sized, the dispersions are thermodynamically unstable which requires more surfactants to stabilize. This can be the major reason behind the stickiness of the formulation. The phospholipids are one class, which is also commonly used in stabilizing the nanoemulsion formulation. The four major types of nanoemulsions are o/w, w/o, w/o/w, o/w/o type emulsion [110–112].

Nanosuspension

They usually consist of hydrophobic drugs that are suspended in the specific dispersion medium. The nanosuspensions can also be prepared using various polymers and resins to sustain the drug release and to achieve therapeutic efficacy by increasing bioavailability [113]. The polymers that are inert and biocompatible without causing any irritation to the iris, cornea, conjunctiva, etc. will be most suitable for ocular drug delivery. The various formulation techniques such as high-pressure homogenization, milling, emulsification-solvent, precipitation, supercritical fluid process, melt emulsification method, lipid emulsion/microemulsion template and solvent evaporation are used to design the nanoformulation [114].

Nanoparticles

They are defined as nano-sized particles, whose diameter ranges from 10 to 1000 nm. They are usually made using several types of biodegradable and biocompatible polymers, resins, phospholipids, etc., either occurred naturally (albumin, sodium alginate, chitosan, guar gum, xanthan gum, gelatine, etc.) or synthesized in the laboratory [polycyanoacrylate, poly(D,L-lactides), polylactides, etc.]. These can be used for delivering the drug to ocular tissues efficiently. The nanoparticles consist of three major properties such as larger surface area, highly mobile in the dispersed state and can exhibit what is known as quantum effects. Based on dimension nanoparticles can be classified as one-, two- and three-dimensional nanoparticles. The various techniques like emulsion solvent evaporation, double emulsion solvent evaporation, salting out, emulsions-diffusion method and solvent displacement/precipitation method are used to design the nanoparticles [115, 116].

Nanomicelles

The nanomicelles are nano-sized (10–1000 nm), micellar-shaped, self-assembling and highly mobile colloidal-like dispersions consisting of a hydrophilic shell and hydrophobic core. They are made of lipids by arranging themselves in a circular form in the solution. The amphiphilic characteristic of fatty acids is responsible for forming a micellar structure since they contain both hydrophilic (polar) and hydrophobic (non-polar) sections. The core of the nanomicelles consists of hydrophilic chains that extend outward, leading to the formation of the clear formulation. Nanomicelles are classified as polymeric nanomicelles, surfactant nanomicelles and polyion complex nanomicelle. The main advantages of nanomicelles are can be prepared easily and finally yields very small size particles which lead to a larger surface area with higher absorption automatically increases the bioavailability of drugs also encapsulates a large number of drugs [117].

Liposomes

They are spherical vesicles containing a minimum of one hydrophobic (Lipid) bilayer. They are made of many non-toxic lipids and cholesterols such as phosphatidylcholine, phosphatidylethanolamine as far as they are compatible with each other. The liposome vesicles size under 10 to 100 nm can be named unilamellar vesicles and huge measured vesicles 100 to 300 nm. Liposomes are promising systems for drug delivery due to their size, amphiphilic properties and biocompatibility. The properties of the liposomes significantly vary upon their size, surface charge, preparing method and composition of lipid/cholesterol. Since they possess a specific surface charge, they can be used in delivering various drugs into the ocular tissues. For example, the negative charge bearing corneal surface can attract the positive surface charged liposomes [118].

Niosomes

The structure of niosomes is quite similar to liposomes except for the composition that is present in liposomes. They are mainly constituted of non-ionic surfactants. They tend to incorporate both hydrophobic and hydrophilic drugs. Unlike liposomes, they are chemically stable and less toxic due to the absence of phospholipids. This makes niosomes select over liposomes in drug delivery. They also exhibit flexibility in structural characterization due to their size, composition and fluidity. This can increase the sustained action of drugs with better bioavailability. The preparation and storage are quite simple in the case of liposomes compared to niosomes due to their composition of non-ionic surfactants over phospholipids [119, 120].

Dendrimers

They are one more novel drug delivery system for the ocular region. They are the macromolecular compounds composed of symmetric branches surrounding a central core (like a tree). These are the nano-sized polymeric system. The hydrophilic and lipophilic drugs in the central core and are entrapped with polymers. The drug can be either encapsulated inside the dendrimers or bonded to the surface functional groups to achieve drug loading. The preparation and functionalization of dendrimers are easy up to the generation 2 (G2) level, beyond that it will be difficult to fabricate since they are in the nano-size range. But, most of the drugs can be incorporated into the dendrimers of G2 level. Thus, it could be an efficient way to deliver drugs to the ocular region [121].

Polymeric micelles

Polymeric micelles are the novel drug delivery system used to target the drug into the specific site and release it in a controlled manner [122]. Polymeric micelles can be defined as nano-sized molecules of core–shell structure that are formed by the self-association of amphiphilic block copolymers when they are added to an aqueous solvent. Usually, polymeric micelles are spherical in shape and size in the range of 10–100 nm. These are widely used in drug delivery systems due to their low toxicity, nano-size, good biocompatibility and mainly high stability [123]. The release of drug from polymeric micelles depends on (i) physicochemical properties of the drug and copolymer (ii) method of preparation (iii) structure of micelle forming copolymer and drug (iv) localization of drug in the micelle [124]. The methods like drug dissolution, dialysis, oil in water emulsion, solvent evaporation, co-solvent evaporation and freeze-drying are commonly used to encapsulate the drug into micelles [125]. Due to their small size, it is easily penetrated through the ocular tissues and automatically increases the bioavailability of the drugs. The unique core–shell structure of polymeric micelles, hydrophobic drugs can incorporate within the micelle core will lead to increase the aqueous drug solubility [126, 127].

Biodegradable microspheres

Microspheres are spherical microparticles with a size range between 1 and 1000 μm [128]. Biodegradable microspheres were prepared by using synthetic and natural biodegradable polymers [129]. Microspheres are mainly of two types, matrix and capsular. The microspheres were fabricated by using biodegradable natural and synthetic polymers [130]. Natural origin biodegradable polymers are sub-classified as polysaccharides and proteins. Polysaccharides are mainly derived from a plant (dextran, starch, pectin), animal (hyaluronic acid), microbial (xanthan, pullulan, alginic acid) and marine source (chitosan) [131]. Proteins are mainly from plant (gluten) animal (gelatin, collagen and albumin) and microbial (polyhydroxyalkanoates) origin. Synthetic biodegradable polymers are classified as polyesters [PLA, polylactic-co-glycolic acid (PLGA), polyglycolic acid (PGA), polycaprolactone (PCL) and polyphenylene ether (PPE)], polyorthoesters and polyanhydrides [132]. Diffusion, dissolution and surface erosion are the major mechanism by which drug release from biodegradable microspheres [133]. The biodegradable microspheres prepared by using various techniques like interfacial polymerization [134], *in situ* polymerization [135], phase separation [136], ionotropic gelation [137], emulsion solvent evaporation [138], double emulsion [139], spray drying [140, 141], spray congealing and air suspension method [142]. In ocular drug delivery, biodegradable microsphere concept has been used to deliver the drug in a controlled manner and to the specific site. Biodegradable microspheres for the intravitreal delivery of acyclovir were formulated and characterized for various characteristics. These microspheres were prepared by spray drying technique which showed good encapsulation efficiency and *in vitro* dissolution mainly dependent on the molecular weight of the polymer. Also i*n vivo* evaluation evidenced that prepared formulation shown sustained release of acyclovir [143]. A study has been carried out for the controlled and extended release of bioactive aflibercept hydrogel for the treatment of ocular neovascular diseases and studied *in vitro* release of the drug. They fabricated afliberceptloaded microspheres by using biodegradable synthetic polymers and concluded that the prepared microsphere hydrogel was safe and delivers aflibercept in a controlled and extended manner for the period of 6 months [144].

Advantages of nanotechnology-based anti-angiogenic therapy

Angiogenesis inhibitors are the revolutionized drug molecules to target existing tumor infiltrating blood vessels and to inhibit the formation of new blood vessels [178]. These agents mainly act on vascular endothelial growth factors and thereby inhibit the angiogenesis process. Currently, intravitreal injections are the treatment of choice but it is associated with several complications [179]. So, here alternative therapy for the treatment of pathological angiogenesis is the nanotechnology-based drug delivery to overcome several complications. Nano-approach-based drug delivery techniques play an important role to overcome the drawbacks of present therapy due to their interesting physicochemical properties like nano-sized particles, prolonged half-life, high targeting efficiency, high surface area and the small size of the particle may cross ocular barriers [180]. The study has been conducted for the topical delivery of anti-VEGF drugs for the treatment of choroidal neovascularization using cell penetrating peptides. They evaluated the biological efficacy of the topical anti-VEGF using cell penetrating peptide that is compared with the intravitreal anti-VEGF injections. They have shown that cell penetrating peptides have high penetrating capabilities and non-toxic to the eye. In this study, they delivered bevacizumab and ranibizumab to the posterior segment of mouse, rat and pig eyes. They concluded that topical delivery of anti-VEGF with cell penetrating peptide was efficacious as a single intravitreal injection. A study has been highlighted that within 24 h the cell penetrating peptide and anti-VEGF drug complexes were cleared from the retinal region [181]. Seah et al. reviewed on use of biomaterials for sustained delivery of anti-VEGF to treat retinal

diseases. They summarized till date nanoformulations, biodegradable implants and hydrogels have emerged as a promising treatment technique. The anti-VEGF drug molecules or biologics are proteins with high molecular weight and these are very sensitive molecules for various environmental conditions. They discussed that biomaterials are the main agent which are involved in the sustained delivery of anti-VEGF drugs to the retina [182]. Selected biomaterials should fulfill several ideal characteristics like it should protect anti-VEGF molecule from degradation by protecting the tertiary and quaternary structure of the protein, should encapsulate a large amount of drugs in minimum volume to avoid intraocular pressure elevation on administration, should capable of sustaining the release of anti-VEGF for a longer period and finally should remain optically clear within the vitreous to avoid blurring of vision [183]. Liu et al. fabricated bevacizumab-loaded PLGA/PCADK (polycyclohexane-1,4-diyl acetone dimethylene ketal) microspheres. *In vitro* bioactivity test was proved through HET CAM assay and biocompatibility was evaluated using New Zealand white rabbits [184]. Sun et al. fabricated bevacizumab-loaded mesoporous silica nanoparticles. Bioactivity test proved through oxygen-induced retinopathy mouse model. Biocompatibility test proved with C57BL/6J mice [185]. Liu et al. fabricated hydrogel technology ranibizumab and aflibercept-loaded PLGA microspheres suspended in a hydrogel. Bioactivity studies proved on laser-induced choroidal neovascularization Long-Evans rat model. These studies showed that novel approach-based topical delivery of anti-VEGF drugs is the choice of a treatment system for pathological angiogenesis [144, 186].

Potentials of nanotechnology-based ocular drug delivery systems for clinical applications

Currently in the pharmaceutical field, ocular drug delivery has become the most challenging area. To overcome this limitation targeted drug delivery system came into existence [187]. Nanotechnology emerged as a promising drug delivery system in the field of ocular therapy. Various nanotechnology-based products have been under investigation and few products have already been clinically approved by the United States Food and Drug Administration (USFDA) and are available for the treatment of medical conditions like autoimmune disorders, cancer, age-related macular degeneration, etc. Currently, many ocular delivery systems are in clinical trials and some products have already been introduced into the market [188]. The development of nanotechnology seems to be a ray of hope for the currently facing challenges. Pre-clinical/clinical/approved formulations (nano/micro) in ocular drug delivery system are listed in Table 4.

Risk analysis

In the current review, we have presented the applications of novel approaches for the treatment of pathological ocular angiogenesis [209]. The literature survey represented the main aim to formulate these novel approaches and nanotechnology-based formulations to improve the uptake and for the better entrapment efficiency of drug which ultimately improves the therapeutic effect. But, stability was the major problem associated with the nano-based formulations [210]. The reason behind the low therapeutic efficacy of the nanoformulation is their ability to self-aggregate at low drug concentration, affecting the drug entrapment and ultimately leads to poor stability of the formulations. For example, it has been reported that self-aggregation of doxorubicin nanoformulation due to their high ionic strength ultimately leads to the high particle size and affects their drug entrapment efficiency [211]. The same problem was reported for the liposome formulation which increases in size due to their high ionic strength [212]. Another challenge is the swelling mechanism of nanoformulation. When swelling occurs, the size of the particles increases and this limitation can be fixed by controlling the swelling mechanism by using pH-sensitive coatings or the capping agents over the formulation. Finally, certain nanoformulations were failed to meet FDA quality profile and difficulties associated with formulation manufacturing, make nano-approach-based drugs formulation unfit for large-scale production. Thus, the upcoming research should focus on above mentioned challenges and concentrate on large-scale manufacturing of nanoformulations abiding by the guidelines of USFDA to resolve all the associated hurdles and inexpensively [188, 213].

Future perspectives

The vision impairment and irreversible vision loss can be decreased or completely prevented by enormous research and developments necessitate the application of novel approaches and strategies. Novel approaches in the development of ocular dosage forms have very wide applications in the treatment of various ocular diseases. Topical delivery of drugs into the ocular region is one of the best approaches in ocular drug delivery in terms of patient compliance. Despite its seemingly easy way, they possess several limitations such as tear turnover, nasolacrimal drainage, blinking, induced lacrimation that leads to quick elimination of drug particles from the surface of the eye. This results in sub-therapeutic drug levels in the target tissue, particularly at the retinal level. Thus, novel approaches can assist in the manufacture of nano-based formulations. A very less amount of research was carried out on the above

Table 4 Pre-clinical/clinical/approved formulations in ocular drug delivery system

Drug name	Product name	Formulations/materials	Condition	Pre-clinical/clinical/approved	References
Cyclosporin	Restasis	Nanoemulsion	Dry eye	Approved	[189]
Difluprednate	Durezol	Nanoemulsion	Eye inflammation	Approved	[189]
Bevacizumab	–	PLGA /PCADK microspheres	Ocular angiogenesis	Pre-clinical	[184]
Bevacizumab	–	Mesoporous silica nanoparticles	Ocular angiogenesis	Pre-clinical	[185]
Bevacizumab	–	PLGA microspheres	Ocular angiogenesis	Pre-clinical	[189]
Bevacizumab	–	Albuminated PLGA nanoparticles	Ocular angiogenesis	Pre-clinical	[190]
Bevacizumab	–	Chitosan nanoparticles	Ocular angiogenesis	Pre-clinical	[191]
Bevacizumab	–	PLA nanoparticles in porous PLGA microparticles	Ocular angiogenesis	Pre-clinical	[192]
Bevacizumab	–	Multi-vesicular liposomes	Ocular angiogenesis	Pre-clinical	[193]
Bevacizumab	–	Egg phosphatidylcholine:cholesterol (liposome)	Ocular angiogenesis	Pre-clinical	[194]
Bevacizumab	–	OTX-IVT (anti-VEGF intravitreal hydrogel implant)	Ocular angiogenesis	Pre-clinical	[195]
Bevacizumab	–	PLGA-PEG-PLGA hydrogel	Ocular angiogenesis	Pre-clinical	[196]
Bevacizumab	–	Vinyl sulfone functionalized hyaluronic acid (HV-VS) and thiolated dextran (Dex-SH) hydrogel	Ocular angiogenesis	Pre-clinical	[197]
Bevacizumab	–	Silk hydrogel	Ocular angiogenesis	Pre-clinical	[198]
Bevacizumab	–	Poly(ethylene glycol)-poly-(serinol hexamethylene urethane) (ESHU) hydrogel	Ocular angiogenesis	Pre-clinical	[199, 200]
Ranibizumab & Aflibercept	–	PLGA microspheres suspended in a PEG-PLLA-DA/NIPAA hydrogel	Ocular angiogenesis	Pre-clinical	[144, 186, 201]
Ranibizumab	Lucentis	Intravitreal injection	Myopic choroidal neovascularization/Diabetic retinopathy	Approved	[202]
Ranibizumab	–	Non-biodegradable implant technology port delivery system	Ocular angiogenesis	Clinical Phase III trials	[203]
Ranibizumab	–	Replenish posterior micropump	Ocular angiogenesis	Phase I trials	[204]
Dexamethasone	Ozurdex	Biodegradable implant	Macular edema, Non-infectious uveitis	Approved	[205]
Triamcinolone acetonide	Trivaris	Nanosuspension	Uveitis	Approved	[205]
Triamcinolone acetonide	Kenalog	Nanosuspension	Macular edema	Approved	[205]
Fluocinolone acetonide	Retisert	Non-biodegradable implant	Non-infectious Uveitis	Approved	[205]
Fluocinolone acetonide	Iluvien	Non-biodegradable implant	Diabetic macular edema	Approved	[205]
Triamcinolone acetonide	Triesence	Nanosuspension	Maculae edema	Approved	[205]
Verteporfin	Visudyne	Liposome	AMD	Approved	[206]
Aptamer	Macugen	Polymer nanoparticle	Wet AMD	Approved	[206]
TLC399 (ProDex)	–	Lipid-based nanoparticle	Macular edema	Approved	[207]
Latanoprost	Polat-001	Liposome	Glaucoma	Approved	[207]
Polyethylene glycol 400 & Propylene glycol	Systane	Nanoemulsion	Dry eye	Approved	[208]

discussed approaches for ocular angiogenesis particularly. The application of nanomedicine in the ocular drug delivery area has shown great potential in the pharmaceutical field of research [104]. Nanomedicine also has its potential in improving the pharmacokinetic and pharmacodynamic properties of few therapeutic agents. Many nanoformulations are under the pre-clinical and clinical stage of development for the treatment

of ocular diseases. Unfortunately, this nanotechnology-based drug delivery has few limitations when it enters the large-scale process. The reason behind the low therapeutic efficacy of the nanoformulation is their ability to self-aggregate at low drug concentration, affecting the drug entrapment and ultimately leads to poor stability of the formulations it again leads to the safety and toxicity issue of the prepared formulation. Also, other factors like size, shape, administration dose can influence toxicity in nanomedicine. So advanced nanofabrication technologies like particle replication in non-wetting templates (PRINT) [214] and the hydrogel template method have been introduced to create ocular nanomedicine. This technology can create uniform nanoparticles and microparticles with controlled shape, size and surface modification at a large scale. Another study conducted using the principle of PRINT technology is AR13503 implant, which was manufactured to provide sustained release of drugs for more than 2 months [214, 215]. Considering the immense amount of past and present research on these techniques, there is potential and a ray of hope for better therapies for the future in the treatment of diseases and is with the eventual goal of stopping ocular angiogenesis. There are several areas to be explored for future research for the benefit of a novel therapy for ocular angiogenesis. Furthermore, the ongoing development of novel therapy or modification to current dosage forms in the context of ocular angiogenesis will be helpful to focus on the new strategy of medication for the treatment of angiogenesis.

Conclusion

As we discussed earlier, drug delivery to the ocular region became challenging to pharmaceutical scientists. The barriers which are present in the eye hinder ocular bioavailability mainly when the drugs are applied topically. So, novel approach-based drug delivery systems are of great importance in the pharmaceutical technology as well as the ophthalmological sector. Thus, for ocular disease management, the design and development of new techniques are mandatory. Only a few works can be seen specifically for ocular angiogenesis. Currently to treat ocular angiogenesis, intravitreal injections of anti-VEGF drugs are the revolutionized treatment. But, repeated intravitreal injections to the eyes lead to several serious complications. So, novel approach-based drug delivery techniques may be a ray of hope for better therapies for the future in the treatment of ocular angiogenesis. Also, the inclusion of novel techniques may be a road map for future research in the field of ocular angiogenesis disease management.

Abbreviations

DR: Diabetic retinopathy; AMD: Age-related macular degeneration; EGF: Endothelial growth factor; FGF: Fibroblast growth factor; PDGF: Platelet-derived growth factor; PDGFR: Platelet-derived growth factor receptor; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; PGF: Placenta growth factor; NRP: Neuropilin; VPF: Vascular permeability factor; RTK: Receptor tyrosine kinase; KDR: Kinase-insert-domain containing receptor; EC: Endothelial cells; HIPC: Hypoxia-inducible protein complex; HIF: Hypoxia-inducible factor; NO: Nitric oxide; NOS: Nitric oxide synthase; TNF: Tumor necrosis factor; TGF: Transforming growth factor; IL: Interleukin; ROP: Retinopathy of prematurity; BRVO: Branch retinal vein occlusion; IgG: Immunoglobulin-G; PAA: Polyacrylic acid; AI: Artificial intelligence; G2: Generation 2; MMP: Matrix metalloproteinase; PEDF: Pigment epithelium-derived factor; siRNA: Small interfering ribonucleic acid; mRNA: Messenger ribonucleic acid; DNA: Deoxyribonucleic acid; LCA: Leber congenital amaurosis; MN: Microneedle; PLA: Polylactic acid; PTT: Photothermal therapy; BP: Black phosphorous; NIR: Near-infrared; PLGA: Polylactic-co-glycolic acid; PGA: Polyglycolic acid; PCL: Polycaprolactone; PPE: Polyphenylene ether; PCADK: Polycyclohexane-1,4-diyl acetone dimethylene ketal; PRINT: Particle replication in non-wetting templates.

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SN substantially contributed to the conception and designing of the work and drafted the manuscript. MGA, JGBH and PKS contributed to the writing of the manuscript and substantially revised the whole manuscript. AN, TM, NN and SA contributed in drafting and writing of the manuscript. All authors have read and approved the manuscript.

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Author details

[1]Department of Pharmaceutics, Yenepoya Pharmacy College and Research Centre, Yenepoya (Deemed to be University), Mangalore 575018, India. [2]Department of Pharmacology, Yenepoya Pharmacy College and Research Centre, Yenepoya (Deemed to be University), Mangalore 575018, India.

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