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Review Article

Recent Developments and Emergent Challenges in Nanotechnology-Based Ocular Drug Delivery Systems

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ABSTRACT

Ocular Drug Delivery (ODD) is an engrossing and challenging task for pharmaceutical researchers. Unique anatomy and physiology of the eye poses numerous challenges for designing targeted drug delivery systems. Ocular discomfort involves the anterior and posterior segment diseases like glaucoma, diabetic retinopathy, glaucomatous optic neuropathies, retinal vascular diseases, posterior uveitis, and age-related macular degeneration that lead to distress, inflammation and severe retinal disorders. Conventional treatments such as eye drops, injections and implants suffer from a low ocular bioavailability due to various anatomical and pathophysiological barriers. To deal with these problems pharmaceutical researchers explored nanotechnology-based drug delivery systems like polymeric and lipidic nanoparticles, liposomes, cubosomes, nanoemulsions, niosomes, nanomicelles, dendrimers, microneedles, etc. These nano-systems have achieved great success in solving the problems like drug retention, bioavailability, sustained and targeted drug delivery without affecting the eye tissues. This review provides an insight into recent advancements and the emerging challenges for nanotechnology-based formulation development in the area of ocular drug delivery and emphasizes applications of nanotechnology in disease diagnostic in ophthalmology.

INTRODUCTION

The unique and complicated anatomy and physiology of the human eye poses critical challenges in targeting drugs to its anterior and posterior segments [1]. The anterior segment of the eye, particularly the cornea, is uncovered to environment and has a vasculature and translucent for unhindered vision. Whereas, the posterior segment holds the vascular linings and optic nerve that regulates vision function [2]. The major challenge in ocular drug delivery lies in maintaining the optimal therapeutic concentration of medicament available in the desired sites in eyes for sufficient time. One eye drop can have 20-50 µl volume, whereas the cul-de-sac can hold only 7-10 µl fluid, which leads to wastage or nacrsolacrymal drainage [3].

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The different pre-corneal, dynamic and static eye barriers also hinder the drug delivery to targeted ocular tissue [4]. Although, these barriers act as protecting covering for eye from exogenous substance and external stress, some irreversible vision impairing problems like, glaucoma, cataract, Diabetic Retinopathy (DR), conjunctivitis, Diabetic Macular Edema (DME), cytomegalovirus retinitis, retinal vein occlusion, Age-related Macular Degeneration (AMD) affect both anterior and posterior segment of eye [5-7] . These irreversible ocular diseases influence the overall quality of life. National Eye Institute, USA, anticipated that by 2050, twice over the people will suffer from glaucoma, DR, AMD etc. and the annual predicted cost will be US$139 billion, which is a huge economic burden on society [8].

Over last two decades, the researchers focused on novelty, safety and patient compliance for ophthalmic product development. The conventional ocular formulations such as, eye

drop, suspensions, emulsions, gels and ointments etc., show better retention time in anterior segment of eye but it is difficult for them to permeate inside the posterior segment. To overcome these barriers, nanotechnology has provided promising solutions and several nanoformulations such as liposomes, niosomes, microparticle, nanoparticle, cubosomes, microneedles etc. were developed in last decade [9]. Nanocarriers facilitated drug bioavailability with enhanced pre-corneal residence time, thereby sustaining and controlling the release of drug in both the anterior and posterior chambers of the eye. In addition, nanoformulations also proved highly effective in drug targeting for chronic vitreo-retinal diseases by increasing drug release [10].

As the technological advancements in the field of ocular drug delivery are up-and-coming every day and the changing landscapes in the field have open-up new arenas of research, the authors felt a need of disseminating these advancements amongst the research fraternity. Therefore, this review article focuses on recent advancements in the nanotechnology-based drug delivery systems for ocular diseases and provides an overview of emerging challenges involved there in.

Constraints to Ocular Drug Delivery

The globular structure of human eye size about 24 mm. and consists of two segments namely; Anterior and Posterior segments. Various biological barriers exist in both the segments and these barriers protect the eyes from foreign substances [11]. Anterior segment contains cornea, iris, lens, and aqueous humor. Posterior portion is made-up of vitreous body, retina, choroid, and back of the sclera [12]. Human corneal epithelium consist several layers of epithelial cells and these cells interconnect with rigid junctions, these junctions strictly limit the penetration of drugs, especially the aqueous soluble drugs. In contrary, the corneal stroma that hinders entry of hydrophobic drugs is composed of charged and highly organized hydrophilic collagen. Blood-aqueous and blood-retina barriers are present in the intraocular environment. Tight junctions of iris epithelium, iris endothelium, and Schlemm's canal endothelium limit both active and paracellular transport. Blood-retinal barrier is composed of vascular endothelium with tight junctions and divided into internal and external parts. These junctions control entry of molecules into the intraocular chamber, resulting in insufficient drug concentration in intraocular tissues [13]. In addition, clearance mechanisms including eye blinking, tear film, tear turnover, solution drainage and lacrimation also limit topical drug administration to the anterior segment of eyes. Further, the rapid restoration time (2-3 min.) of tear film clear the drug from segment in no time after instillation [14]. Thus, ocular barriers and physical factors as illustrated in Fig. 1 greatly hamper the drug penetration and bioavailability.

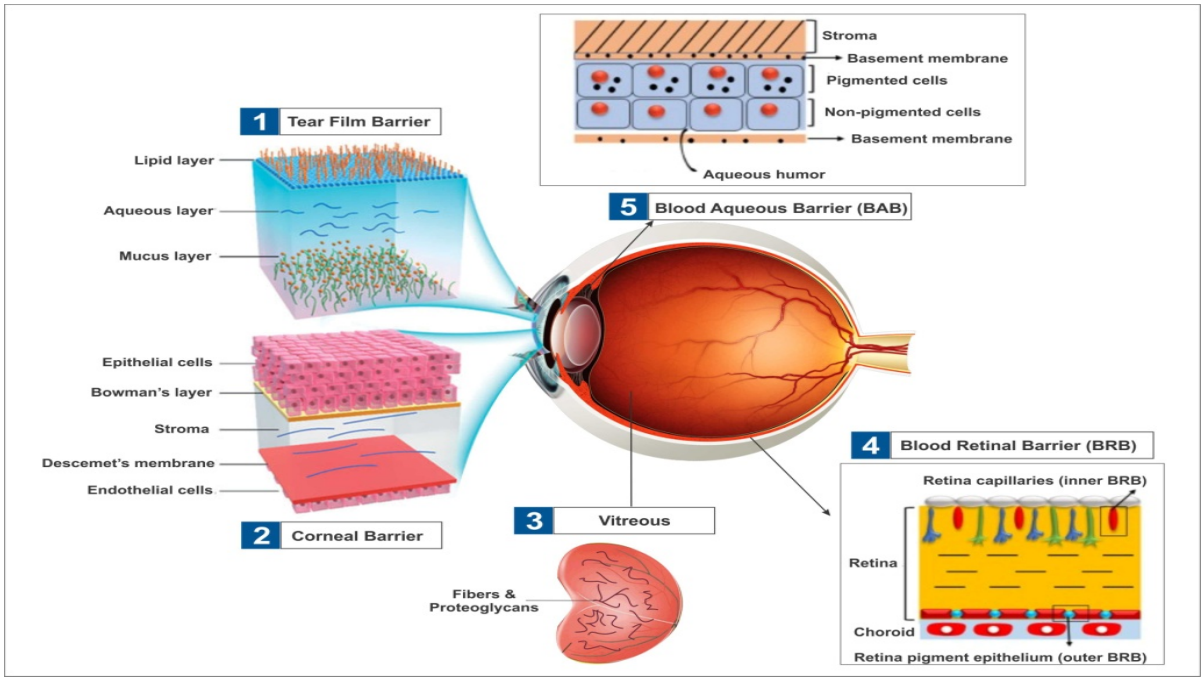

Figure 1: Physiological and physical barriers for ocular drug delivery in anterior and posterior segments of the eye.

Benefits of Nanotechnology in Ocular Drug Delivery

Conventional dosage forms in ocular drug delivery suffer lower bioavailability and local tissue irritation due to the presence of biochemical and physiological barriers in eyes. These limitations result in sub-therapeutic dose administration and poor patient compliance. Thus, a suitable ocular drug delivery formulation ideally should be able to deliver drug/s in minimum (two or three) administrations per day without causing local irritation or blurring of vision [15]. Drug administration into the anterior segment of the eye mainly demands topical delivery however a very little of topically applied drug reaches to the posterior segment which necessitate systemic administration of certain drugs; such as anti-glaucoma drugs, corticosteroids and certain antibiotics. Systemic delivery of drugs also suffers from lower drug concentrations at the desired ocular sites and can cause considerable adverse effects [16].

Nanotechnology-based drug delivery systems like nanosuspensions, solid-lipid nanoparticles, liposomes, etc. have led to the solution of various problems related to ocular delivery of drugs. Nanoparticle formulations of weakly soluble drugs like dexamethasone, budesonide, gancyclovir and more have proved beneficial in enhancing the drug solubility in ocular tissues. Utilizing nanoparticle-based systems also allowed region specific delivery to mononuclear phagocyte systems and minimized side effects on other organs. Fig. 2 summarizes several other beneficial aspects of utilizing nanotechnology in ocular drug delivery [17, 18].

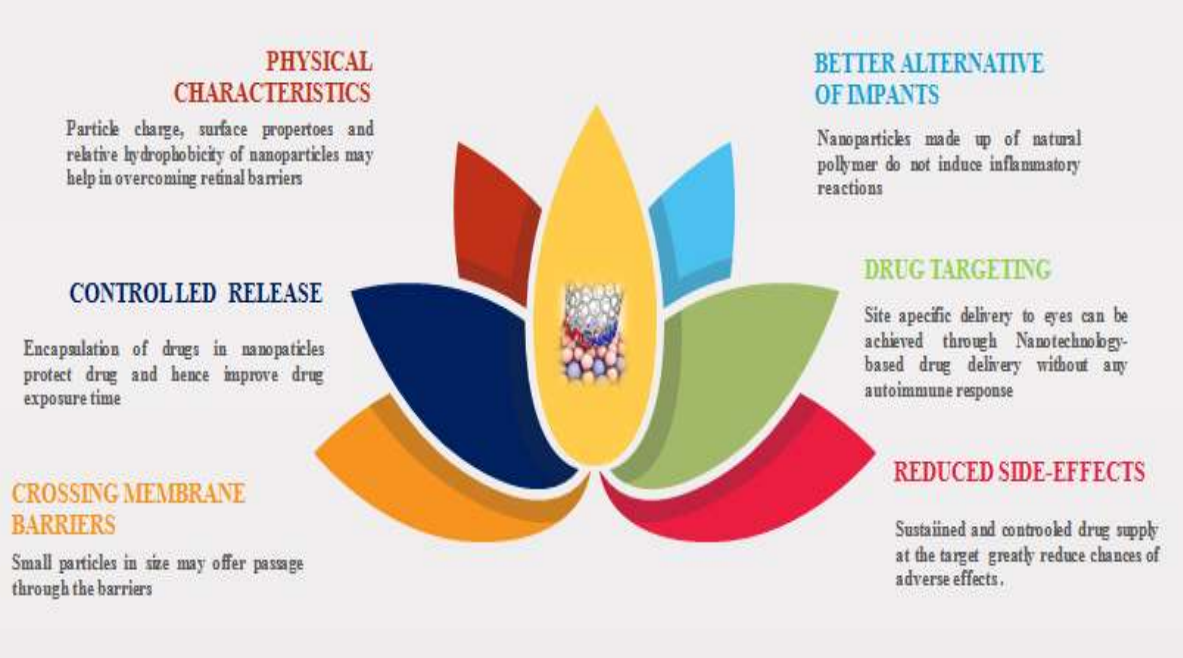

Figure 2: Benefits of nanotechnology-based ocular drug delivery systems.

Nanotechnology-Based Drugs Delivery Systems

Nanotechnology involves materials, devices and systems that are designed at nanometer scale. Several forms of nanotechnology-based formulations emerged in the last decade, these formulations greatly contributed in providing solutions to ophthalmic drug delivery by enhancing the site-specific drug supply in a controlled manner [19, 20]. Here we discuss some of the nano-formulations that have been successfully utilized for the management of ophthalmic diseases.

Nanoparticles (NPs)

The smaller size and better penetration capacity of nanoparticles served the purpose of targeting drug(s) for specific tissues in eyes [21]. NPs have been successful in targeting drugs to both the anterior and posterior segments of eyes. For managing Glaucoma, Brimonidine tartrate (BT) loaded chitosan (CS) NPs prepared by inducing the ionic gelation upon addition of sodium tripolyphosphate (TPP) helped to reduce dosage frequency by sustained drug release [22]. Methazolamide, bound to CaP nanoparticles prolonged its duration of lowering the Intraocular Pressure (IOP) and helped managing

glaucoma [23]. Hyaluronic acid modified chitosan NPs (CS-HA-NPs) may be a promising carrier for glaucoma drug delivery [24]. Positively-charged pilocarpine HCl-loaded polymeric and lipid NPs by quasi-emulsion solvent evaporation technique was potent for glaucoma [25].

Charged nanoparticles of flurbiprofen with a size of 100 nm, polydispersity index of 0.26 and zeta potential charge of 40–60 mV, created using Eudragit RS 100 and RL 100, showed better inflammation control as compared to normal eye drops of flurbiprofen in surgical trauma model of rabbit. This effect was attributed to higher drug concentration in aqueous fluid than in conjunctiva, thereby increasing bioavailability of drug [26]. Indomethacin (IM)-Chitosan (CS) nanoemulsion showed clearer healing of the corneal chemical ulcer compared with NPs preparation and a high level of IM in inner ocular structure thereby increasing drug delivery efficiency [21]. Solid-Lipid nanoparticles (SLN) of baicalin prepared by emulsification/ ultrasonication exhibited better drug retention capacity and lesser eye irritation. High concentration of baicalin in aqueous humors was achieved due to better retention capacity of these SLNs [27]. Inhibition of corneal neovascularization was successfully achieved by Celastrol-filled PEG-block polycaprolactone polymeric nanomicelles (size of 48nm). These nanomicelles released the drug in two phases; first phase of rapid release followed by a slow and prolonged release phase [28].

Microemulsions

Microemulsions are dispersion of water and oil, which are made miscible by stabilizing interfacial area with surfactant or cosurfactant agents. There are several advantages of formulating microemulsions as they have a high capacity of dissolving drugs, can be easily prepared and sterilized and allow better membrane permeability of drugs in eyes [29]. Nanoemulsions containing the Dorzolamide hydrochloride and methazolamide-loaded SLNs enhanced the patients' adherence and reduced dosing frequency in comparison to eye drops [21]. Voriconazole microemulsions showed shear-thinning properties with acceptable viscosity. *In-vitro* release studies confirmed sustained release property and *ex-vivo* studies also supported the enhanced drug flux through cornea from microemulsions [30]. Nanoemulsion-gels of Terbinafine Hydrochloride developed as alternative to its eye drops by Tayal and coworkers successfully reduced dosing by displaying a controlled release profile. The *in-situ* analysis of the gels in rabbit aqueous humor showed significantly ($P < 0.01$) higher C_{max}, delayed T_{max}, prolonged mean residence time and increased bioavailability [31]. Cyclosporine A (Cy-A) loaded polymeric mucoadhesive nanoemulsion (Cy-A-mN) was formulated by Akhter and associates for topical occular conditions such as keratoconjunctivitis sicca (so called dry eye disease) and cornea transplant rejection. These conditions require therapeutic concentration of immunosuppressant drug onto the ocular surface for a prolonged period. Optimized Cy-A-mN has successfully maintained therapeutic concentrations (≥50-300ng/g) of Cy-A in the cornea and conjunctiva over the period of 24 hrs [32].

Liposomes

Liposome-based drug delivery systems are very effective due to its biocompatibility and structural similarity in comparison with the cell membrane. In the formulation of liposome, cholesterol is incorporated to maintain the stiffness of lipid bilayer as well as to avoid the outflow of drug from the formulation. Another benefit of liposome is that it can carry both hydrophilic drug in the core region and hydrophobic drug in the outer lipid layer, which makes it ideal for the drug delivery system [33]. NPs prepared by sialyl-Lewis X conjugated liposomes (size of 103nm) loaded with dexamethasone displayed better targeting of autoimmune uveoretinitis in mice animal models, accumulation took place in five minutes and inhibited by the anti-E-selectin antibody. These systems showed two times increase of dexamethasone concentration in the retina (6.67±0.32 ng/mg) [34]. Diclofenac-encapsulated liposomes prepared by Fujisawa and coworkers demonstrated 97% entrapment efficiency which was twice higher as compared to diclofenac solution in the form of eye drops. Further, *in-vivo* studies of these liposomes conducted in Japanese albino rabbit eyes showed controlled release of drug (50µl) after single administration. Stability studies conducted over 60 days at 25°C confirmed controlled size with considerable leakage (> 98% EE on day 60) of diclofenac from the liposomes [35]. Similarly, Hathout and associates used a simplified approach of developing gelatinized core liposomes of Timlol maleate for the treatment of Glaucoma. The gelatinized liposomes significantly enhanced drug entrapment (50%) by gelatin with a particle size of 38.81 µm. The formulation exhibited

significant reduction of Intraoccular Pressure (IOP) as compared to marketed liposomal preparation when evaluated *in-vivo* on glaucomatous rabbit's eyes [36].

Spanlastics

Spanlastic are elastic nanovesicular system consist of span and non-ionic surfactant (edge activators). They have a specific feature of loading hydrophobic, hydrophilic and amphiphilic drug moieties into its multilamellar nanovesicular system. Kakkar & Kaur in 2011 firstly developed these systems and using tween 80 and span 60 they synthesized ketoconazole-loaded spanlastics. These novel nanovesicles showed two times higher corneal permeation ($p \leq 0.001$) in comparison to niosomal formulation. Cytotoxicity (MTT Assay) and Genotoxicity (Ames Test) assays were tested negative for the formulation. Further, the presence of spanlastics along with drug in internal eye regions was confirmed with fluorescence assay using carboxyfluorescein [37].

The utilization of edge activators such as tweens and spans has significant importance in reducing the interfacial tension and increasing fluidity and deformability, which results in the improved penetration activity of spanlastic [38]. Using non-ionic edge activators (EAs) Al-mahallawi *et al.* utilized thin film hydration technique for synthesizing ciprofloxacin-loaded nanospanlastics. *Ex-vivo* permeation studies performed on tympanic membrane (TM) of rabbits explained high entrapment efficiency (51.81±1.57%) of the nanospanlastics as compared to Ciprocin® drops. The formulation was also physically stable for six months at 4-8°C [39]. Recently, Yang Liu and associates prepared novel cationized hyaluronic acid coated spanlastics (CHASVs), with the immunosuppressive peptide cyclosporine A (CsA) as the model drug. This study claimed superiority of CHASVs with enhanced corneal permeation coefficient (5.22×10^{-6} cm/s) and CsA residual (312.18±1.34µg/g) compared with commercial emulsions. Schirmer tear test, tear forming test and histologic analysis also confirmed considerable therapeutic effect and enhanced tear production in the dry eye [40].

Cubosomes

Cubosomes are crystalline particles made-up of surfactants with a proper ratio of water that are self-structured and size between 100 to 300nm. Amphiphilic lipids such as Monoolein and phytantriol were mainly used as surfactants with or without stabilizer/surfactant (Poloxomer 407). The molecular structure and structural symmetry of liquid molecule are like cubic shape. These cubic structure themselves have various water channels, therefore, as they have amphiphilic lipids, so they can easily hold the hydrophilic, lipophilic and amphiphilic molecules with high loading efficiency [41, 42].

Utilizing high-pressure homogenization Han *et al*. developed flurbiprofen (FB) loaded cubosomes for ocular drug delivery. The therapeutic efficacy of FB in FB-cubosomes was found to be 486.36±38.93ng $mL^{-1}min$ μg^{-1} which was significantly greater as compared to the FB eye drop ($P \leq 0.01$) [43]. In another study, Huang and coworkers, for sustained drug delivery in Glaucoma prepared cubosomes of Timolol Meleate (TM) using glycerol monooleate and poloxamer 407 as surfactants. The *in-vivo* testing of these cubosomes in rabbit eyes explained higher reduction in intraocular pressure by TM-cubosomes (21.4 to 32.6 mmHg) as compared to commercial TM-eye drops (27.8 to 39.7 mmHg) [44].

Microneedles

Microneedles (MNs) are microscopic applicators, which are applied through small arrays. These arrays are generally composed of polymers that carry drug(s) to be delivered at any specific site. This advanced pharmaceutical technique provides effective, non-invasive and targeted delivery also to the ocular site(s). Various studies around the world are emerging for utilizing MNs in various ophthalmic conditions such as uveitis, retinal vascular occlusion, glaucoma, age-related macular degeneration and retinitis pigmentosa, etc [45]. Using Pilocarpine as a model drug Jiang and associates demonstrated use of coated stainless steel MNs for targeting Glaucoma. Prepared Pilocarpine-MNs were administered through the intrascleral route, which increased the absorption rate of drug by around 45 fold [46]. Moffatt and colleagues fabricated hollow MNs using borosilicate micropipette tube, which allowed delivery of drug at a particular concentration i.e. 10–35µL from each MN present in the array [47]. To treat central retinal vein occlusion, Kadonosono *et al.* illustrated the use of MN for retinal endovascular cannulation. Glass cannula, which were used earlier, were fragile and difficult to use, hence to dilate retinal vein occlusion, they developed a novel method of using MNs, they fabricated MNs of stainless steel having 50µm length and 20µm inner diameter.

The prepared MNs were then attached to a syringe having 10µl saline solution, designed to pierce the occulated central retinal vein for removing thrombus inside the vein. Surgical treatment with MN showed effective results in 12 patients enrolled by improving visual acuity [48]. In another study, Kim and associates prepared stainless steel microneedles coated with Bevacizumab for the treatment of corneal neovascularization. 18 days study in New Zealand rabbits measured a significant reduction in neovasularization upon intrastromal delivery (44%) of Bevacizumab-MNs compared with untreated eyes, whereas only 6% reduction was seen by subconjuctival delivery of MNs treated eyes [49]. Selecting an anti-angiogenic monoclonal antibody (DC101), eye patch equipped with an array of detachable microneedles were developed by Than A. *et al.* using corneal neovascularization as a disease model, research explained that this microneedle patch reduced neovascular area by more than 90% [50].

Dendrimers

Dendrimers are star shaped, nanosized, multiple branched polymeric web structures, containing chain terminals made-up of functional groups as amine, carboxyl or hydroxyl groups. Their molecular weights may vary from 5-20 nm. For their drug carrying capacity, these systems are optimized based on functional groups, molecular geometry, charge of the surface and molecular weight. Based on their extraordinary structures, Dendrimers can encapsulate both lipid and water soluble drugs [51]. Initially, polyamidoamine (PAMAM) dendrimers have only been commercialized based on their clinical efficacy and safety [52]. Yang *et al.* first developed and tested dendrimer-poly(lactic-co-glycolic) acid hydrogels. This approach has been highly successful in delivering anti-glaucoma drugs from its loose gel network for over a 4 days period [53]. Glucocorticoid Dexamethasone (DEX) is one of the most likely anti-inflammatory therapeutic following eye injuries but it suffers with low bioavailability. Soiberman and colleagues to sustain DEX delivery after subconjuctival injection synthesized PAMAM dendrimers with hydroxyl terminal. These formulations were highly promising in enhancing both the bioavailability and residence time of DEX in cornea compared to the injection of simple solution [54]. In a recent breakthrough, novel cyclic arginine-glycine-aspartate (RGD) hexapeptide and penetratin (PEN) co-modified PEGylation polyamidoamine (PAMAM) were designed as nanocarriers (NCs). PAMAM-PEG (reaction molar ratio 1:32) exhibited a relatively high grafting efficiency and low cytotoxicity. *In-vitro* permeation study of these NCs explained that PEN modifications had significantly enhanced permeation capacity (1.5 times higher) and *in-vivo* examinations in mice eyes confirmed significant ($p<0.001$) distribution of modified NCs in cornea and retina also the retinal retention time was increased to more than 12 hrs [55]. These studies explain tremendous potential of dendrimers as ocular drug delivery vehicles.

Nanowafers

Nanowafers are tiny transparent discs placed on the surface of the eye that contains an array of drug-loaded nanoreservoirs. Ghanashyam Acharya and associates invented these novel systems in year 2015 for the purposes of enhancing the residence and contact time of the drug with corneal and conjunctival surfaces. Utilizing hydrogel template strategy with a few modifications, they fabricated axitinib-nanowafers (Axi-NW). To demonstrate efficacy of nanowafers, researchers used murine ocular burn (OB) model for treating corneal neovascularization (CNV) taking Axitinib as a model drug. Once a day Axi-NW treatment restricted the proliferation of blood vessels to the limbal area and the treated eyes very closely resembled the healthy uninjured cornea as compared to Axi-eye drops [56]. Similarly, TG Coursey *et al.* developed dexamethasone-loaded nanowafer (Dex-NW) for the treatment of dry eye disease. Using carboxymethyl cellulose as polymer, the array of nanoreservoirs were developed and these Dex-NW were then subjected for *in-vivo* testing in the dry eye disease mouse model. The results suggested Dex-NW was able to restore the corneal barrier function along with a healthy ocular surface which was comparable to twice a day dexamethasone eye drops. Surprisingly, Dex-NW was also lowered over expression of inflammatory cytokines like TNF-α, IFN-γ, IL-1β, IL-6 and chemokines like CXCL-10 and CCL-5 and MMP-3 and MMP-9 [57]. Thus, nanowafers not only enhance drug bioavailability, but also act as a protective polymer membrane to heal injured and abraded corneal surface commonly found in Choroidal neovascularization (CNV) and dry eye disease.

Promising Ophthalmic Drug Delivery Formulations

A market research analysis published online in 2016 estimated that the global pharmaceutical market of ophthalmic products valued at almost $30 billion and expected to expand upto $42 billion by 2023. Currently, ophthalmic devices and equipments majorly dominate the ophthalmic market. In India, this market is currently operating at about US$1.3 billion, which is expanding rapidly. Ophthalmic conditions such as cataract surgery and diagnostic equipments greatly contribute to revenue generation in India, while the drugs used for dry eye and glaucoma are second in terms of ophthalmic drug market drivers [58].

Novel ocular drug deliver approaches such as; nanoparticles, cubosomes, dendrimers etc. have given a great pace to the currently marketed ophthalmic formulations and in recent years, sudden increase in the clinical trials of ophthalmic products has been resulted [59]. In addition, the approval of biotechnologically derived immune modulator Bevacizumeb as Vascular Endothelial Growth Factor (VEGF) antibody has open-up new dimension for biotech industries to explore possibilities in this market. Consequently, higher numbers of drug development studies are being conducted for ophthalmic product development [60]. Table 1 describes some recently published novel formulation designs that are promising for large-scale production and market representation.

Table 1: Recently published nanotechnology-based strategies for ocular diseases applications

S. No.	Drug	Nanoparticulate system	Disease treatment	Reference
1.	Indomethacin	Polymeric nanoparticles	Autoimmune uveitis	[61]
2.	Brimonidine tartrate	Eudragit nanoparticles	Glaucoma	[62]
3.	Dorzolamide hydrochloride	Hyaluronic acid-modified chitosan nanoparticles	Glaucoma	[63]
4.	Methazolamide	SLNs nanoemulsions	Glaucoma	[62]
5.	Sialyl-Lewis X	Conjugated liposomes	Autoimmune uveitis	[64]
6.	Plasmids	Nanoparticles that exhibit Flt23k	Corneal neovascularization	[65]
7.	Myriocin	Solid-Lipid Nanoparticles (SLNs)	Age-associated macular degeneration	[66]
8.	Transforming growth factor beta 1	Annexin A5–based liposomes	Drug levels in vitreous in rabbit	[67]
9.	Bevacizumab	Annexin A5–based liposomes	Drug levels in retina of rat and rabbit	[68]
10.	Triamcinolone acetonide (RETAAC)	PLGA nanoparticle (Patent-NCT00407849)	Intravitreal Implant for Diabetic Macular Edema (DME)	[69]
11.	-	Nanoscale dispersed ointment	Dry eye disease (better efficacy in repairing tear film)	[70]
12.	Diclofenac	Hydrogel	Dry eye disease (increase retention time and bioavailability of drug)	[71]
13.	Gene	Chitosan nanoparticles	Superior transfection efficiency in anterior chamber of eye	[72]
14.	Axitinib	Nanowafer	Corneal neovascularization (enhanced therapeutic efficacy)	[73]
15.	Latanoprost acid	Nanocarrier	Sustained drug release by sub-conjunctival administration	[74]
16.	Prednisolone	PLGA-Nanoparticle-laden contact lens	sustain drug release and improve patient compliance	[75]
17.	Liposomes	Triamcinolone acetonide	Sustained drug release intravitreal administration	[76]
18.	Gene	Dendrimers	Effective gene transfection in RPE cells.	[77]
19.	Gene	RGD-Lipid conjugate modified Liposome	Four fold increase in siRNA delivery compared to non-modified liposomes	[78]
20.	Etoposide	PLGA nanoparticles	Retinoblastoma	[79]
21.	Lupeol	PLGA nanoparticles	Angiogenesis	[80]
22.	Bevacizumab	Hyaluronic acid, embedded with chitosan nanoparticles	Choroidal neovascularization	[81]

Challenges and Future Directions

Even with the growing technological advancements in the field of nanotechnology, commercialization of nanoparticles-based ocular drug delivery systems is slow. Although the space for nanoparticles-based ocular drug delivery systems is much promising as they carry potential advantages such as permeation through barriers, higher drug retention, increased bioavailability etc, over other delivery systems [29, 33, 53]. There are challenges in assessing long-term safety of these systems as insoluble NPs and metabolites of soluble NPs both have chances of inversely affecting biological systems. Another bottleneck is the reliability and purity of polymers and other novel materials used in synthesizing these drug delivery systems. Further, scale-up for the production and purification of complex conjugates will demand novel techniques that are completely out of the purview of labs that develop these technologies. In regulatory space also there is huge uncertainty regarding categorizing nanoparticles-based drug delivery systems into drugs or medical devices. In addition, the high DNA loading capacity of nanoparticles is another critical challenge for gene delivery. Despite all these challenges, it is clear from the recent research that nanoparticles hold tremendous potential as ocular drug delivery vehicles [9, 16, 29, 58, 59]. Future directions of research in this area should include a 'quality by design' approach, stringent evaluation of safety profile of these systems and exploring the use of these techniques in developing nanodevices for complex eye surgeries like; glaucoma, retinal vascular surgery and so on [82]. The emerging translational efforts would ensure utilization of these approaches in creating new opportunities of research and commercialization of products for ophthalmic diseases.

LIST OF ABBREVIATION

AMD- Age-related Macular Degeneration
Axi-NW- Axitinib-nanowafers
CNV- Choroidal neovascularization
DEX- Dexamethasone
Dex-NW-Dexamethasone-loaded nanowafer
DME- Diabetic Macular Edema
DR- Diabetic Retinopathy
IOP-Intraocular Pressure
MN- Microneedles
NCs - Nanocarriers
NPs-Nanoparticles
ODD- Ocular Drug Delivery
PAMAM- Polyamidoamine
SLN- Solid-Lipid nanoparticles
VEGF- Vascular Endothelial Growth Factor.

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REFERENCES

[1] Schoenwald, R.D.,*Ocular pharmacokinetics. In: Zimmerman TJ editor. Textbook of Ocular Pharmacology*. Philadelphia, PA, USA: Lippincott-Raven, 1997.p.119-138.

[2] Worakul, N., Robinson, J.R., *Ocular Pharmacokinetics/Pharmacodynamics*. European journal of Pharmaceutics & Biopharmaceutics, 1997.44(1):p.71–83.

[3] Kuno, N., Fujii, S., *Recent advances in ocular drug delivery systems*. Polymers, 2011.3:p.193–221.

[4] Nayak,K., Misra, M., *Recent drug delivery systems for posterior segment of eye*. Biomedicine & Pharmacology, 2018.107:p.1564-82.

[5] Thrimawithana, T.R., et al., *Drug Delivery to the Posterior Segment of the Eye*. Drug Discovery Today, 2011.16(5-6):p.270-277.

[6] Fernandez-Robredo, P., *Current treatment limitations in age-related macular degeneration and future approaches based on cell therapy and tissue engineering*. Journal of Ophthalmology, 2014. 4:p.1–41.

[7] Khan, M., et al., *Present and possible therapies for age-related macular degeneration*. ISRN Ophthalmology, 2014.p.608390.

[8] Barar, J., et al., *Advanced drug delivery and targeting technologies for the ocular diseases*. Bioimpacts, 2016.6:p.49–67.

[9] Weng, Y., et al., *Nanotechnology-based strategies for treatment of ocular disease*. Acta Pharmaceutica Sinica B, 2017.7(3):p.281-291.
[10] Kaur, I.P., Kakkar, S., *Nanotherapy for posterior eye diseases*. Journal of control release, 2014.193:p.100–112.
[11] Ali, M., Byrne, M.E., *Challenges and solutions in topical ocular drug-delivery systems*. Expert Review of Clinical Pharmacology, 2008.1(1):p.145–161.
[12] Gaudana, R., et.al., *Ocular drug delivery*. The american association of pharmaceutical science, 2010.12(3):p.348–60.
[13] Kwatra, D., Mitra, A.K., *Drug delivery in ocular diseases: barriers and strategies*. World Journal of Pharmacology, 2013. 2(4):p.78-83.
[14] Agrahari, V., et.al., *A Comprehensive insight on ocular pharmacokinetics*. Drug delivery & translational research, 2016.6(6):p.735–754.
[15] Kannan, R., Xu, Q., Kambhampati, S., *Nanotechnology approaches for ocular drug delivery*. Middle east african Journal of Ophthalmology, 2013.20(1):p.26.
[16] Weng, Y., et al., *Nanotechnology-based strategies for treatment of ocular disease*. Acta Pharmaceutica Sinica B, 2017.7(3):p.281–291.
[17] Omerović, N., Vranić, E., *Application of nanoparticles in ocular drug delivery systems*. Health Technology, 2020.10:p.61-78.
[18] Agarwal, P., et al., *Nanotechnology for ocular drug delivery. In: design of nanostructures for versatile therapeutic applications*. Philadelphia, USA: Elsevier ,2018.p.137–188.
[19] Zarbin, M.A., et al., *Nanotechnology in Ophthalmology*. Canadian journal of ophthalmology, 2010.45:p.457–76.
[20] Satalkar, P., et al., *Defining nano, nanotechnology and nanomedicine: why should it matter?*. Science Engineering Ethics, 2016.22:p.1255–1276.
[21] Zhou, H.Y., et al., *Nanoparticles in the Ocular Drug Deliver*. International journal of Opthalmology, 2013.6(3):p.390-396.
[22] Singh, K.H., Shinde, U.A., *Chitosan nanoparticles for controlled delivery of brimonidine tartrate to the ocular membrane*. Pharmazie, 2011.66 (8):p.594-599.
[23] Chen, R.,et al.,*Methazolamide calcium phosphate nanoparticles in an ocular delivery system*. Yakugaku Zasshi, 2010.130(3):p.419-424.
[24] Wadhwa, S., et al., *Hyaluronic acid modified chitosan nanoparticles for effective management of glaucoma: development, characterization, and evaluation*. Journal of Drug Targeting, 2010.18(4):p.292-302.
[25] Lutfi, G., Muzeyyen, D., *Preparation and characterization of polymeric and lipid nanoparticles of pilocarpine HCL for ocular application.* Pharmaceutical development and technology, 2013.18(3):p.701-709.
[26] Pignatello, R., et al., *Flurbiprofen-loaded acrylate polymer nanosuspensions for ophthalmic application*. Biomaterials, 2002.23(15):p.3247–55.
[27] Liu, Z., et al., *Preparation and evaluation of solid lipid nanoparticles of baicalin for ocular drug delivery system in-vitro and in-vivo*. Drug Development and Industrial Pharmacy, 2011.37(4):p.475-481.
[28] Li, Z., et al., *Celastrol nanoparticles inhibit corneal neovascularization induced by suturing in rats*. International Journal of Nanomedicine, 2012. 7(1):p.1163–73.
[29] Sahoo, SK, et al., *Nanotechnology in occular drug delivery*. Drug Discovery Today,2008.13(3):p.144-51.
[30] Kumar, R., Sinha, V.R., *Preparation and optimization of voriconazole microemulsion for ocular delivery*. Colloids and surfaces B. Biointerfaces, 2014.117(Supplement C):p.82-88.
[31] Tayel, S.A., et al., *Promising ion-sensitive in situ ocular nanoemulsion gels of terbinafine hydrochloride: design, in-vitro characterization and in-vivo estimation of the ocular irritation and drug pharmacokinetics in the aqueous humor of rabbits*. International journal of pharmaceutics, 2013. 443(1):p.293-305.
[32] Akhter, S., et al., *Improving the topical ocular pharmacokinetics of an immunosuppressant agent with mucoadhesive nanoemulsions: formulation development, in-vitro and in-vivo studies*. Colloids and Surfaces B. Biointerfaces, 2016.148:p.19-29.
[33] Fan, Y., Zhang, Q., *Development of liposomal formulations: from concept to clinical investigations*. Asia Journal of Pharmaceutical Science, 2013.8:p.81-87.
[34] Hashida, N., et al., *High-efficacy site directed drug delivery system using sialyl-lewis x conjugated liposome*. Experiment Eye Research, 2008.86(1):p.138–49.

[35] Fujisawa, T.,*Liposomal diclofenac eye drop formulations targeting the retina: formulation stability improvement using surface modification of liposomes*. International Journal of Pharmaceutics, 2012.436:p.564- 567.

[36] Hathout, R.M.,et al., *Gelatinized core liposomes: a new trojan horse for the development of a novel timolol maleate glaucoma medication*. International journal of Pharmaceutics, 2019.10(556):p.192-199.

[37] Kakkar, S., Kaur, I.P., *Spanlastics-a novel nanovesicular carrier system for ocular delivery*. International Journal of Pharmaceutics, 2011.413:p.202-210.

[38] Deol, P.,et al., *Potential of nanomaterials as movers and packers for drug molecules*. Solid State Phenomenon, 2015.222:p.159-178.

[39] Al-mahallawi, A., et al., *Enhanced non invasive trans-tympanic delivery of ciprofloxacin through encapsulation into nano-spanlastic vesicles: fabrication, in-vitro characterization, and comparative ex-vivo permeation studies*. International Journal of Pharmaceutics, 2017.522(1-2):p.157–164.

[40] Liu, Y., et al., *Cationized hyaluronic acid coated spanlastics for cyclosporine a ocular delivery: prolonged ocular retention, enhanced corneal permeation and improved tear production*. International Journal of Pharmaceutics, 2019.565:p.133-42.

[41] Garg, G., Saraf, S., *Cubosomes: An Overview.* Biological and Pharmaceutical bulletin, 2007.30 (2):p.350-53.

[42] Duttagupta, A.S.,et al., *Cubosomes: Innovative nanostructures or drug delivery*. Current Drug Delivery, 2016.13:p. 482-493.

[43] Han, S., et al., *Novel vehicle based on cubosomes for ophthalmic delivery of flurbiprofen with low irritancy and high bioavailability*. Acta Pharmacological Sinica B, 2010.31(8):p.990–998.

[44] Huang, J., et al., *Ocular cubosome drug delivery system for timolol maleate: preparation, characterization, cytotoxicity, ex-vivo, and in-vivo evaluation*. AAPS, 2017. 18(8):P.2919-26.

[45] Prausnitz, M.R.,et al., *Microneedles. In: Smith E, Maibach H eds. Percutaneous penetration enhancers*. Boca Raton, FL: CRC Press, 2005.p.239-255.

[46] Jiang, J., et al., *Coated Microneedles for Drug Delivery to the Eye*. Investigative Ophthalmolology and Visual Science, 2017.48(9):p.4038-43.

[47] Moffatt, K., et al., *Microneedles for enhanced transdermal and intraocular drug delivery*. Current Opinion in Pharmacology, 2017.36:p.14–21.

[48] Kadonosono, K., et al., *Endovascular cannulation with a microneedle for central retinal vein occlusion*. JAMA Ophthalmology, 2013.131(6):p.783-786.

[49] Kim, Y.C.,et al., *Intrastromal delivery of bevacizumab using microneedles to treat corneal neovascularizatio*n. Investigative Ophthalmology and Visual Science,2014.55:p.7376-86.

[50] Than, A., et al.,*Self-Implantable double-layered micro-drug-reservoirs for efficient and controlled. ocular drug delivery*. Nature Communications, 2018.9(4433):p.1-12.

[51] Abbasi, E.,et al., *Dendrimers: Synthesis, applications, and properties*. Nanoscale Research Letters,2014. 9:p.247.

[52] Vandamme, T.F., Brobeck, L., *Poly(Amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide*. Journal of Control Release,2005.102:p.23–38.

[53] Yang, H., et al., *Hybrid dendrimer Hydrogel/PLGA nanoparticle platform sustains drug delivery for one week and antiglaucoma effects for four days following one-time topical administration*. ACS Nano, 2012.6(9): p.7595–7606.

[54] Soiberman, U., et al., *Subconjunctival injectable dendrimer-dexamethasone gel for the treatment of corneal inflammation*. Biomaterials,2017.125:p.38–53.

[55] Yang, X.,et al., *A novel dendrimer-based complex co-modified with cyclic RGD hexapeptide and penetratin for noninvasive targeting and penetration of the ocular posterior segment*. Drug Delivery, 2019.26(1):p.989–1001.

[56] Acharya, G., et al., *Nanowafer drug delivery to treat corneal neovascularization*. Investigative Ophthalmology and Visual Science, 2015.56(7):p.5032.

[57] Coursey, T.G.,et al., *Dexamethasone nanowafer as an effective therapy for dry eye disease*. Journal of Control Release, 2015.213:p.168–174.

[58] Narayanan, V., *Pharmaceutical ophthalmic market perspectives in India and emerging trends*. Clincal and Experimental Visual and Eye Research,2018.1:p.35–37.

[59] Gote, V., et al., *Ocular drug delivery: present innovations and future challenges*. Journal of Pharmacology and Experimental Therapy, 2019.370 (3):p. 602-624.

[60] Stewart, M.W., *The expanding role of vascular endothelial growth factor inhibitors in ophthalmology*. Mayo Clinic Proceedings,2012. 87(1): p.77–88.

[61] Gomes-Bittencou, et al., *New treatment options for noninfectious uveitis*. Developments in Ophthalmology, 2012.51(1):p.134–61.

[62] Zhou, H.Y.,et al., *Nanoparticles in the ocular drug delivery*. International Journal of ophthalmology, 2013.6(3):p.390–6.

[63] Wadhwa, S., et al., *Hyaluronic acid-modified chitosan nanoparticles for effective management of glaucoma: development, characterization, and evaluation*. Journal of Drug Targeting, 2010.18(4):p.292–302.

[64] Hashida, N., et al., *High-efficacy site-directed drug delivery system using sialyl-lewis X conjugated liposome*. Expert Eye Research, 2008.86(1):p.138–49.

[65] Cho, Y.K., et al., *Flt23k Nanoparticles offer additive benefit in graft survival and anti-angiogenic effects when combined with triamcinolone*. Investigative Ophthalmolology and Visual Science, 2012.53(4):p.2328–36.

[66] Strettoi, E.,et al., *Inhibition of ceramide biosynthesis preserves photoreceptor structure and function in a mouse model of retinitis pigmentosa*. Proceedings of National Academy Science, 2010.107(43):p.18706–11.

[67] Platania, C. B. M., et al.,To*pical ocular delivery of TGF-Beta1 to the back of the eye: implications in age-related neurodegenerative diseases*. International Journal of Molecular Science,2017.18(10):p. 2076.

[68] Davis, B. M., et al., *Topical delivery of avastin to the posterior segment of the eye in-vivo using annexin A5-associated liposomes*. Small,2014. 10(8):p.1575-1584.

[69] Cardillo, J.A., et al., *Intravitreal bioerudivel sustained-release triamcinolone microspheres system (RETAAC). preliminary report of its potential usefulnes for the treatment of diabetic macular edema*. Arch. Soc. Esp. Opthalmology, 2006.81(12):p.675-681.

[70] Zhang, W., et al., *A novel nanoscale-dispersed eye ointment for the treatment of dry eye disease*. Nanotechnology, 2014.25:p.125101.

[71] Zhang, Z., et al., *Fabrication of A micellar supramolecular hydrogel for ocular drug delivery*. Biomacromolecules, 2016.17:p.798–807.

[72] Jiang, M., et al., *Cationic Core-Shell Liponanoparticles for Ocular Gene Delivery*. Biomaterials, 2012.33:p.7621–30.

[73] Yuan, X., et al., *Ocular drug delivery nanowafer with enhanced therapeutic efficacy*. ACS Nano., 2015.9:p.1749–58.

[74] Natarajan, J.V., et al., *Sustained drug release in nanomedicine: a long-acting nanocarrier-based formulation for glaucoma*. ACS Nano, 2014.8:p.419–29.

[75] Elshaer, A., et al., *Nanoparticle-laden contact lens for controlled ocular delivery of prednisolone: formulation optimization using statistical experimental design*. Pharmaceutics, 2016.8:p.14.

[76] Gonzalez-De la Rosa, A., et al., *Novel triamcinolone acetonide-loaded liposomes topical formulation for the treatment of cystoid macular edema after cataract surgery: a pilot study*. Journal of Ocular Pharmacology Therapy,2019.35(2):p.106-115.

[77] Mastorakos, P.,et al., *Hydroxyl PAMAM dendrimer-based gene vectors for transgene delivery to human retinal pigment epithelial cells*. Nanoscale, 2015.7:p.3845–56.

[78] Chen, C.W., et al., *Novel RGD-lipid conjugate-modified liposomes for enhancing sirna delivery in human retinal pigment epithelial cells*. International Journal of Nanomedicine, 2011.6:p. 2567–80.

[79] Solano, A.G.R., et al., *Etoposide-loaded poly(lactic-co-glycolic acid) intravitreal implants: in vitro and in vivo evaluation*. AAPS, 2018.19:p.1652– 1661.

[80] Soares, D.C.F., et al., *Antiangiogenic activity of PLGA-lupeol implants for potential intravitreal applications*. Biomedicne Pharmacotherapy, 2017.92:p.394–402.

[81] Badiee, P.,et al., *Ocular implant containing bevacizumab-loaded chitosan nanoparticles intended for choroidal neovascularization treatment.* Journal of Biomedical Material Research Part A, 2018.106 (8):p.2261–2271.

[82] Kannan, R., et.al., *Nanotechnology approaches for ocular drug delivery*. Middle East African Journal of Ophthalmology, 2013.20(1):p.26-37.