International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 8, Issue 2, 2016

Review Article

NANOTECHNOLOGY FOR OPHTHALMIC PREPARATIONS

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Received: 16 Feb 2016, Revised and Accepted: 14 Mar 2016

ABSTRACT

Despite numerous efforts, ocular drug delivery still remains a challenge for pharmaceutical scientists. Most of the ocular diseases are treated by topical drug applications. But this suffers from poor bioavailability and other drawbacks. Budding interest in nanopharmaceuticals has generated a number of advancements throughout recent years with a focus on engineering novel applications. Nanotechnology also offers the ability to detect diseases at much earlier stages. Recent developments in ocular drug delivery system research have provided new insights into drug development. This review summarizes recent findings and applications of various nanoparticulate systems like nanospheres, nanosuspensions, microemulsions, liposome, etc in ocular drug delivery.

Keywords: Nanosuspensions, Ocular drug delivery, Nanoparticulate

INTRODUCTION

Nanotechnology and micro technology involve creating and using the materials, devices or systems on the nanometer and micrometer scale respectively. These technologies are expected to play a critical role in number of biomedical applications like drug delivery, molecular imaging, biomarkers, and biosensors. The human eye is a complex organ that is separated from the rest of the body by number of layers of biological barriers. However, the internal ocular structures and tissues are protected from the external environment by the tight junctions of the corneal epithelium and the mucosal surface. The ophthalmic application of drugs is the primary route of administration for the treatment of various eye diseases, and is well-accepted by patients; usually, only small amount of the drug administered penetrate the cornea to reach the desired intraocular tissue due to corneal barriers and dilution caused by lacrimation [1-3]. Hence, frequent instillation of concentrated solutions is needed to obtain the desired therapeutic effect in both the anterior and posterior hemispheres of the eye. But this can cause corneal damage and undesirable side effects resulting from the systemic absorption of drugs through the nasolacrimal duct [4, 5] Therefore, the main challenge for ocular drug delivery is how to deceive these protective barriers in order to achieve therapeutically effective concentrations of drugs in the intraocular tissues. In this regard, it is important to increase the effectiveness of drugs by enhancing their bioavailability [6]. In order to increase drug bioavailability and overcome these problems, several strategies like preparation of viscous solutions, micro/nanoparticles, and hydrogels have been developed and investigated [1,4,7-10] Ophthalmic formulations containing nanoparticle drug show a better solution to the limitations surrounding ocular drug penetration [16-19], and it is known that to circumvent the side effects related to drug delivery, decreasing direct cellular stimulation and reducing the amount drug used by increasing its bioavailability are useful ways [6]. It is expected that ophthalmic drug systems using nanoparticles may provide an alternative way for increasing ocular drug penetration [16-19]. This review addresses the usefulness of nano and micro particles in ophthalmic drug delivery systems.

Design considerations for ocular drug nanomaterials

The particle size influences its functionality in terms of its uptake, residence in circulation, adherence, degradation, clearance [20-24]. The particles' fate inside the body has been reported as: ≥ 2 μm, trapped inside liver cells; ≥ 300-400 nm, captured by macrophages and excreted; ≥ 200 nm, filtered in the spleen; ≥ 100 nm, escape from blood vessels through the endothelial lining. Thus, the movement of nanoparticles inside tissues is governed by size. In the ophthalmic field, nanoparticles of size range 10 to 1000 nm allow for the improved topical passage of large, water insoluble molecules through the barriers of the ocular system [25]. Superficial barriers delay direct and systemic drug access to the specific site of action. Drug-loaded nanoparticles show prolonged residence time for eye drops, increased ability of the drug to penetrate into the deeper layers of the ocular structure and aqueous humor thus minimizing precorneal drug loss caused by rapid tear fluid turnover and decreased toxicity. [6, 26] Techniques were planned to transform nanoparticles from lipophilic to hydrophilic and to down-regulate irritation to the eye. Preparations of nanoparticles are very useful for the extended delivery of ophthalmic drugs [2, 27, 28]. Nanoparticle-containing preparations have been used to deliver ocular drugs to target sites in the treatment of many eye diseases. An ideal ocular drug delivery system should possess key properties that include:

1) controlled and sustained release profile to maintain the therapeutic concentration of the drug over a prolonged period of time to reduce the frequency of administration;

2) Specific targeting and prolonged retention in the diseased tissues to improve therapeutic efficiency and avoid side effects;

3) Patient-friendly delivery routes that eliminate or minimize side effects resulting directly from these administration methods.

Table 1: Criteria for the selection of optimal formulation parameters when developing an ophthalmic drug delivery system

Factor	Preferences
Drug	Preferentially lipophilic. Non-ionizable lipophilic compounds will concentrate into the corneal epithelium while ionizable lipophilic ones will partitionate into the aqueous humor
Vector type	Depends on encapsulated molecule. Should allow a high loading dose to reduce the instilled volume
Carrier size	Lowest as possible to facilitate corneal uptake and passage
Osmotic pressure	Isotonic with physiological fluids to avoid irritation and lacrimation
pH	Close to physiological pH to avoid irritation and lacrimation. If buffering is necessary, the lowest possible buffer concentration is used.

Microemulsions

Microemulsions are dispersions of water and oil facilitated by a combination of surfactant and co-surfactant to reduce interfacial tension. These systems are usually characterized by small droplet size (100 nm) higher thermodynamic stability, and clear appearance [70]. The parameters which can affect the stability of the system are a selection of aqueous phase, an organic phase, and surfactant/co-surfactant. Optimization of these components results in significant improvement in solubility of the drug molecule e. g. chloramphenicol, indomethacin, [71]. Apart from solubility, microemulsion systems have also shown improved permeation across the cornea. An oil-in-water system consisting of pilocarpine using lecithin, propylene glycol, PEG 200 as surfactant/co-surfactants, and isopropyl myristate as the oil phase has been designed, which is non irritating to the eye [72]. Such formulations often provide sustained drug release thereby reducing the frequency of the drug administration. In the case of pilocarpine, microemulsion based system lowers the frequency of administration to two times when compared to four times with conventional eye drops in a day. This was due to enhanced permeation by the surfactant-co-surfactant combination. Another microemulsion system consisting of pilocarpine hydrochloride [73] was shown to convert in different forms like (liquid crystalline and coarse emulsion) with a change in rheological parameters which changed depending upon the change in water content. This results in higher viscosity which will retain the formulation on the cornea resulting in its enhanced effect. Timolol in microemulsion system was laden in a 2-hydroxyethyl methacrylate (HEMA) gels which were studied to modulate its transport across the gel [74]. Higher drug loading was achieved but could not control its release. In another attempt to deliver timolol, a stable o/w and w/o emulsion was formulated which m *et al.* l the requirements of an eye drop according to Polish Pharmacopeia V. Sirolimus, a highly lipophilic drug with aqueous solubility of 2.6 µg/ml was formulated in microemulsion system which could hold 1 mg of drug in the system with excellent tolerability and stability [75]. An alcohol-free, microemulsion-based formulation consisting chloramphenicol was developed. This formulation exhibited excellent stability when compared to the commercially available formulation. Though micro emulsions have excellent advantages, limitations in the selection of surfactant/co-surfactant system and toxicity associated with higher concentrations of surfactant/co-surfactant usually restrict their use [76].

Nanosuspensions

It is defined as a sub-micron colloidal system which consists of the poorly water-soluble drug, suspended in an appropriate dispersion medium and stabilized by surfactants. They usually consist of colloidal carriers like polymeric resins that are inert in nature and help in enhancement of drug solubility and thus bioavailability. They are also popular because of their nonirritant nature. Flurbiprofen encapsulated in eudragit RS 100® and RL 100® polymer resins prevents myosis, which might be induced during extracapsular cataract surgery [77]. The charge on the surface of nanoparticles facilitates its adhesion to the cornea. Methylprednisolone acetate (MPA) was encapsulated in a copolymer of poly (ethyl acrylate, methyl methacrylate, and chlorotrimethyl-ammo-nioethyl methacrylate) and examined for its effect on the anti-inflammatory symptoms in rabbits with endotoxin-induced uveitis (EIU) [78]. Animal studies have revealed that anti-inflammatory effect of nanosuspensions was more than micro suspensions. Similar studies were carried out using piroxicam in eudragit RS 100. *In vivo* studies in rabbits have shown significant anti-inflammatory effects when compared to micro suspension [79]. In another approach, three different types of glucocorticoids; hydrocortisone, dexamethasone, and prednisolone were formulated as nanosuspensions. *In vivo* study in rabbits suggested that the nanosuspensions significantly enhanced the ocular absorption of glucocorticoids [80]. These nanosuspensions also produce sustained drug release and were more effective over a longer duration. Nanosuspensions also impart stability to the drug in the formulation. Cloricromene (AD6) was formulated in nanosuspensions by using eudragit RS100 and RL100. AD6-loaded eudragit retarded nanoparticle suspension offered a significant edge in enhancing the bioavailability and shelf life of the drug following ophthalmic application [81].

Nanoparticles

Nanoparticles are defined as particles with a diameter of less than 1µm, comprising of various biodegradable or nonbiodegradable polymers, phospholipids, lipids, or metals [21]. They can be classified as nanospheres or nanocapsules depending upon whether the drug has been uniformly dispersed or coated with the polymeric material. Recent studies have revealed the migration of intact nanoparticles to the RPE cells following intravitreal injection of nanoparticles suspension [82, 21]. This migration resulted in the rupture of the internal limiting membrane (ILM) and activation of non-specific retinal microglial cells. Such mild transient mechanism in the inflammatory process also modifies permeability and the anchoring mechanism of the ILM. These findings are crucial for the diseases affecting the posterior eye. Uptake and distribution of nanoparticles depend on the size of the nanoparticles. Kinetics of fluorescein nanospheres (2000, 200 and 50 nm) was studied following intravitreal injection in rabbits. Nanospheres smaller than 200 nm were also observed in the retinal cells other than the vitreous cavity and trabecular meshwork where only larger diameter particles were distributed. This study has shown the importance of particle size in ocular tissue distribution [83]. Many formulation parameters have to be considered in designing an ideal formulation. Surface charge interaction of the drug and polymer has played an important role in drug release from the polymer. Incomplete release of progesterone from the polybutylene cyanoacrylate nanospheres resulted to the surface charge interaction of the drug and polymer [84, 251]. A solid lipid nanoparticulate system of tobramycin was developed for topical drug delivery. Such a particulate system can be retained for a longer duration on the corneal surface and also on the conjunctival sac compared to an aqueous solution of the drug. *In vivo* testing has shown sustained drug release over a period of 6 h compared to short duration from an equal dose of eye drops [85]. Recently it was evaluated how the ocular disposition and distribution of the different size of nanoparticles (20 and 200 nm) vary due to blood and lymph circulations following periocular administration in Sprague Dawley rats [86]. They found that particles with 20 nm size were transported across the sclera to a small extent, and no significant transport was noted across the sclera-choroid-RPE. Such low permeation was attributed to periocular circulation (blood and lymphatic) which play a crucial role in clearing the 20 nm particles. A higher concentration of particles in the ocular tissues was observed in dead animals by the post-mortem studies which they concluded because of the lack of physiological barrier following periocular administration. An ideal nanoparticulate formulation should have low clearance by blood and lymphatic circulation in order for it to be effective in the treatment of posterior segment diseases following periocular administration.

Various naturally occurring polymers were studied as carriers for the nanoparticulate system. Albumin nanoparticles can effectively encapsulate both positively charged (GCV) and negatively charged (oligonucleotides (ODNs)) molecules [87]. Chitosan-coated poly (epsilon-caprolactone) nanoparticles of indomethacin resulted in enhancement of ocular bioavailability [88]. Enhanced permeation across the cornea was also observed when poly (epsilon-caprolactone) nanoparticles were coated with polyethylene glycol [89]. In another study, a formulation comprising dexamethasone acetate encapsulated in biodegradable PLGA nanoparticles was administered by the intravitreal route and the effect on CNV was studied. This study demonstrated a triphasic pattern of drug release. The drug level was found to be more than the level required to treat CMV [90]. In another study, mucoadhesive chitosan-sodium alginate nanoparticles were prepared and evaluated for topical delivery of gatifloxacin. This system resulted in burst release during the first hour and then followed by sustained release for 24 h. This approach helps in reducing the dosing frequency of the antibiotic because of the sustained action observed after single administration [91].

Nanospheres

Nanospheres are of truly uniform sizes ranging from 50 nm to 1000 nm [48]. Drugs are encapsulated in synthetic and natural polymers to permit sustained local release and tissue targeting of the drugs.

The most common substrates are polylactic acid (PLA), polyglycolic acid (PGA), and their copolymer, and poly (lactic-co-glycolic acid) (PLGA). Injected intravitreally PLA and PLGA do not show any electrophysiological or histological toxicity in the retina [49, 50]. A GCV intraocular implant is the first FDA-approved sustained-release formulation that is nondegradable *in vivo* and is being used in the treatment of cytomegalovirus retinitis in AIDS patients. When fluorescent 2000 nm, 200 nm, and 50 nm nanospheres were injected into the vitreous body of rabbits, the 2000 nm particles were found in the intravitreal cavity and the trabecula, whereas the 200 nm and 50 nm particles were found even inside the retina [51].

Nanoemulsions

The diameter of the micelles is approximately 100 nm or less. Micro/nanoemulsions have good tissue permeability because of the small size of the micelles and the presence of a surfactant among the components; as a result, studies on DDSs have been conducted mainly in the field of ophthalmic drugs [52]. The installation of dexamethasone-containing microemulsions in the eyes of rabbits has been shown to result in enhanced intraocular permeability [53]. In comparison with nanospheres and liposomes, nanoemulsions are also unsuitable for long-term sustained drug release.

Applications of nanotechnology for the eye diseases

a) Nanoparticles capable of bio-adhesion and/or rapid internalization

Topical route of administration, although most commonly employed for ophthalmic drug product use, suffers from rapid precorneal clearance, leading to little or no drug delivery to the back of the eye. This route of administration can primarily benefit from nanomedicines that rapidly adhere to and/or internalize in the surface eye tissues including corneal and conjunctival epithelia. A number of approaches have been assessed to improve ocular surface adhesion including the use of polyethylene glycol, poly(acrylic acid), and other mucoadhesive polymers to enhance corneal or conjunctival adhesion and hence retention. However, these approaches allowed limited prolongation in precorneal residence. Positively charged polymeric materials, on the other hand, may allow more prolonged retention on the eye surface. Using DPT dendrimers, it was determined that dendrimers gained rapid entry into human corneal epithelial cells and sustained gatifloxacin levels in eye tissues for at least 24 h.

Another approach to enhance the bioadhesive properties of nanoparticles is to associate them with chitosan or its derivatives. Chitosan is a polysaccharide widely assessed for pharmaceutical applications [75]. It has also been demonstrated that chitosan adheres to mucus layers *in vivo*, via electrostatic interactions between the positively charged amino groups within chitosan, and the negatively charged sialic groups of mucin in addition to intermolecular hydrogen bonds. Furthermore, chitosan may enhance the paracellular absorption of hydrophilic molecules by promoting a structural reorganization of the tight junction-associated proteins. Chitosan nanoparticles can increase ocular surface tissue drug delivery, possibly through mucoadhesion and/or enhanced paracellular delivery.

b) Nanomedicines with one or more surface modifications that enhance target recognition and/or cell entry

While plasma membranes of cellular barriers allow passive diffusion of small molecule drugs, they are more restrictive for the entry of small hydrophilic molecules as well as macromolecules, which are typically hydrophilic. For the entry of such poorly permeable molecules, specialized mechanisms of cell entry may exist. For instance, solute transporters may facilitate the entry of small molecules while proteins and large peptides may gain entry into cells via receptor-mediated endocytosis. Utilization of receptor-mediated endocytosis is an attractive approach to enhance cellular uptake of nanoparticles. It can be envisioned that a few protein or peptide ligands coated on the surface of a nanoparticle might enable receptor interaction followed by internalization of the nanoparticle. Nanoparticles modified on their surface with unique features for enhanced delivery are referred to as functionalized nanoparticles. Such an approach can permit cellular entry of a larger amount of drug encapsulated in the nanoparticle, which may otherwise not enter the cells. While selecting a receptor that is suitable for cell entry of a nanoparticle, it is critical to choose a receptor that undergoes rapid internalization. Transferrin receptor is well known to undergo internalization and recycling [48]. Further, earlier investigations indicated that respiratory epithelial cells internalize deslorelin, a peptide agonist of luteinizing hormone-releasing hormone (LHRH) receptor. To enhance nanoparticle-cell affinity and uptake in ocular tissues, the potential value of conjugating transferrin or deslorelin on nanoparticle surface (nanoparticle fictionalization) was investigated. Nanoparticles (20 nm, polystyrene) functionalized with transferrin or deslorelin showed rapid (within 5 min) entry into bovine cornea and conjunctiva, and exhibited enhanced uptake as well as trans tissue transport in these tissues when compared to the non-functionalized nanoparticles [25]. Such enhanced uptake and transport in the conjunctiva, is likely to facilitate transscleral drug delivery to the back of the eye from nanoparticles.

c) Capable of sustained release

Several diseases are afflicting the posterior segment of the eye including diabetic retinopathy and age-related macular degeneration require chronic treatment for periods of several years. The two main routes that can potentially deliver effective drug levels to the retina include intravitreal and periocular routes of delivery. Frequent injections by either route can lead to serious complications, raising safety concerns and decreased patient compliance. To obviate or reduce injection frequency, sustained drug delivery systems can be employed to deliver the drug to the retina for prolonged periods. Several nano and micro technology based drug delivery systems have been investigated for transscleral sustained delivery of drugs to the retina. These systems include particulate systems like nano and micro particles. When selecting a slow release drug delivery system, the rationale of selecting nanoparticles as opposed to microparticles is debatable. Although polymeric nanoparticles are effective in sustaining delivery compared to the drug in solution, they are generally not as effective as microparticles in sustaining delivery due to their high surface to volume ratio. For instance, polylactide nanoparticles (345 nm) loaded with budesonide exhibited a high initial burst release followed by a very slow rate of release unlike microparticles (3.6 μm), which exhibited low burst release followed by greater release rats and more continuous release *in vitro* [69]. Consistent with this, *in vivo* retinal drug levels were higher with microparticles when compared to nanoparticles on days 7 and 14 after periocular administration. In another *in vivo* study, particularly administered microparticles of triamcinolone acetonide maintained drug levels in the retina for up to 2 mo, whereas triamcinolone acetonide levels were undetectable for both nanoparticles and drug in suspension [81]. These studies demonstrate that microparticles better sustain drug levels *in vitro* and *in vivo* compared to nanoparticles or drug in solution. When embedded in a hydrogel, burst release of drug from nanoparticles and microparticles may be reduced, and the overall drug release duration may be prolonged. Although the above hydrogels have demonstrated potential in sustaining drug delivery, the intravitreal route is an invasive route with potential injection-related adverse events such as vitreal hemorrhage and retinal and choroidal detachment. Thus, topically applied hydrogel formulations that enhance back of the eye drug delivery would be ideal. Hydrogels administered by the subconjunctival route have also demonstrated sustained release and offer a safe alternative to intravitreal injections for targeting the posterior segment. For instance, insulin-loaded biodegradable, sub conjunctivally implantable hydrogels can effectively sustain drug release and treat neurodegenerative disorders such as diabetic retinopathy [92]. Other nanomedicines including liposomes [72], micelles and dendrimers have also demonstrated potential in sustaining drug release.

d) Responsive to stimuli including light, heat, ultrasound, electrical signals, pH, and oxidative stress

If triggered release of a high dose is desired in a localized manner, stimuli-responsive nanomedicines would be useful. Triggers for drug release can include light, heat, ultrasound, electrical signals, pH, and oxidative stress among others. In addition, induction of a phase

change such as a transition from a gel to a solution state or solid to a gel state can be used to trigger release due to enhanced diffusion in the transformed phase. Eye, being a receptacle for light, is particularly suited for light responsive nanomedicines [58]. Light can induce changes in liposomal membranes such as an elevation in temperature, leading to disruption of the lipid bilayer followed by drug release. Additionally, light-sensitive polymeric systems can be envisioned for the back of the eye applications. Photodynamic therapy, approved for treating subfoveal choroidal neovascularization, employs liposome encapsulated photosensitizer for localization in the neovascular lesion following intravenous administration. Following accumulation, a nonthermal laser is used to activate the photosensitizer, subsequently leading to occlusion of the neovasculature. pH sensitive liposomes can be triggered to release their content in endosomal compartments that are acidic. Iontophoresis can potentially be employed for triggered release of solutes from nanosystems, by driving suitable ions into the vicinity of the drug delivery system in the eye. Microbubbles, currently employed for diagnostic purposes in cardiovascular medicine, are responsive to ultrasound. The bubbles can be disrupted by ultrasound, resulting in triggered release of any cargo within the microbubble or in the membrane. Stimuli-responsive materials are also under investigation for their potential use in gene transfection as an alternative to viral systems, which are difficult to manufacture and may incur toxicity [79]. Magnetolipofection, a method utilizing magnetic beads and magnetic forces, was developed as an alternative to viral vectors without compromising high transfection efficiency. Magnetite and green fluorescent protein plasmid are loaded cationic liposomes was prepared which demonstrated the ability of magnetic forces to enhance the cellular expression of the green fluorescent protein (GFP) when compared to lipofectamine [100]. Although lipofectamine performed as well as magneto lipofection in inducing GFP expression, lipofectamine was more toxic than magneto lipofection as indicated by a cytotoxicity assay. An alternative to triggered release is the formation of delivery systems including controlled release systems in situ. It can be envisioned that some of the above triggers can be used to form delivery systems in situ. For instance, UV light sensitive polymers [52] can potentially be co-administered with a drug to the eye, followed by UV crosslinking to form controlled release systems in situ.

e) Diagnostics and imaging of the eye

A number of diagnostic imaging applications for the eye are anticipated based on advances in nanotechnology and nanomedicine. Light signals from the nanoparticles and changes in emission properties (e. g., fluorescence lifetime) as a function of the environment are useful measures that can be used to assess non-invasively biomarkers of disease [59]. One imaging based application is polychromatic angiography. Current diagnostic imaging for detection of retinal angiography is conducted by intravenously administering a fluorescent molecule, fluorescein, which permeates across the blood-retinal barrier in the diseased eye, but not in a normal healthy eye. This diagnostic technique cannot differentiate early from the late stage and is an “all or none” diagnostic of retinal angiography. Therefore, a method that can distinguish early from late stage retinal angiography would allow for a better assessment of disease progression, improve ability to choose appropriate treatment and dose, and allow for monitoring effects of treatment and dose. A polychromatic angiography diagnostic that will be able to distinguish early from moderate and late stages of disease was proposed and hence, offers potentially several advantages in the treatment and management of retinal angiography [54]. The idea is that small particles extravasate through the leaky vasculature or compromised blood barriers in early stage disease, but not larger particles. However, in late stage disease, large and small particles alike will leak through vasculature or permeate across blood barriers and colocalize in the tissue. If the small particles contain a different colored dye than large particles, then the color can be tracked to monitor the stage of the disease. The detection of both large and small particles indicates breakdown or dysfunction of blood barriers, whereas the detection of only small particles indicates that lesser breakdown or dysfunction exists.

Polychromatic angiography can also be applied to detect vasculature blockage; for instance, both large and small particles will travel through normal vessels, but when a blockage occurs, only the small particles or no particles will travel across the blockage. Therefore, immediately after the blockage either no fluorescence or only fluorescence from small particles will be detected after the blockage and fluorescence of large and small particles will be detected before the blockage. In addition, the polychromatic diagnostic described may also potentially serve as a therapeutic wherein drugs are loaded into the particles and are delivered to the damaged tissue. Different therapeutics can be loaded into the particles such that small particles will contain a different therapeutic than larger particles in order to specialize therapy for each stage of disease and hence, provide more appropriate and effective treatment for the stage of the disease.

f) Nanotechnology for retinal prosthesis

Ocular diseases such as diabetic retinopathy and age-related macular degeneration permanently damage photoreceptor cells, which impairs vision. There are no therapies or approaches to restoring vision in these patients, and therefore, there is a need to develop methods that are capable of restoring vision. Several implants and devices are currently being investigated for their potential to stimulate the retina to produce visual percepts. Materials on the nanoscale are being used to improve interaction with the surrounding tissue (including photoreceptor cells) and hence, improve biocompatibility. One such device, a nanophotonic device, has been designed for optimal product properties such as reduced footprint, power consumption and computational needs of the current retinal prosthesis, while reproducing high-resolution vision [29]. Nanotopography, the deviation of a surface within a spatial wavelength of around 0.2 to 20 mm, is an important parameter when designing silicon wafers. In other words, a surface with a high wavelength and low frequency is considered true surface nano topography). This surface type is used to bridge the gap between rough and flat surfaces. Indeed, the unique structure of nano topography has been shown to improve tissue integration of prosthetic devices and recovery from injury [71]. Nanotopography is expected to reduce the amount of current needed to stimulate neural tissue, which would minimize power consumption of the device and hence, reduce potential tissue damage. The nanophotonics device has inherent nano topography, which would interface with ganglion cells. In addition, having nanowires (200 nm diameter) on the surface of the devices is expected to improve tissue integration of prosthetic devices. However, the utility of this device *in vivo* as a retinal prosthetic implant needs to be assessed.

g) Nanoparticles and retinal diseases

Particles can interact with cells via different mechanisms which, in turn, results in exposure of nanoparticles to different intracellular environments.[21] The development of a drug delivery system (DDS) that can be used for the posterior segment of the eye that involves nanocarriers to overcome the issue of frequent intravitreal administration has received great consideration. In this review, a description of nanocarriers used in the field of the retina, focusing on cyclodextrin nanoparticle suspension, liposomes, nanospheres and, nanoemulsions has been provided. The use of nanoparticles for gene therapy has also been highlighted.

h) Nanoparticles and gene therapy

Scientists and clinicians have used nanoparticles that contain gene transcription factors and other modulating molecules that permit reprogramming of cells *in vivo*, [54] as well as nanomaterials to induce selective differentiation of neural progenitor cells [55] and to create neural–mechanical interfaces.

CONCLUSION

This nanotechnology is certainly an emerging technology, and it helps in overcoming all the limitations encountered by other routes of delivery. Due to its versatility in the fact that the formulation can be tailored to deliver the drug through various routes like oral, parenteral, and other mucosal routes and is approved by the regulatory agencies for use in humans. Some of the products are available in the market in the ophthalmic area. As this is still a budding technology and lot of work still needs to be done. This technology can be easily scaleable on larger scale and sterilization is

also possible, hence has a lot of potential in the pharmaceutical products.

ACKNOWLEDGMENT

The authors express their gratitude to the JSS University and JSS College of Pharmacy for providing necessary support in the due course of the work.

CONFLICT OF INTERESTS

Declare none

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