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A REVIEW ON PATENTED NANOTECHNOLOGY USED FOR OCULAR DRUG DELIVERY

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ABSTRACT

Blindness is a significant health concern worldwide that has a substantial impact on afflicted individuals and their families, and is associated with enormous socio-economical consequences. Numerous scientific efforts have been made till date to provide an efficient ocular drug delivery system, but still, it is challenging for pharmaceutical scientists. A suitable drug/gene delivery system that can sustain and deliver therapeutics to the target tissues and cells is a key requirement for ocular therapies. Most of the ocular diseases are treated by topical drug application in the form of suspensions, solutions and ointments. But because of various anatomical and pathophysiological barriers prevailing in the eye, these conventional dosage forms suffer from the problem of poor ocular bioavailability. The application of nanotechnology in medicine is experiencing rapid progress, and the recent developments in nanomedicine-based therapeutic approaches may bring essential benefits to address the leading causes of blindness associated with cataract, glaucoma, diabetic retinopathy and retinal degeneration. This review provides an insight of various limitations associated with ocular drug delivery, summarizes recent findings and patents on various nanotechnology products in ocular drug delivery.

KEYWORDS: Ocular, Drug delivery, Patents, Dendrimers, Nanoparticles, Ocular Gene Therapy.

INTRODUCTION

Drug bioavailability of ophthalmic eye drop formulations is dependent on ocular barriers that restrict the drug permeability. The eye is an extremely protective organ, and its multiple physiological barriers make topical ophthalmic drug delivery a challenging area for

formulation scientists.[1] It is reported that ≤5% of the drug in solution form is absorbed when administered topically.[2]

Nanoparticles are colloidal drug carriers of submicron range on a nanoscale (< 100nm). These systems were developed to overcome solubility problems of poorly soluble drugs, long-acting injectable depot formulations and specific drug targeting options.[3,4] Nanotechnology is undergoing massive development and was described as "The Next Industrial Revolution" by the National Nanotechnology Initiative 2000.[5] Recent advances in nanotechnology have demonstrated successful outcomes like the treatment of blinding diseases of the eye, such as proliferative retinopathy or macular degeneration that requires effective and safe delivery of drugs to posterior eye segment tissues.[6,7] The number of patent applications filed, disclosing nanotechnology used in the ocular delivery system have increased from last decade which ensures that the role of nanotechnology is emerging in ophthalmology.

Challenges in Drug Delivery in the Eye

Various factors interfere with successful drug delivery to the eye like appropriate particle size, ensuring low irritation, compatibility with ocular tissue, nasolacrimal drainage, and adequate bioavailability.[8] Although the delivery of drugs to the anterior segment of the eye is achieved mainly through topical delivery, a minimal quantity of the drug can reach inside the eye. Therefore some classes of drugs, i.e., antiglaucoma drugs, corticosteroids and certain other antibiotics are administered through systemic route. However, the doses required to give a therapeutic effect via this route can lead to considerable side effects.[9] For example, beta blockers such as "Timolol", used in the treatment of wide-angle glaucoma are having a deleterious impact on the heart [TIMPOTIC prescribing information provided by MERCK]

Importance of Nanotechnology in Ophthalmic

Nanotechnology-based drug delivery systems like liposomes, solid lipid nanoparticles and nanosuspensions have given a solution to various solubility-related problems of poorly soluble drugs, like dexamethasone, budesonide, ganciclovir etc.[10] To allow local specific delivery and minimize side effects in other organ drugs can also be targeted to mononuclear phagocyte systems.[11] Besides this, depending on their relative hydrophobicity, surface properties and particle charge, nanoparticles can be designed to overcome retinal barriers. In addition to this, encapsulation of drugs in nanospheres, liposomes, etc. can also protect the drug and therefore prolong exposure of the drug through controlled release mechanism.[10]

Nanotechnology-based drug delivery is not only efficient in crossing membrane barriers, such as the blood-retinal barrier in the eye[12,13], but this type of drug delivery systems based on nanotechnology may prove to be the best drug delivery tools for some chronic ocular diseases, which require frequent drug administration.

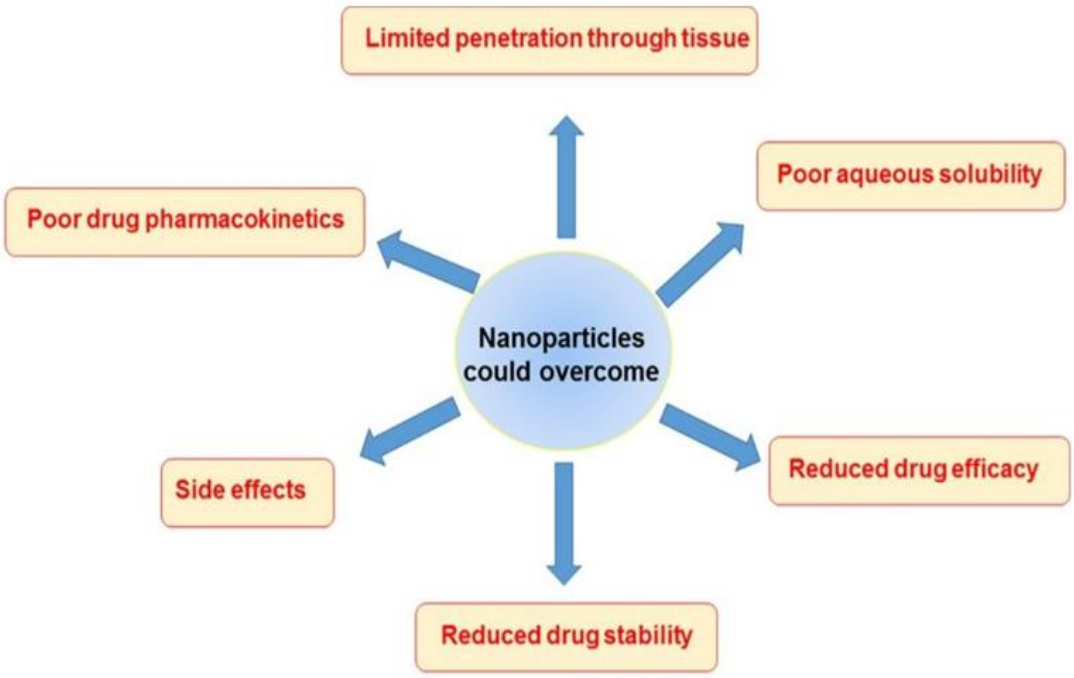

Figure 1: Unfavourable drug properties that can be enhanced through incorporation into different Nanoparticles formulations.[31]

Nanomedicine Applications for Therapies to the Anterior Segment Diseases

The incidence of topical and corneal infections have increased in recent years owing to an increased number of corneal surgeries for cataracts, glaucoma and corneal transplantations, and the increased use of contact lenses. Even though the cornea is protected from the external environment by a continuous tear fluid film that turns over rapidly, a variety of microorganisms can invade the cornea, leading keratitis or conjunctivitis. Such ocular diseases can cause major health problems if untreated, causing corneal reddening, opacification, rupture, irritation and inflammation, leading to obscure vision and even permanent blindness.[14]

Improving corneal residence time

Even though eye drops are the most traditional formulation for ocular drug delivery, they typically provide low bioavailability (less than 5%) owing to poor pre-corneal retention and penetration. The factors affecting pre-corneal retention include rapid tear turnover, blinking,

and solution drainage, which result in the loss of drug after topical administration. Therefore, frequent instillations of eye drops are required to maintain a therapeutic drug level on the pre-corneal surface. Regular use of concentrated eye drops can induce toxicity, corneal dryness and possible severe systemic side effects.[15,16]

Drug-eluting contact lenses for sustained delivery

Extended wear soft contact lenses are frequently preferred by both younger and older generations. Therefore, nanoparticle-drug formulations could be incorporated into contact lenses for sustained therapy. Contact lenses loaded with drugs have been studied by Chauhan *et al*.[17,20] Increased corneal bioavailability achieved by the drug-laden contact lenses can improve patient compliance and provide extended drug delivery. Glaucomatous dogs with inherited open-angle glaucoma were successfully treated with timolol, with NIGHT&DAY™ silicone hydrogel contact lenses. Higher bioavailability of timolol was achieved by contact lenses with only one- third of the loaded drug compared to eye drops, to attain similar intraocular pressure (IOP) reduction. The inclusion of Vitamin-E (VE) into the contact lenses prolonged the release of timolol.[19]

Dendrimer-based topical delivery systems for cornea

Dendrimers are globular, nanostructured polymers (~3-20 nm) with a well-defined shape, narrow polydispersity. Some dendrimers possess antimicrobial properties and can be used as surface coating agents and drug carriers.[21]

Corneal gene delivery

Cornea is readily accessible and somewhat separated from the general circulation and the systemic immune system, which make it a good candidate for gene therapy. The goal of corneal gene therapy is to deliver and transfer a gene to the cornea itself or the nearby ocular tissue by various vectorsystems.[22,24] The expressed transgenic proteins could have a structural function (such as collagen) or be active in modulating a pathological condition (such as cytokines and growth factors). Furthermore, RNA interference could be used to silence gene expression in the cornea. In preclinical studies, corneal gene therapy was successfully applied to prevent the cornea rejection, corneal neovascularization and herpetic stromal keratitis.[22]

Nanomedicine Applications for Treatments to the Posterior Segment

Neovascular and neurodegenerative retinal diseases are the principal cause of vision impairment in both developed and developing countries. Neuroinflammation and ocular neovascularization are the common features of many retinal diseases such as DR, wet-AMD and retinitis pigmentosa. The anatomical features significantly prevent the penetration of drugs from the front of the eye to the posterior segment of the eye (vitreous humour, retina and choroid), and the direction of drug penetration is opposite to the direction of the intraocular liquid circulation. Furthermore, the corneal epithelium, corneal endothelium, retinal endothelial cells and retinal pigmented epithelium are composed of tight junctions, which limit the diffusion of drug molecules.[25]

Nanoparticle drug delivery systems may decrease the frequency of injections, and improve efficacy, leading to reduced side effects and improved patient compliance.

Biodistribution of nanoparticles in the retina

Investigating the ocular biodistribution of nanoparticles can contribute insights into the bioavailability, cellular uptake, duration of drug action, and toxicity. Various factors such as particle size, composition, surface charge and mode of administration influence the biodistribution in the retinal structures and also their drainage from the ocular tissues. Ocular biodistribution of well-defined fluorescently-labelled polystyrene nanoparticles (50 nm, 200 nm and 2 μm) was investigated by Sakurai et al. in a pigmented rabbit model.[26]

Safety/Toxicity of Nanoparticles in the Eye

Intravitreal injection of anti-VEGF reagents is widely used to treat AMD, DR and diabetic macular edema. Intravitreal injection of nanoparticles is a feasible mode of administration, and many of the safety/toxicity studies have focused on intravitreal administration. The toxicity of nanoparticles inocular tissues can be influenced by many factors, such as the chemistry, time of assessment, size, dose, and biodistribution pattern of the particles in the eye. Even though numerous studies have concentrated on the efficacy of the formulations, current studies have begun to assess the toxicity based on the histological evaluation, immunohistochemistry, inflammation and neuronal toxicity. Recently, Goldberg *et al*. reported the effect of magnetic nanoparticle size on ocular toxicity in Sprague-Dawley rats assessed by IOP, ERG, and histopathology.[27]

Recent Patents on Nanotechnology-Based Ocular Delivery

Patents on Liposomes in Ophthalmics

WO/2012/021107 It is a PCT Application Assigned to Nanyang Technological University Based on Liposomal Formulation for Ocular Drug Delivery, published on 16 Feb 2012.

The liposome is a lipid vesicle that possesses a hydrophilic core and hydrophobic boundary wall along with the potential for specificity by a surface modification which makes liposomes effective for delivering a wide range of drugs and prevents the drug from being degraded by external physiological conditions. Delivery of ocular drugs using liposomal formulation relates to various problems associated with drug penetration, stability, efficacy, and sustainability and it becomes more challenging for the delivery of a hydrophobic drug.

Limited space availability in the lipid bilayer often restricts the loading of a lipophilic drug and is the major barrier in developing liposomes for sustained delivery of hydrophobic entities, such as latanoprost. A transparent drug-loaded liposomal formulation that can evade mononuclear phagocytic uptake may provide as a good alternative. Liposomes, which have been shown to be biocompatible nanocarriers for ocular use, due to their physical structure of a polar core and lipophilic bilayer, allows for delivery of both the lipophilic drug molecule as well as its hydrophilic active products. Liposomal encapsulation protects drug molecules from enzymatic hydrolysis in the physiological environment while in circulation, and thus increasesstability.[28]

The patent on Cyclodextrin Nanotechnology for Ophthalmic Drug Delivery

US 7,893,040 Assigned to Oculisehf, Granted on February 22, 2011

Retinal diseases can effectively be treated with drugs delivered topically to the eye as solid water-soluble particles or as eye drop suspensions. The invention provides an ophthalmic composition which is an aqueous suspension comprising a drug, cyclodextrin and water. The composition has an aqueous phase of about 0.1%(w/v) to about 90% (w/v) of the drug in solution (dissolved free drug) and as dissolved drug/cyclodextrin complex(es).

The size of the solid particles is 10 nm to about 1 mm, with the drug-cyclodextrin particles being capable of dissolving in aqueous tear fluid, the cyclodextrin comprising of at least one natural cyclodextrin selected from the group containing alpha.-cyclodextrin, beta.-cyclodextrin and gamma-cyclodextrin. The aqueous eye suspension can be in the form of eye gel, eye mist or eye drops. The following experiment has been performed and disclosed in the

patent: the Aqueous isotonic solution is made up of 0.5% [1,2,4,6,7-.sup.3H]-dexamethasone, 5.3% randomly methylated beta.-cyclodextrin DS 1.8, benzalkonium chloride (0.02%), EDTA(0.10%), hydroxypropyl methylcellulose (0.10% w/v) and sodium chloride (0.72%), all w/v %. This solution (50_l) was administered to three groups of rabbits to the left eye only as eye drops, intravenous injection and nasal spray. The rabbits were sacrificed after 2 hours, and blood samples were collected every 30 minutes after drug administration. Both the eyes were then removed and the dexamethasone concentration determined in blood, cornea, aqueous humour, lens, iris-ciliary body, vitreous humour, anterior sclera, retina, optic nerve and urine, using a liquid scintillation counter. The relative contribution of topical permeation in comparison to systemic delivery was determined by comparing the dexamethasone concentrations in the right and the left eyes after different routes of drug administration. Systemic bioavailability after topical administration to the eye (0 to 120 min) was about 60%. The drug reached anterior sclera (93%), aqueous humour (97%), cornea (98%), iris-ciliary body (86%) and lens (80%) mainly *via* permeation from the eye surface. About half of the drug found in the retina (59%) and vitreous (54%) appeared to reach these segments *via* topical permeation, but only about 17% of the drug was found in the optic nerve. Nasal delivery and intravenous injection did not show any advantages over topical drug delivery. The patent claims an ophthalmic composition which is an aqueous suspension containing drug, cyclodextrin and water, the composition having an aqueous phase of from 5% (w/v) to 50% (w/v) of the drug in solution, as dissolved free drug and as dissolved drug/cyclodextrin complex(es), and a solid phase from 50%(w/v) to 95% (w/v) of the drug as solid drug/cyclodextrin complex particles. The size of the particles in the solid phase being from about 0.1 µm to about 500 µm, the drug/cyclodextrin complex particles are capable of dissolving tear fluid.[29]

CONCLUSION

Blindness is a significant healthcare issue (after cancer) worldwide, with substantial socio-economical consequences. The crucial need to combat blindness is also assisted by the large commercial ophthalmic market, which together can be a dominant driving force for clinical translation of novel nanotechnology-based drug delivery approaches.

A current study by the Association for Research in Vision and Ophthalmology (ARVO) described the essential aspects of translating primary research to clinical translation for ocular diseases and recognized the five barriers that need to be overcome.[30] These involved:

(1) Development of an effective and safe product.
(2) Recognizing the best mode of delivery and the suitable delivery system.
(3) Estimation of the product in relevant animal models, recognizing the diversity in the human equivalence between various small and large animal models.
(4) Proper design of the clinical trials to achieve a satisfactory endpoint.
(5) Commercialization through spin-offs or finding a commercial partner.

The design of the nanomedicine products should include a ‘quality-by-design' approach, strict evaluation of safety and efficacy by a multi-disciplinary group, including regulatory agencies in the early planning stages for clinical trials. New regulatory guidelines are being developed with close cooperation between the US and Europe. The keen interest in nanotechnology also brings with it enormous public and regulatory scrutiny. Successful translation of nanomedicine efforts would require a careful risk-benefit analysis, which is often skewed towards risk when it comes to novel nano therapies. The emerging translational efforts in the whole world can bring the best of these methods to have a favorable impression on the health of the people, along with creating new commercial and research opportunities.

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