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Nanoparticles for Ocular Drug Delivery

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Abstract

Because of the considerable breakthroughs that have been made in nanotechnology over the last few decades, it has found widespread use in the treatment of eye problems. In order to successfully overcome the constraints of the technologies that are currently used to provide medications to the eye, nano-delivery devices have been developed. These systems have a lot of positive qualities, including biocompatibility, stability, effectiveness, and a lower risk of adverse reactions. For use in ophthalmic applications, nanoparticles have been acknowledged as a highly successful and, for the most part, non-toxic drug delivery method. Within the scope of this review, a complete investigation into the sophisticated application of nanoparticles in the delivery of medications to the eyes is presented. Moreover, it explains the many kinds of nanoparticles that are utilized.

Keywords: Ocular, nanoparticles, mesoporous, solid-lipid, blood-retinol-barrier.

1. Introduction

Drug delivery to the eye is difficult due to its anatomy and function. The anterior portion of the eye includes aqueous fluid, conjunctiva, cornea, and lens. This location is easily accessible; therefore, eyedrops are used for medicine administration [1]. The neural retina, optic nerve and retinal pigment epithelium have reduced bioavailability at the site of action. The drug stays in the eye for a brief time due to lacrimation, reflex blinking, and nasolacrimal duct drainage, which quickly removes drug-containing eyedrops. Formulations must overcome obstacles to reach the back that limit treatment drugs to corticosteroids and cyclooxygenase inhibitors, which are more effective [2]. Alternative drug delivery methods include systemic administration. The blood-retinal barrier hinders drug penetration, requiring high doses for therapeutic benefits and may cause systemic side effects [3,4].

Nanoparticles (NPs) can aggregate on the ocular surface, vitreous cavity, and retina, causing ocular toxicity [5]. Nanoparticle (NP)' toxicity depends on exposure pathways and NP properties [6]. The superficial eye is vulnerable to extrinsic toxins [7]. Some investigations have revealed that nanoparticles (NPs) can access the bloodstream and affect other organs [8,9].

2. Types of Nanoparticles

2.1 Polymeric Nanoparticles

Natural and manufactured polymer NPs exist. Chitosan, hyaluronic acid, and alginates are natural polymers; poly (lactic-co-glycolic acid) and poly(ethylene glycol) are synthetic. Many retinal medications do not work because of their physical and chemical qualities and the eye's unique anatomy. For instance, sirolimus is effective for age-related macular degeneration (AMD), but its unique eye environment and physiochemical profile prevent its clinical use. Thus, sirolimus-loaded PLGA NPs functionalized with chitosan were successfully produced and delivered via noninvasive ocular surface drops, avoiding subretinal or vitreous injection [11, 12].

2.2 Inorganic Nanoparticles

2.2.1 Silica Nanoparticles

Mesoporous silica NPs are employed to deliver drugs to the eyes because of their biocompatibility, extended surface area, and the possibility of manufacture [13]. Bevacizumab encapsulated in mesoporous silica NPs improved its vitreous cavity residence duration and anti-neovascular efficacy [14]. Hollow mesoporous silica NPs can encapsulate pharmaceuticals and improve their efficacy due to their high drug-loading capacity. Mesoporous silica NPs can load 7% tacrolimus [15]. These NPs were injected into the vitreous cavity for 15 days without causing retinal abnormalities, including neovascularization or detachment. Tacrolimus administration is an eye disease therapeutic method. Wu et al. inhibited pterygium subconjunctival fibroblasts with mesoporous silica NPs loaded with mitomycin. Drug delivery in ophthalmology was made possible by these NPs' minimal retinal tissue toxicity. In this investigation, long-term medication release and toxicity were unknown [16].

2.2.2 Gold Nanoparticles

Stability, biocompatibility, and modifiability make gold NPs popular in ophthalmology [17]. Previously, intravenous injection of 20 nm gold NPs in mice indicated that they may cross the blood-retinal barrier [18]. This study found no retinal damage from gold NPs. Recent investigations have revealed that gold NP-hyaluronic acid can bypass anatomical barriers to enter the retina. Choroids overcome the eye's physiological barrier and reach the retina, increasing bioavailability and providing therapeutic benefits [19].

2.2.3 Carbon Nanotubes

Carbon nanotubes (CNTs) are a new kind of medication delivery technology that uses nanocarriers. CNTs' exceptional optical characteristics, stability, and large surface area have led to their extensive

use in drug delivery, biosensing, and diagnostics [20]. The drug-loading capacity can be enhanced by taking advantage of the large specific surface area. In tumors, CNTs can infiltrate and serve as imaging agents or medication transporters. In addition to being potentially hazardous, CNTs have low biodegradation rates, poor water solubility, and dispersion [21].

2.3 Silver Nanoparticles

Silver nanoparticles (AgNPs) are frequently used as drug carriers in nanomedicine due to their unique physical and chemical properties, large surface area to volume ratio, affordability, and compatibility with living beings [22]. To make and keep AgNPs stable, scientists use a wide range of physical and chemical techniques. The most common methods for reducing substances include physiochemical reduction, reducing agents, electrochemical processes, and chemical reduction [23]. Stability, agglomeration, form, and size issues afflict the chemical processes that generate AgNPs. Silver precursors, such as organic, inorganic reducing agents, capping agents, or stabilizing agents like polyvinylpyrrolidone (PVP) are needed for the production of AgNPs [23]. Capping agents stabilize AgNP suspensions electrostatically and sterically [24]. Because of their potent antibacterial and tumor-killing characteristics, AgNPs find application in cancer and infection treatment. Coating contact lenses and delivering medicinal drugs to the eyes are two uses for silver nanoparticles (AgNPs). Multiple cell culture systems and animal models for ocular disorders have shown that AgNPs, either alone or in combination with natural plant extracts, exhibit strong antiangiogenic, antioxidant, anti-glycation end product, and anti-cataractogenic effects [25]. Using AgNPs ranging in size from 15 to 50 nm, Anbukkarasi et al. [26] studied their antioxidant and anti-cataractogenic properties where the ethanolic extract of T. divaricate leaves, which is recognized for its antioxidant and anticataractogenic properties, was used to synthesize these AgNPs. Furthermore, the study tested the efficacy of AgNPs in avoiding lens opacification in dense Wistar rats using an in vitro model of selenite-induced cataract development. The study's AgNPs showed impressive antioxidant capabilities [26].

2.4 Magnetic Nanoparticles (MNPs)

MNPs are magnetic nanoparticles made of iron, cobalt, chromium, and manganese. It is used for medication, tissue healing, transfection, and targeted [27]. Their reactive surface can be changed with biocompatible coatings or bioactive chemicals to increase sensitivity to biological targets and limit contact with healthy cells, making them durable drug delivery devices [28]. Noncontact pressures can control MNPs for customized nano-drug delivery [28]. Most MNPs are iron-oxide. Biocompatible coatings on iron-oxide magnetic particles prevent aggregation, biodegradation, and alteration. The coatings also entrap bioactive agents through covalent attachment or adsorption [29]. Polymers like antibodies, biotin and amines form the shell. These surround a magnetite or maghemite core. Magnetic

nanoparticle shells hold drugs. Magnetic resonance imaging and magnetic fields immobilize drug-loaded magnetic iron oxide nanoparticles, their main benefit. Yanai et al. [31] targeted magnetic stem cells (MSCs) to deliver them to the injured retina by implantation into retinal degenerative transgenic rats. These findings suggest that this strategy may be best for treating outer retinal diseases that require tailored cell dispersion. This technology enables a greater amount of medication to be delivered to the appropriate spot, resulting in positive biochemical changes in the injured retina [31].

2.5 Nanomicelles

Nanomicelles are a type of colloidal dispersion that self-assembles into a core-shell structure, with a particle size of 100 nm or smaller. It is straightforward to create nanomicelles of specific size and shape that are highly stable in water and may easily enter cells. Prior research has demonstrated that the use of drugs in the eye was enhanced by the use of nanomicelle formulation [32]. Bacterial keratitis is a prevalent infection in the field of ophthalmology and can lead to problems such as endophthalmitis and potential loss of vision. The standard approach for treating this particular condition involves the use of antibiotics, which often leads to the development of antibiotic resistance. Hesperidin (Hes) is a naturally occurring chemical that has potent antibacterial properties. However, its limited water solubility restricts its practical use [33] in experiments using rabbits as models for bacterial keratitis, the antibiotic Hes was encapsulated in micelles of dipotassium glycyrrhizate (DG-Hes). This encapsulation improved the drug's effectiveness in treating the infection by enhancing its usage in the eye, resulting in stronger antibacterial effects [34]. The effective manufacture of DG-Hes offers a novel blueprint for developing alternative eye medications and enhances the ability of existing pharmaceuticals to be absorbed by the body.

2.6 Liposomes

Liposomes are lipid vesicles that resemble cell membranes and are biocompatible. They have a spherical shape. For the transportation of both hydrophobic and hydrophilic medications, their exceptional stability and permeability are suitable [35,36]. The tear film is composed of mucin, an intermediate aqueous layer, and a lipid layer; it acts as a bridge between the outside world and the epithelium that lines the surface of the eye [37]. Dry eye, a common ailment, occurs when the eye's tear glands aren't functioning correctly, which disrupts the lipid layer of the tear film. Liposomes are able to restore moisture to a dry eye by acting as a lipid layer analogous to the tear film [36]. After cataract surgery, endophthalmitis is the worst probable consequence [38]. Wong et al. recently conducted a clinical experiment using prednisolone phosphate-loaded liposomes. A single subconjunctival injection was used to give the NPs to patients after cataract surgery. The results

demonstrated that the NPs successfully reduced inflammation following surgery. A bigger sample size is necessary to validate the impact of NPs since the experiment only included five instances [39].

Normal liposomes are unable to overcome physiological and anatomical obstacles in posterior segment eye disorders. Thus, polyhydroxy compound-modified liposomes have excellent motility and stability, making them a promising candidate for drug delivery to the posterior section [40]. In addition, liposomes have benefited endophthalmitis treatment by encapsulating ciprofloxacin and increasing its bioavailability [41].

2.7 Quantum Dots

Nanoscale semiconductor crystal formations known as quantum dots have extraordinary optical characteristics [42]. The quantum dot-coupled bevacizumab influence on retinal neovascularization disease was investigated in a study by Santana and colleagues [43]. Results showed that, mainly as a result of the coupling rate, the anti-vascular impact of bevacizumab in conjunction with quantum dots was slightly less than that of bevacizumab alone. As a bonus, the inflammation in the retina was totally disappearing 28 days after the medicine was given. There was no evidence of retinal impairment in the group that got quantum dots. When put in the eye's retina, quantum dots have the potential to produce long-term harm. Finding the optimal dose of the medicine and conducting a comprehensive characterization of quantum dots should be the goals of future research [43].

2.8 Nanoemulsion

A nanoemulsion (NE) is a dispersed liquid in which each droplet is 100 nanometers in size or less. Because of its transparency and extended shelf life, NE is suitable for ocular medication delivery [44]. It was found that NE plus cyclosporine effectively alleviated dry eye symptoms over time [45]. The results showed that the produced NEs could constantly release the medicine, and that the two nanoemulsions tested had a permeability to the cornea of bovines that was 2.85 and 2.9 times higher than the control group, respectively [46]. To treat glaucoma, Ismail et al. [47] looked into the possibility of using NEs as a vehicle for drug delivery of travoprost. Results showed that compared to regular Travatan® eye drops, NEs comprised travoprost were more bioavailable and effectively sustained the drug's impact of decreasing intraocular pressure [47].

2.9 Hybridized Nanoparticles

As far as nanocarrier technology is concerned, hybridized nanoparticles could be a collection of nanoparticle types. As an example, liposomes and polymer nanoparticles can self-assemble at the same time to form lipid polymer hybridized nanoparticles (LPHNPs) [48]. A polymer with medicinal encapsulation capabilities is the core component of this hybrid nanoparticle. Lipids compose the middle layer, and polyethylene glycol encases the outer layer. This structure prevents water from diffusing through lipids, which keeps the medicine stable after delivery and also keeps the treatment effective for longer. Some improvements

in the delivery of medications to the eye may emerge from this. Still, their biocompatibility and functionality need to be confirmed by more preclinical studies. Scientists are currently investigating smart conjugated polymers, inorganic-organic hybrid nanoparticles, and organic-organic hybrid nanoparticles as potential oral pharmaceutical delivery systems with sustained drug release capabilities [49]. The goal of engineering conjugated nanoparticles with intelligent features is to treat cancer. These particles can react to changes in pH, temperature, and other conditions that are due to the fact that the environments around tumors exhibit different temperature and pH values compared to surrounding healthy tissue. Furthermore, this provides a fresh understanding of how to provide medications for ocular diseases [49].

2.10 Lipid Nanoparticles

2.10.1 Solid Lipid Nanoparticles

Fatty acids, glycerol esters, waxes, and other lipids that solidify at body temperature make SLNs. The stabilizing agents, mostly surfactants, in an SLN formulation aid in the creation of nanoparticles. Since most medications have poor water solubility, the active ingredient is frequently included in the lipid phase. It is also possible to encapsulate hydrophilic drugs using a variety of preparation methods [50–52].

2.10.2 Nanostructured Lipid Carriers

The instability problems with SLNs inspired the creation of NLCs, the second generation of lipid nanoparticles. The particles' matrix is comprised of a solid lipid and a liquid lipid. In comparison to SLNs, nanostructured lipid carriers (NLCs) have a number of benefits. Their flawed structure allows them to load more drugs per unit volume, and they are more stable since they do not recrystallize solid lipids [53, 54].

2. 2. Future Perspective

The main obstacle to developing an ocular medicine delivery device is the unknown pathophysiology of back-of-the-eye disorders and chronic diseases demand long-term treatment. Despite extensive study and ongoing development, the ocular drug delivery system (DDS) has many potential applications. None directly transfer the medicine to them; all release it in neighboring tissues such as the vitreous chamber, sclera, suprachoroidal region, and ocular surface topical preparations. Due to its neurogenicity, direct retinal implantation is not an option. Underutilized and with minimal temporary drug diffusion through sclera and noncorneal routes, topical nanoformulations and periocular channels are advised for targeted delivery. These days, people choose a topical or least invasive method of administration that is also regulated, long-lasting, symptom-free, and patient-compliant. The medication should be delivered directly to the retina or choroid in a sustainable manner, with no dose waste. Due to its proximity to the retina, lack of quick drug clearance, and ability to accommodate long-term implant occupancy, intravitreous injection is the optimal ocular method. One day, scientists may find a way to make advanced materials that react to light by releasing their formula. Biocompatible, semi-rigid, vesicular, particulate DDS that is homogeneous in size and shape that may cross or remain at the vitreous chamber, retina, or choroid for an extended period of time without causing any negative

side effects are necessary for ocular therapies. Biocompatibility, rigidity/semi-rigidity, and size over 100 nm to avoid clearance and improve ocular fluidic barrier circulation are needed to avoid negative effects. Preclinical studies on nanoformulations show that improving DDS retention at the site of action increases drug/therapeutic concentration. Hydrogel systems with delayed release, nanoparticles, and liposomes with ligands can improve tear film, aqueous humor, and choriocapillaris circulation time, solving this problem that can be done through academic and industrial research. A variety of approaches with integration is needed to maximize ocular delivery, as no single device/technology will suit all needs.

3. Conclusions

The substantial anatomical and physiological barriers of the eye significantly hinder medication penetration into the inner tissues of the eye. In most cases, the therapeutically active pharmaceutical levels needed to treat eye problems such as AMD, diabetic retinopathy, and glaucoma cannot be achieved with conventional eyedrops. However, there are other ways to administer it that allow us to reach the inside tissues. The use of these technologies has its drawbacks, though, and one of those is the potential for serious adverse effects. Nanoparticles have been produced over the past few decades with the aim of enhancing the ability of drugs to penetrate the eye inner part. The physiological and biodegradable nature of these nanosystems, together with their high ocular tolerance and the possibility of mass production, are among their many advantages. The encapsulation of several drugs is a common function of many NPs. For conditions affecting the retina, this presents a chance to treat them with safe and effective medication delivery techniques**.**

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