A Review on Ocular Nanoparticles to Treat Ocular Diseases

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***Abstract*—Ocular retinal diseases such as age-related macular degeneration (AMD), diabetic macular oedema (DMO), bacterial infections and retinal vascular occlusions (RVO) affecting the eye vision.**

With the development of ocular nanotechnology, in the field of ocular drug delivery system, for the treatment of ocular diseases as compared with conventional drug administration, nanocarriers offer numerous advantages to overcome ocular barriers, promote permeability, prolong target drug residence time, reduce drug degradation, reduce dosing frequency, improve patient compliance, achieve sustained/controlled release, drug targeting and gene delivery.

Nanoparticle (size range from 10 nm to 1 µm) and microparticle (size range from 1 to 1000 µm) systems are more suitable drug delivery strategy due to its wide availability of different materials (natural or synthetic) that can be developed for specific drugs and applications. Currently, synthetic, biodegradable polymers are commonly used to formulate particles because they are biocompatible and hydrolytically degradable with byproducts that can be metabolized and elimination from the body effectively.

This review primarily provides an overview of the progress of development of ocular Nanoparticles for treating ocular diseases and the characterization of nanoparticles for the evaluation as a quality control to ensure safety and efficacy of drug loaded nanoparticles and designed product meet its intended purpose.

***Index Terms*—AMD, Ocular Nanoparticles, W.H.O, Topical Eye Drops**

I. INTRODUCTION

The eye is a highly complex, isolated and specialized organ and sensory organ of the human body because about 80% of all sensory input is acquired via the eye [1,2,3,4]. Anatomically, eyes are shielded by dynamic and static barriers [2].Tear turnover, reflex blinking, and nasolacrimal drainage prevent movement of substances into the eye surface [2, 3] . The eyelid, conjunctiva, corneal epithelium covers and protect the eye surface from foreign substance [4]. In addition, the blood- aqueous barriers (BAB) and blood-retina barriers (BRB) limit the entry of compounds from the systemic circulation into the eyes [5].

The World Health Organization reports that at least 2.2 billion people around the world have visual impairment [6,7]. Ocular diseases, such as keratitis [8], cataract [9], glaucoma [10], age-related macular degeneration (AMD) [11] and diabetic retinopathy (DR) [12], Cataract can seriously damage the patient's visual acuity and affect their life quality. The National Eye Institute estimated that the annual economic burden associated with eye conditions and vision impairment in the US is about $139 billion [13].

Drug therapy is the primary treatment for most eye diseases [14]. Delivering drugs to target eye tissues at the desired therapeutic concentration without damaging healthy tissues is a current research approach [15]. Ocular drug delivery systems (ODDS) are designed to: (1) overcome the ocular barriers to deliver drugs to target eye tissues, (2) improve drug stability and treatment efficiency, (3) prolong drug retention time and reduce dosing frequency, (4) enable multiple drug combinations, and (5) improve patient adherence and reduce drug-related adverse events [16,17].

With the development of nanotechnology, dynamic progress has been made in the field of ocular drug delivery, which provides new therapeutic interventions for ocular diseases [20]. Compared with traditional drug administration, nanocarriers offer numerous advantages, including the capacity to overcome ocular barriers, promote transcorneal permeability, prolong drug residence time, reduce

drug degradation, reduce dosing frequency, improve patient compliance, achieve sustained/controlled release, drug targeting and gene delivery [21]. Novel drug carriers, such as nanomicelles, nanoparticles (NPs), nanoemulsions (NEs), microemulsions, nanofibers, dendrimers, liposomes, niosomes, nanowafers, microneedles (MNs), have been investigated for the therapy of anterior and posterior ocular diseases [22].

Ocular diseases seriously affect the vision and life quality of patients today. More than 250 million people are affected by visual impairment globally, and the morbidity prediction is still not optimistic [28]. It is projected that by 2050, around 115 million people will be blind if treatment is not improved from 2020′s statistic of approximately 43.3 million worldwide, contributing to the high population growth in undeveloped areas and the global population ages [23]. There are multiple treatment options currently available for the ocular diseases like, surgery, laser, and medication administrations. Among them, medication administration is the most therapeutic method, but still has disadvantages, including short ocular retention time, reduced drug accumulation, loss of drug in tear drainage and insufficient bioavailability, as a result in limited ocular therapeutic benefits [24]. These drawbacks reinforce the need to bring innovative drug delivery approach to the forefront for effectively combating ocular diseases [25, 26,27].

The application of nanocarriers represents a promising means to selectively deliver and concentrate drugs in ocular lesions. Among all the nanocarriers, polymer-based nanocarriers (PNCs) and lipid-based nanocarriers (LNCs) are particularly attractive. Specifically, both PNCs and LNCs have been shown to enhance penetration, retention and solubility, reduce toxicity, prolong release, and enable targeted delivery of the drug [28, 29,30].

The anatomy of the eye makes it a very big challenge to deliver therapeutic agents. Due to the blood-retinal barrier (BRB), the eye is resistant to exposure of foreign materials, and pharmaceutical [31,32]. The BRB is maintained by tight junctions at the retinal vascular endothelium, the iris vascular epithelium, and the non-pigmented ciliary epithelium and the barrier is essential part of eye to maintain retinal homoeostasis [33]. The outer component consists of junctional complexes of retinal pigmented epithelium (RPE) and the pigment epithelial cells of the pars plana. The inner segment consists of tight junctions between the endothelial cells of the retinal capillaries. Due to the blood-retinal barrier, there is little convection of molecules since it has no cellular components and highly selectively permeable to more lipophilic molecules to the ocular surface [34].

Advances in biomaterials and nanotechnology have led to major development in research of biodegradable microparticles and nanoparticles, hydrogels and ocular implants, all of which may contain ocular pharmacologic agents thereby providing improved delivery of a variety of medications to ocular surface. Furthermore, sustained release drug therapies may improve the side effects associated with conventional dosages forms and current clinical treatments and lower the overall socio-economic impact of ocular diseases. With ever evolving strategy to targeted drug delivery, ocular drug delivery development is progressing at a rapid pace.

A. Ocular diseases

At present, more than 500 kinds of eye diseases are known, such as glaucoma, macular degeneration, diabetic retinopathy, dry eye disease (DED), etc. The prevalence of ocular diseases is steadily increasing due to changing eye usage patterns and the ageing population. These conditions profoundly impact individuals' health and quality of life, emphasizing the urgent need for effective interventions. Drug therapy undoubtedly plays a pivotal role in treating many ocular diseases.

Primarily ocular diseases are Glaucoma, Age-related macular degeneration (AMD), Diabetic retinopathy, Dry eye disease (DED) are the major concern. Eyes is vital organ which require highly controlled delivery drug product.

B. Nanoparticles (NPs)

NPs are colloidal drug carriers with ideal sizes ranging from 10nm to 100 nm. They are mainly divided into polymer and lipid NPs [35]. NPs used in ocular preparations are composed of lipids, proteins, and natural or synthetic polymers such as albumin, sodium alginate, chitosan, polylactide-coglycolide (PLGA), polylactic acid (PLA), and PCL [36]. Besides, the surface charge of NPs highly affects their effective ocular absorption. Since corneal and conjunctival tissues have negatively charged surfaces, cationic NPs have a higher retention time on the ocular surface than anionic NPs [37].

NPs have been used widely to deliver drugs to the targeted tissue in the eye, with the advantages of: (1) smaller and less irritating; (2) providing sustained drug release to avoid repeated dosing; (3) preventing non-specific uptake or premature degradation; (4) providing better absorption and improving intracellular penetration; and (5) targeted delivery to desired tissues [38.39].

As a synthetic polymer, PLGA has been widely used to prepare NPs for ocular drug release due to its biodegradability, excellent biocompatibility, and capacity to modulate drug release by altering molecular weight, terminal groups, and the lactide-to-glycoside ratio [40,41]. The US Food and Drug Administration (FDA) has approved various drug delivery products with PLGA.

These NPs were made of PLGA and had the advantages of releasing the latanoprost sustainably and prolonging the drug residence time. The 300 nm NPs showed the most durable drug effect in vivo. It lasted more than 7 days and increased its efficacy by approximately 23-fold compared to Xalatan® (a commercially available latanoprost eye drop), which offers a new strategy for prolonging the efficacy of drugs and reducing the frequency of drug administration in the treatment of glaucoma.

II. CHALLENGES AND FUTURE PERSPECTIVES

Due to the anatomical barriers and physiological conditions of the eye, effective delivery of ocular medicine is a big challenge to pharmacologists and researchers. The topical administration route is the most widely used method of drug delivery for treating anterior eye segment diseases. Conventional ophthalmic formulations such as eye drops occupied about 85%-90% of the market. The reason might be the patient compliance and ease of administration. However, the ocular drug bioavailability with topical administration of eye drop is very low, and less than 5% of the topically used drug reaches deeper eye tissues. As well, it is challenging to reach therapeutic drug concentration in the posterior eye segment after topical administration of eye drops.

The traditional drug administration having acceptable in treating ocular diseases, some limitations remain, such as poor permeability, ineffective distribution, and insufficient bioavailability. Novel drug delivery methods, such as nanomicelles, Nanoparticles, nanosuspensions, microemulsions, dendrimers, liposomes, contact lenses, aqueous gels, MNs, and other novel drug delivery methods can significantly improve the efficacy of current treatment.

The considerable advantages that are commonly present in most existing ocular nanomedicines include great stability and biodegradability, low cytotoxicity, high biocompatibility and bioavailability, high surface area and pore volume, controlled release, and their capability to penetrate across complex ocular barriers, particularly BRB and the corneal-retinal barrier, with minimal unwanted ocular/systematic adverse effects. However, common side effects commonly seen in ocular nanomedicines include blurry vision, sensitivity to light, eye irritation, eye redness, pain, corneal edema, raised intraocular pressure, infection, conjunctivitis, eye discharge, and headache.

Despite some progress in developing novel ocular drug delivery systems, several challenges still exist. These include the complexity of production technology and processes, which limit the clinical translation of nanotechnology-based ocular drug delivery systems. Additionally, there is a need to improve the stability and safety of nanocarriers to minimize potential complications. Many new drug delivery techniques are primarily tested in animal experiments or in vitro studies, lacking comprehensive in vivo evaluations in human eyes. The targeting capabilities of nanocarriers need enhancement, and their metabolic fate within the eye remains unclear. Furthermore, these technologies' high technical requirements and manufacturing costs have hindered their commercial production and widespread clinical application. Addressing these challenges is crucial to advance ocular drug delivery and promoting its successful implementation in clinical practice. The advantages of novel drug-delivery systems for ocular applications are undeniable, and these innovative nanocarriers will be increasingly used in clinical practice in the future.

III. ACKNOWLEDGMENT

Not applicable

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