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Review article

Polymeric micelles for ocular drug delivery: From structural frameworks to recent preclinical studies

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ABSTRACT

Effective intraocular drug delivery poses a major challenge due to the presence of various elimination mechanisms and physiological barriers that result in low ocular bioavailability after topical application. Over the past decades, polymeric micelles have emerged as one of the most promising drug delivery platforms for the management of ocular diseases affecting the anterior (dry eye syndrome) and posterior (age-related macular degeneration, diabetic retinopathy and glaucoma) segments of the eye. Promising preclinical efficacy results from both in-vitro and in-vivo animal studies have led to their steady progression through clinical trials. The mucoadhesive nature of these polymeric micelles results in enhanced contact with the ocular surface while their small size allows better tissue penetration. Most importantly, being highly water soluble, these polymeric micelles generate clear aqueous solutions which allows easy application in the form of eye drops without any vision interference. Enhanced stability, larger cargo capacity, non-toxicity, ease of surface modification and controlled drug release are additional advantages with polymeric micelles. Finally, simple and cost effective fabrication techniques render their industrial acceptance relatively high. This review summarizes structural frameworks, methods of preparation, physicochemical properties, patented inventions and recent advances of these micelles as effective carriers for ocular drug delivery highlighting their performance in preclinical studies.

Contents

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1. Introduction

The past decades have witnessed a significant progress in the development of nano-sized (1–200 nm) ocular drug delivery systems. Such increasing interest in nanomedicine may be attributed to the tremendous advances in nanotechnology, polymer chemistry and chemical engineering [1,2]. However, additional research is required in the area of ocular drug delivery, particularly with regards to the delivery of hydrophobic compounds, nucleic acids and proteins, in order to improve their therapeutic outcomes and thus the quality of life of the patients [3,4]. Hydrophobic NSAIDs such as indomethacin, ibuprofen, and diclofenac, indicated for inflammatory disorders, are an excellent example to demonstrate the need for improved ocular delivery. Although, in-vitro studies have suggested their pharmacological effectiveness, studies involving animal models and patients generally fail to achieve sufficient therapeutic activity [5,6]. Such failure is most likely due to insufficient retention and accumulation at the target site resulting in suboptimal therapeutic levels. Additionally, significant amounts of intravitreally administered drugs accumulate inside healthy ocular tissues and can potentially lead to serious side effects, discomfort and blurred vision [7,8].

Several nanomedicines have been formulated and evaluated for ocular drug delivery over the years. The most relevant formulations are depicted in Fig. 1. All of these have been designed keeping the following two key characteristics of nanomedicines in mind: (i) stable, efficient and reversible drug loading, as well as (ii) prolonged retention and circulation time. In the case of age-related macular degeneration (AMD), for instance, NSAIDs such as indomethacin and ibuprofen are known to be extensively utilized to reduce inflammation and cystoid macular edema [9]. However, because of their high hydrophobicity, both intravenous and intravitreal administrations are problematic and complicated. They are thus generally administered in combination with solublization enhancers, such as hydroxypropyl-β-cyclodextrin, diethylene glycol monoethyl ether (Transcutol P), n-octenylsuccinate starch, α-tocopheryl polyethylene glycol succinate, polysorbate 80 and tromethamine [10–13].

FDA approved polymeric implants for posterior segment drug delivery include Vitrasert (for CMV retinitis), Retisert (for uveitis), Iluvien (diabetic macular edema) and Ozurdex (for macular edema associated with uveitis and diabetes). Vitrasert and Retisert, based on the same delivery platform but with Retisert being slightly smaller in size, require sclerotomy at the pars plana region for implantation. On the other hand, Iluvien and Ozurdex are injected into the vitreous cavity via a 23–25 gauge needle. Since, Vitrasert, Retisert and Iluvien are non-biodegradable, the drug-depleted devices need to be surgically removed or may accumulate in the vitreous cavity as in the case of Iluvien. Taking frequent intravitreal implantation of these devices into consideration, many patients and insurance companies are taken aback by their price tags (USD $20,000 for Retisert and $2000 for Ozurdex) [15]. Additionally, intravitreal administration of these implants requires skilled professional execution while carrying the risk of side effects potentially requiring patients to undergo cataract and/or glaucoma surgery as well as treatment with pressure lowering medications [11,12]. Thus, exploring the feasibility of topical administration to deliver drugs to the posterior segment may drastically improve drug delivery in coming years, while minimizing costs and potential complications.

The physicochemical nature of nano-sized micelles also termed as "nanomicelles" consisting of a hydrophobic core and a hydrophilic shell, renders these spherical vesicles highly acceptable for passive drug delivery of hydrophobic compounds. Polymeric micelles (10–200 nm) are based on amphiphilic molecules or block copolymers which can generally self-assemble into organized core-shell/supramolecular structures in aqueous media at concentrations exceeding their critical micellar concentrations (CMC) [16]. On the other hand, low-molecular weight surfactant-based micelles exhibit higher CMC in contrast to polymeric micelles, leading to diminished stability and potential side effects. The potential of polymeric micelles to solubilize and stabilize

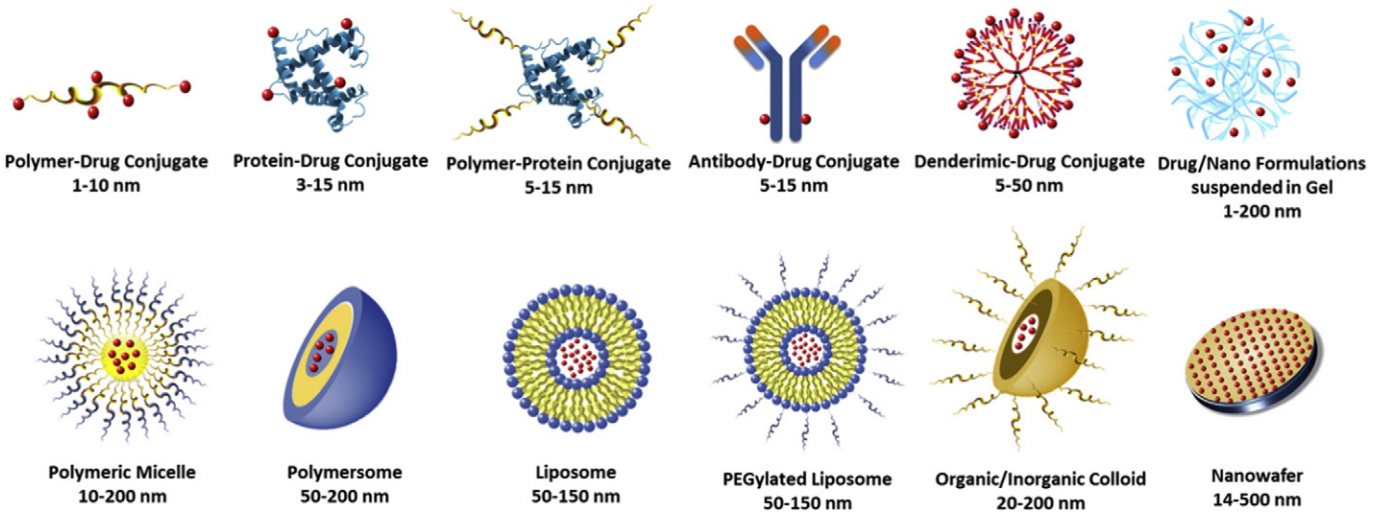

Fig. 1. Schematic depiction of the most relevant nanomedicine formulations for ocular delivery [14].
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