Application of Different Biodegradable Ocular Drug Delivery Systems

Subjects: Ophthalmology

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The complex nature of the ocular drug delivery barrier presents a significant challenge to the effective administration of drugs, resulting in poor therapeutic outcomes. To address this issue, it is essential to investigate new drugs and alternative delivery routes and vehicles. One promising approach is the use of biodegradable formulations to develop potential ocular drug delivery technologies. These include hydrogels, biodegradable microneedles, implants, and polymeric nanocarriers such as liposomes, nanoparticles, nanosuspensions, nanomicelles, and nanoemulsions.

Keywords: biodegradable drug delivery ; ocular drug delivery ; biodegradable polymers

1. Introduction

The anterior and posterior segments of the eye are vulnerable to vision-threatening ailments, including glaucoma, uveitis, and ocular surface diseases for the former, and age-related macular degeneration, diabetic retinopathy, and retinal vascular occlusion for the latter. Biodegradable drug delivery systems are being explored as a potential therapy for ocular disorders, as they provide targeted and sustained release of therapeutic agents, increasing drug effectiveness.

2. Dry Eye Disease

According to the latest revised second version of the International Dry Eye Workshop report of the Tear Film and Ocular Surface Society, released in 2017 [1], dry eye disease (DED) is defined as a multifactorial disorder of the ocular surface, characterized by destabilization of the tear film and accompanied by ocular symptoms. Tear film instability and hyperosmolarity, ocular surface inflammation and injury, and neurosensory abnormalities play a crucial role in the etiology of DED [2]. The management of DED necessitates the utilization of multiple medication forms, including lubricants such as artificial tears and sodium hyaluronate eye drops, anti-inflammatory agents such as corticosteroid and nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressants such as cyclosporine A (CsA) and tacrolimus, and other pharmaceuticals such as secretory agents and autologous serum eye drops [2][3].

Corticosteroids are widely used anti-inflammatory drugs known for their efficacy in managing eye inflammation. To enhance bioavailability and minimize systemic side effects, the development of biodegradable corticosteroid formulations for anterior segment diseases is ongoing. Several investigations have reported successful administration of corticosteroids, namely prednisolone acetate, dexamethasone sodium phosphate, fluorometholone, and triamcinolone acetonide, through distinct nanosystems [4][5][6][7][8][9][10]. Tan et al. have developed a chitosan thermosensitive hydrogel with dexamethasone-loaded NLCs which can be administered as an eye drop and transform into hydrogel upon contact with the conjunctival sac [9]. The release study indicated the sustained release of dexamethasone, but is limited to in vitro experiments and lacks in vivo results. Soiberman et al. developed a subconjunctival injectable dendrimer-dexamethasone gel that was found to be more effective than free-Dex in attenuating corneal inflammation, as evidenced by reduced macrophage infiltration and pro-inflammatory cytokine expression [8]. The gel exhibited prolonged efficacy for 2 weeks following a single injection, and improved corneal thickness and clarity without increasing IOP. However, the study's design was limited to 14 days and a single injection, raising concerns about potential clinical application. Hanafy et al. developed self-assembled prednisolone acetate-loaded NP hydrogels using chitosan and sodium alginate as counter-ions [4]. In female guinea pig eyes, the gel demonstrated superior anti-inflammatory effects compared to a micronized drug-loaded gel. However, comparing these formulations may not be ideal as they have different properties and mechanisms of action. A comparison to a conventional topical ophthalmic aqueous solution or suspension would provide a more relevant and practical comparison. Considering that, Ryu et al. put forward a novel approach involving the incorporation of dexamethasone-loaded PLGA NPs into a quickly dissolving dry tablet for ocular administration [6]. In contrast to the

established commercial dexamethasone eye drop Maxidex®, the aforementioned strategy resulted in sustained drug release for a duration of 10 h and a 2.6-fold boost in ocular drug bioavailability.

For example, indomethacin-loaded microemulsions and nanoemulsions have been proposed as an alternative delivery system to the topical application due to their ability to enhance corneal penetration and reduce ocular irritation in a rat model [11]. However, the long-term effectiveness and safety of the formulations are not evaluated, since the assessment of the efficacy was limited to a duration of 5 h in the study. Additionally, encapsulation of another NSAID, dexibuprofen, in PLGA nanoparticles has been demonstrated to enhance its release and efficacy in the treatment of ocular inflammation in a rabbit model [12].

Topical CsA is an effective treatment for DED for its anti-inflammatory properties, with several FDA-approved non-biodegradable formulations available, such as Restasis® (CsA 0.05%, Allergan Inc, Irvine, CA, USA), Ikervis® (CsA 1 mg/mL, Santen Pharmaceutical, Osaka, Japan), and Cequa® (CsA 0.09%, Sun Pharma, Cranbury, NJ, USA) [13][14][15]. In the past decade, biodegradable drug delivery systems have been studied to enhance the therapeutic effect of CsA. Luschmann et al. found that CsA-loaded NSs and micelles were able to maintain higher concentrations in the corneal tissue of rabbits compared to Restasis® [16]. Nevertheless, the study's duration was limited to 180 min, which renders the long-term safety and efficacy of the formulations uncertain. Similarly, Yan et al. demonstrated the efficacy of CsA-loaded cationic NSs in therapeutic concentrations to anterior ocular tissues via topical drop instillation [17]. An ophthalmic CsA in-situ gel based on LNCs developed by Eldesouky et al. was shown to prolong ocular retention and enhance tissue penetration [18]. The study identified a potential limitation in its inability to demonstrate a significant difference in the effectiveness of the 0.1% and 0.05% LNC formulations using the Schirmer tear test, despite both showing similar results to the marketed CsA-NE under the same conditions.

Tacrolimus is another widely used immunosuppressant for DED treatment. Biodegradable formulations of tacrolimus, such as cationic liposome [19] and thermoresponsive in situ gel formulations [20] have been developed to improve ocular retention, enhance corneal tacrolimus concentration, and decrease levels of reactive oxygen species and inflammatory factors associated with DED.

3. Conjunctivitis and Keratitis

Conjunctivitis, characterized by inflammation of the conjunctiva, is a prevalent ocular surface disease that can be caused by infectious agents or non-infectious factors, such as allergens, toxins, immune-mediated processes, and neoplastic processes [21]. Keratitis results from the inflammation of the cornea and can be classified as either infectious or non-infectious based on the etiological agent, with bacterial, protozoal (Acanthamoeba), fungal, and viral keratitis being the subcategories of the infectious form [22].

Ocular pharmacological interventions for conjunctivitis and keratitis involve targeting specific causes with antibiotics, antivirals, antifungals, and anti-inflammatory drugs. However, their limited water solubility and short residence time on the ocular surface pose a challenge. To improve therapeutic efficacy, biodegradable formulations have been studied to extend drug release. The utilization of a liposomal delivery system loaded with ciprofloxacin was investigated by Taha et al. [23] and Al-Joufi et al. [24] in a rabbit model. The studies revealed that this ciprofloxacin-loaded liposome formulation exhibited enhanced performance as compared to the available commercial product with respect to elimination rate constant, corneal permeability, and relative bioavailability. Nonetheless, the studies did not encompass the evaluation of the safety and toxicity of the formulation, which is a critical aspect in the development of a new drug delivery system, solely focusing on pharmacokinetic parameters.

Polymeric NPs are commonly utilized for delivering hydrophobic drugs in ocular infections. Ameeduzzafar et al. formulated chitosan-based NPs for delivering levofloxacin, which demonstrated biocompatibility for topical ophthalmic use and showed a longer retention time in the ocular area compared to levofloxacin solution [25]. However, the study did not compare the developed formulation with other commercially available formulations. Moreover, it only assessed the antibacterial activity against two bacterial strains (*P. aeruginosa* and *S. aureus*), and the efficacy against other strains was not evaluated.

Roy et al. developed a microneedle ocular patch (MOP) containing amphotericin B (AmB) to treat fungal keratitis [26]. The MOPs showed a significant reduction in Candida albicans load in ex vivo and in vivo infection models. However, the article has limitations as it did not compare the effectiveness of MOPs with other ocular drug delivery systems. Additionally, the long-term stability and shelf life of the MOPs were not addressed.

4. Uveitis

The uveal tract, which consists of the iris, the ciliary body, and the choroid, can be subject to inflammation. Based on the primary site of inflammation, uveitis can be further categorized into anterior, intermediate, posterior, and panuveitis [27]. The treatment of uveitis may encompass anti-inflammatory and corticosteroid agents, either as monotherapy or in conjunction with other immunosuppressants, which to some extent coincide with the management of DED and ocular infections.

In contrast to drugs targeted toward the anterior segment of the eye, those aimed at the posterior uveitis have multiple ocular barriers that must be overcome to reach the intended site of action. Therefore, the use of biodegradable carriers is attracting attention. Polymeric nanomicelles have been shown to have the potential for effective drug delivery to the targeted site. The concept of dexamethasone-encapsulated polymeric nanomicelles was introduced by Vaishya et al. [28]. The outcomes of ex vivo permeability studies demonstrated that the rigid nanomicelle core could effectively transport dexamethasone to the posterior segment when administered topically, thus offering a promising treatment approach for intermediate to posterior segment uveitis. Nevertheless, it is crucial to acknowledge that these experiments were conducted in vitro and ex vivo. After that, Xu et al. created the chitosan oligosaccharide-valylvaline-stearic acid nanomicelles incorporating dexamethasone and evaluated its efficacy in rat and rabbit models [29]. The nanomicelles showed a prolonged release pattern, a high level of adhesion to mucosal surfaces, and improved penetration capabilities. However, the study did not provide a comparative analysis of the designed nanomicelles with other existing ocular DDSs, thereby limiting the determination of the superiority of the developed nanomicelles over other formulations. Future research directions should focus on comparative analysis to further explore the potential advantages of the developed nanomicelles.

Wu et al. demonstrated an additional application of nanomicelles through intravitreal injection of rapamycin-loaded polymeric micelles [30]. In rats, these micelles have been shown to retain rapamycin in retinal pigment epithelial cells for at least 14 days, leading to improved therapeutic outcomes for the treatment of autoimmune uveitis compared to the administration of rapamycin suspension alone.

5. Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a major contributor to blindness in developed countries, and its complications such as choroidal neovascularization (CNV) and geographic atrophy can be serious and potentially devastating [31]. Intravitreal injection is the preferred method of administering anti-vascular endothelial growth factor (VEGF) drugs or corticosteroids for AMD; however, therapeutic small molecules have poor permeability. The utilization of biodegradable DDSs enhances the permeation of therapeutic agents across biomembranes, thereby improving the treatment of ocular CNV.

Liposomes have been studied as a potential drug delivery system for ocular neovascularization. Blazaki et al. developed a novel Liposome Aggregate Platform (LAP) system encapsulated with calcein, FITC-dextran-4000 (FD4), and flurbiprofen. The LAP system increased the retention of flurbiprofen in the posterior segment after intravitreal injection [32]. However, the potential inflammatory response and side effects of the LAP system, which are crucial for its future applications, were not assessed in the study. Tavakoli et al. demonstrated the inhibitory effect of intravitreal administration of sunitinib-loaded liposomes on established neovascularization in a mouse model of laser-induced CNV [33]. A potential drawback of this experiment is its restricted investigation on a mouse model of laser-induced CNV, which may not accurately represent the pathophysiology of CNV in human patients. As a result, future research should focus on examining the effectiveness of liposomal sunitinib in comparison to existing anti-VEGF treatments and its relevance in a clinical setting.

Current research aims to enhance the penetration and prolong the drug action for ocular CNV treatment by combining polymeric NPs with other vehicles. Badiee et al. encapsulated bevacizumab in a chitosan NP, which was incorporated into a hyaluronic acid-based ocular implant [34]. While in vivo experimentation was not conducted, the in vitro studies indicated a prolonged drug release lasting for a duration of two months. Wu et al. presented an example of a ovalbumin-encapsulated PLGA NP-loaded bilayer dissolving microneedle as a method of protein delivery [35]. This approach has the potential to deliver a sustained release of the encapsulated protein for a duration of over 2 months ex vivo and effectively circumvent the scleral barrier. The co-administration of dexamethasone with anti-VEGF agents such as aflibercept and bevacizumab as polymeric NPs has been demonstrated to exhibit a prolonged release profile, a potent anti-angiogenic effect [36][37]. The studies discussed provide a potential avenue for a promising therapeutic approach in treating CNV through the combination of different biodegradable formulations and co-administration of two drugs in a single injection.

6. Glaucoma

Glaucoma is a major contributor to blindness worldwide and it affects approximately 1% of the global population, with a global age-standardized prevalence of 3.5% among individuals aged 40 years or older [38][39]. The elevated IOP experienced by patients with glaucoma disrupts the dynamic balance of aqueous circulation and results in optic nerve atrophy and visual field defects. The use of topical administration to treat glaucoma is problematic due to several factors, such as poor patient compliance, potential long-term damage to the corneal surface, and low drug bioavailability [40]. Sustained drug delivery could provide a potential solution to these challenges. Antiglaucoma medications, including latanoprost, dorzolamide, brinzolamide, timolol maleate, brimonidine, and pilocarpine, have been explored as formulations in different biodegradable DDSs in various studies, including polymeric nanoparticles [41], liposomes [9][42][43], microneedles [44], and in situ hydrogel systems [45][46][47][48][49][50], demonstrating promising results in terms of bioavailability and sustained release.

In March 2020, a remarkable advancement was achieved in the field of glaucoma therapy with the approval of a biodegradable sustained-release IOP lowering implant by the FDA. The implant, known commercially as Durysta® and produced by Allergan plc (Dublin, Ireland), consists of a rod-shaped polymer matrix with 10 µg of bimatoprost, which is gradually released into the eye over a period of several months. The implant aims to address the challenge of non-adherence among glaucoma patients by providing a convenient, long-lasting, and consistent treatment option [51]. The safety and efficacy of the implant were demonstrated by two Phase III clinical trials (ARTEMIS 1 and 2) [52][53]. Results indicated that the majority of patients experienced substantial biodegradation of the implant within 12 months. Furthermore, the implant was effective in lowering IOP, with approximately 80% of patients not requiring additional medication for up to one year after their third implant. Notably, the bimatoprost implant's clinical use has raised concerns about corneal side effects, with a higher incidence of corneal endothelial cell loss and iritis observed in the implant groups compared to the timolol group. Therefore, the speed of implant degradation and the potential accumulation of debris in the iridocorneal angle warrant further investigation as future targets to improve the safety and efficacy of this innovative DDS.

ENV515 travoprost Extended Release (XR) is a rod-shaped, biodegradable intracameral implant under investigation, designed to provide a steady supply of travoprost for 6 to 12 months. Several studies have confirmed its efficacy. A Phase IIa study compared Travoprost XR implant to topical Travatan Z in 21 glaucoma patients, with the implant group showing a 6.7 mmHg decrease in diurnal IOP by day 25. Another 12-month study was conducted on open-angle glaucoma patients previously treated with prostaglandins. The study compared the IOP reduction in the eyes treated with the implant to that of the fellow eye treated with topical timolol once daily. The results showed a mean IOP reduction of 6.3 mmHg, or 25%, in the study eyes, and was deemed non-inferior to timolol [54][55].

The OTX-TIC intracameral implant is another biodegradable implant that is being researched. It is a biodegradable device from Ocular Therapeutix, featuring a soft hydrogel platform embedded with travoprost-loaded microparticles and a meshwork structure to hold the microparticles. A Phase 1 study assessed the safety, efficacy, durability, and tolerability of the OTX-TIC implant. The study was prospectively designed, multi-center, and open label, with a dose escalation approach. The first 9 subjects in two cohorts showed a reduction in mean IOP from baseline that lasted throughout the 18-month study with no serious adverse events reported [56].

Latanoprost FA SR is a biodegradable rod-shaped intracameral implant under development by PolyActiva in Parkville VIC, Australia. It is designed to deliver latanoprost for the treatment of primary open angle glaucoma and is currently in Phase II studies. The primary and secondary efficacy endpoints aim to achieve a 20% reduction in IOP in the low dose cohort. The next advancement in DDSs for the treatment of glaucoma would be the integration of fixed-dose combination drugs in a sustained delivery device. Additionally, a novel sustained delivery system that is coupled with an IOP-monitoring device would also be desirable.

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