Non-Invasive Ocular Posterior Segment Delivery System Based on Nanomedicine: A Systematic Review

[Abstract] Most visual impairment or degenerative originates in the posterior segment of the eye, however, it remains a major challenge to localize on-demand delivery of drugs due to its unique and complex anatomy, metabolic cycles, and limited options of administration route. In this regard, nanomedicine with innate bio-barrier permeability offers a promising approach of improving delivery performance and releasing drugs under the physiological environment of the eye. Based on these advantages, nanomedicine receives tremendous attention in the field of posterior ocular disease treatment via a non-invasive approach, which is expected to significantly improve medical efficiency and experience in the near future. Here, we discuss recent research advances in ocular posterior segment delivery systems based on nanomedicine, including preclinical formulations and indications, along with opportunities and challenges faced in their clinical translation. We also conclude with a perspective on how we envisage the importance of understanding complex barrier functions so as to continue to develop innovative ocular drug delivery systems.

[Keywords] non-invasive treatment strategy; posterior segment; nanomedicine

Introduction

Posterior segment of the eye is the main site of lesion that causes vision disorder and blindness, however, it is difficult for the drug to penetrate into the site of action due to the physiological and anatomic characters of the eye, such as ocular surface retention, metabolic cycles, dynamic and static bio-barriers [1][2]. Meanwhile, external factors including patient compliance and acceptability, limited options of administration route, and the limited capacity of administration also make the design of delivery system more difficult. At present, clinically commonly used therapeutic drugs for posterior segment diseases including diabetic retinopathy (DR) and age-related macular degeneration (AMD), the most two common and severe retinal diseases, are mainly delivered by intravenous, periocular or intraocular injection [3]. Such invasive drug delivery systems inevitably increase the risk of infection, cause side effects such as systemic toxicity, and even further lead to complications including retinal detachment [4]. Therefore, the development of a non-invasive posterior ocular drug delivery system is of great clinical application value. Nanomedicines are expected to become a new way of constructing a new non-invasive ocular drug delivery system because of their high biocompatibility and bio-barrier permeability, and thus have received tremendous attention in the field of posterior ocular disease treatment [4].

Herein, we summarize we discuss the existing treatment for posterior segment diseases, and highlight the latest study on nanomedicine-based non-invasive posterior ocular delivery systems. They are classified into (i) nanostructured lipid carriers (NLC), (ii) liposome, (iii) nanocrystal, (vi) microemulsions (ME), (v) nanosphere, (vi) dendrimer, (vii) nanomicelle, (viii) nanogel and (ix) other drug delivery systems. We also discuss their opportunities and challenges in clinical translation.

Types of available treatment for posterior segment diseases

1. Systemic route

Intravenous drugs are mainly used to reach the posterior oculus to prevent the formation of choroidal neovascularization (CNV) and delay the progression of disease [4]. However, such drug delivery systems usually bring about the problems including toxicity and low bioavailability caused by high-dose systemic delivery, due to the high clearance rate of systemic circulation and the presence of blood-retinal barrier (BRB). Among such therapeutic strategies, photodynamic therapy (PDT) is most commonly used. That is, after intravenous injection of photosensitizer, verteporfin, the target area of CNV and its cascade are irradiated with laser, thereby preventing CNV proliferation [4]. Although it has a certain therapeutic effect, it has a limited impact on the patient's overall vision, and CNV recurrence and vision loss have been reported [5].

Administration route	Representative drug	Application
Intravitreous implantation	Vitrasert (Bausch&Lomb)	Antisepsis
	Retisert (Bausch&Lomb)	
Intrascleral implantation	I-vation (SurModics)	Branch retinal vein occlusion
	Ozurdex (Allergan)	Central retinal vein occlusion
Vitreous injection	Lucentis (Novartis)	DR
	Bevacizumab (Novartis)	
Intravenous injection	Verteporfin (Novartis)	Choroidal angiogenesis

Table 1. Clinically used posterior ocular drugs

2. Periocular route

Intravitreous injection (IVT), subfascial or subconjunctival injection or implantation of anti-vascular endothelial growth factor (VEGF) drugs are mainly used to prevent fiber proliferation and referred retinal detachment by inducing retinal arteriole vasoconstriction and inhibiting pathological angiogenesis [6]. Although anti-VEGF therapy improves the quality of life of patients with ocular diseases involving neovascularization, anti-VEGF drugs have been reported to cross the blood-retinal barrier into the systemic circulation and inhibit serum VEGF to further cause systemic side effects [7]. In addition,although IVT can directly inject drugs into flat part of ciliary body, increase the drug concentration of retina and minimize systemic side effects,injection can cause complications such as retinal detachment

and retinal bleeding.Implants can prolong the action time of drugs, but there are still problems such as surgical implantation and limited drug loading capacity [8].

Challenge of non-invasive ocular drug delivery

Traditional non-invasive ocular drug delivery systems, such as eye drops, ointments and eye films, often result in the difficulty of reaching posterior segment due to physiological barrier and metabolism of the eye. Therefore, these formulations are usually used to treat anterior ocular diseases and cannot be used for drug delivery to the posterior segment. Consequently, the leading challenge in developing a posterior ocular drug delivery system is to increase bioavailability. Main factors that determine the drug bioavailability are corneal permeability, and ocular surface retention time of the drug [9].

1. Physiological ocular barriers

Physiological barriers of the eye include static ones and dynamic ones. Understanding the importance of complex barrier functions has an important guiding role in developing innovative ocular drug delivery systems [10]. Static barriers include tear film, cornea and conjunctiva barriers (Table 2); dynamic barriers include BAB and blood-retina-barrier BRB (Table 3). Cornea and BRB are the main obstacles to posterior ocular drug delivery. Cornea has a hydrophobic epithelial layer, and it is difficult for water-soluble molecules to enter the eye through corneal epithelium; corneal epithelial cells are closely arranged, and relatively large fat-soluble drugs will also be blocked from further penetration [11]. Due to the presence of BRB, the further penetration of drugs into the retina and other parts is restricted although the eye has a rich local vascular network [12].

	Physiological structure	Physicochemical property	Influence
Tear film	Three-layer structure: Outer lipid layer, middle aqueous layer and inner mucin layer	Buffered aqueous liquid at pH 7.4, containing electrolytes, lysozyme, albumin and glycoprotein, etc.	Drugs may bind proteins or be hydrolyzed by enzymes
Cornea	No vascular tissue. Five-layer structure: epithelial cells, Bowman layer, substrate layer, Descemet membrane and endothelial cells	1.Corneal epithelium is lipophilic; 2.Epithelial cells are closely arranged to limit the aperture size	1.It is the static barrier with the largest penetration of drugs; 2.Limit the penetration of hydrophilic drugs and macromolecular hydrophobic drugs
Conjunctiva	Thin vascularized tissue. Outer epithelial cells are closely arranged, and inner endothelial cells cover the anterior sclera	1.Conjunctival scleral stroma and the blood and lymphatic vessels form a barrier to hydrophobic drugs; 2.Conjunctiva has esterase activity; 3.The cell membrane expresses efflux protein (P-glycoprotein);	1.Prevent intercellular drugs from penetrating the cell layer; 2.The drug may be cleared in the conjunctival lymph or blood circulation;

Table 2. Static ocular barriers

Dynamic barriers	Location	Influence
BAB	(i) Endothelium of iris and ciliary blood vessels; (ii) Non-pigmented cilia and iris epithelium	Prevent macromolecules from entering iris stroma from vascular cavity of the iris; Protect the posterior chamber from circulating macromolecules
BRB	(i) External: Endothelium of retinal capillaries; (ii) Internal: Retinal pigment epithelium (RPE)	Limit drugs from the blood into retina

Table 3. Dynamic ocular barriers

2. Dose control

Unique physiological features of the eye, including tear renewal and canalis nasolacrimalis drainage, pose a challenge to dose control. That is, after administrating the drug, it intends to flow into the canalis nasolacrimalis with tear from ocular surface; tear renewal will also lead to drug dilution, resulting in a decrease in drug concentration [13].

3. Ocular metabolic system

Although fat-soluble drugs are relatively easy to be released into anterior chamber through corneal epithelial cells, drugs may be quickly cleared by aqueous fluid circulation, resulting in the clearance rate of fat-soluble drugs in anterior chamber is higher than that of hydrophilic drugs [3]. Subconjunctival injection can help the drug penetrate into the sclera, but the drug diffuses to the choroid and RPE, it will enter blood clearance in large amounts when it enters the retina through local vascular network [11]. Vitreous injection can penetrate directly into the retina, but positively charged macromolecules are more difficult to penetrate due to the barrier effect of RPE. There are two ways to clear drugs injected in a vitreous manner: the drug enters aqueous fluid from anterior segment to be cleared by circulating the aqueous fluid into the blood, the drug enters the blood from posterior segment to be cleared through BRB [13]. There is also enzyme-mediated drug metabolism in the ocular tissue, that is, there are a large number of esterases and cytochrome P-450 reductases in the conjunctiva, ciliary body and RPE; metabolic enzymes of RPE can degrade and detoxify the drug molecules, limiting the transfer to the retina [14].

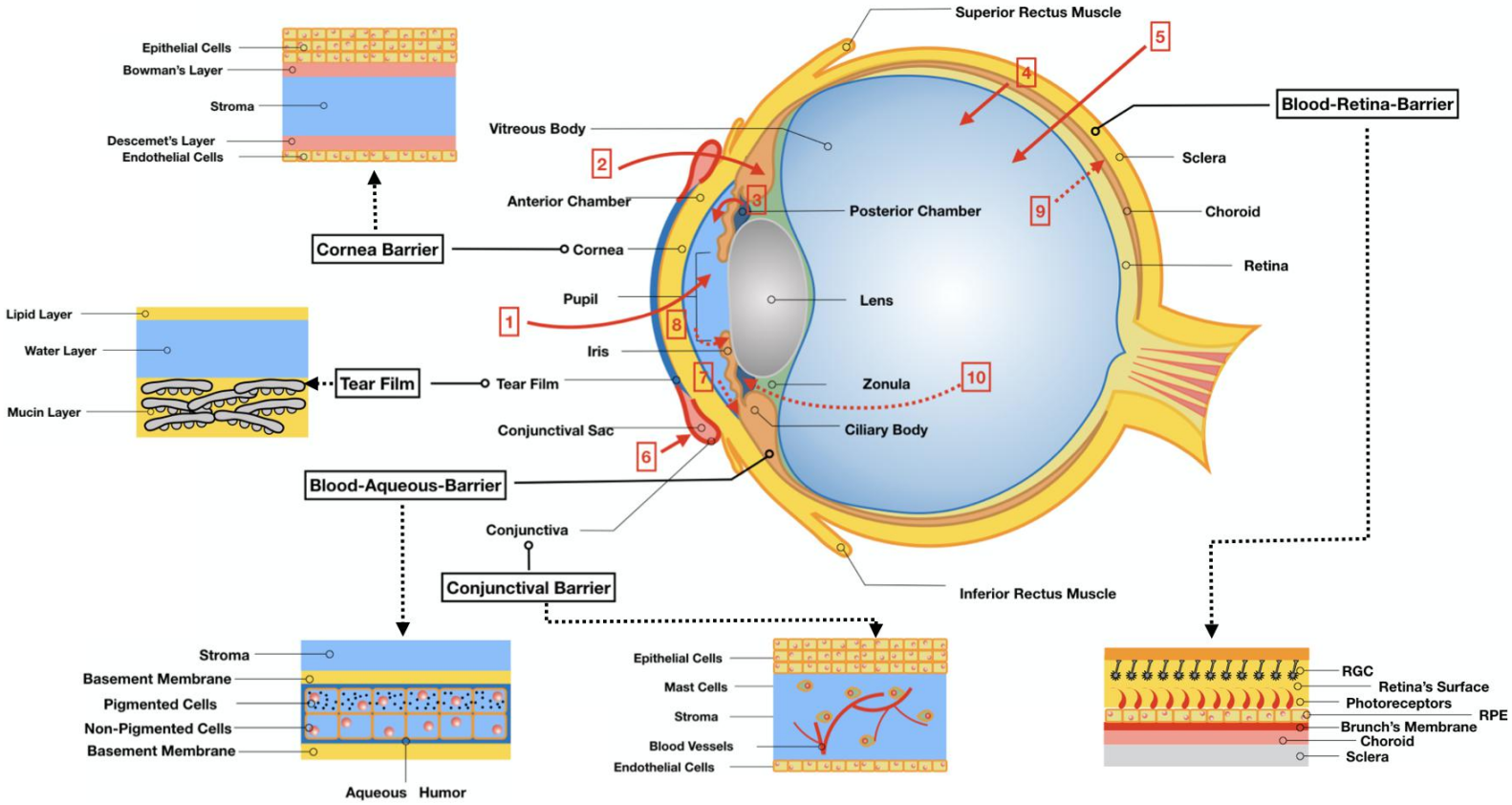

Fig.1.Ocular structure, physiological barrier and drug penetration and clearance

(1). Corneal absorption pathway: Permeated into the anterior chamber through tears and cornea, and reach the posterior part through aqueous circulation or absorption by local vascular network; (2) Non-corneal absorption pathway: Permeated into the anterior chamber through conjunctiva or sclera, and reach the posterior part through local vascular network; (3) Permeated into the anterior part from blood through BAB; (4) Permeated into the posterior part from blood through BRB; (5) Subconjunctival injection; (6). Intravitreous injection; (7) Cleared from the anterior chamber through aqueous circulation; (8) Cleared by BAB entering systemic circulation from aqueous fluid; (9) Cleared by BRB entering systemic circulation; (10) Cleared after the drug in vitreous body entering into the posterior chamber.

4. Goals for the construction of a non-invasive posterior ocular drug delivery system

For ocular diseases that require repeated administration, the penetration rate and targeting ability must be maximized to minimize potential complications and improve the therapeutic effect. The following goals on the non-invasive posterior ocular drug delivery system are put forward: 1. less irritation and injury to ocular issue with better biocompatibility to avoid complications; 2. stronger permeability to bio-barrier of the eye and longer retention time, with higher bioavailability; 3. sustained and control-release mode that can reduce the frequency of administration; 4. better targeting ability to avoid toxic and side effects at non-acting sites.

Nanomedicines for non-invasive ocular drug delivery

Posterior ocular delivery system should overcome the ocular barrier and have high targeting to ensure the drug bioavailability at the site of action. Nanomedicines help to precisely control particle size, ionization, solubility, net surface charge, etc., so as to improve their ocular bioavailability [15]. Meanwhile, nanoparticles have a innate passive targeting effect, which is mainly related to the phagocytosis of specific cells, and the main target is RPE cells [16]. The latest study shows that active targeting can be achieved by modifying proteins on the surface of nanoparticles [17]. Main advantages of the nano ocular delivery system are: 1. mucosal adhesion of the nanomedicines helps to achieve sustained and controlled release; 2. smaller size of nanoparticles helps to reach the site of action through physiological barrier; 3. reduced frequency of drug administration help increase treatment compliance; 4. encapsulated drugs in nanocarrier help reduce the degradation of drugs in enzymatic action of peptidases and nucleases; 5. smaller size of nanocarriers reduces irritation and has a greater biocompatibility in ocular tissue; 6. innate passively targeting ability to retinal pigment epithelium (RPE) cells. Although the potential of nanocarriers for a periocular drug delivery purpose has been proven, they have some drawbacks. Advantages and disadvantages of commonly used nano delivery systems are shown in Table 4.

Nanotechnology-based system	Advantage	Disadvantage	Drug	Application
Liposome	Less common immunogenicity; good biodegradability	Chemically unstable; limited drug loading; high concentration of surfactants causes local toxic and side effects	Timolol maleate [18] Acetazolamide[19] Ganciclovir [20]	Glaucoma Glaucoma Cytomegalovirus and Herpes Virus
Nanostructured lipid carrier	Has good biocompatibility; as well as certain resistance to enzymolysis	Not easy to store	Pilocarpine [21] Tetrandrine [22] Triamcinolone acetonide [23]	Glaucoma Glaucoma Neovascularization
Nanocrystal	No surfactant needed to improve corneal safety	Crystals with specific forms can cause irritation to ocular tissue	Brinzolamide [24]	Glaucoma
Microemulsions	Has good penetration and absorption	High concentration of surfactants may cause corneal toxicity	Ofloxacin [25] Loxacin [18] Timolol [18]	Bacterial infections Bacterial infections Glaucoma
Nanosphere	Has a certain sustained release effect	Increased particle size leads to blurred vision and increased discomfort; easy to cause sudden release; difficult to biodegrade	Piroxicam [26]	Uveitis
Dendrimer	Better retention in the anterior corneal area	May cause blurred vision in the cornea area	Bevacizumab [27]	Glaucoma
Nanogel	Extend anterior corneal action time	Degradation	Pilocarpine [21]	Glaucoma

Table 4. Summary of nanotechnology-based delivery systems encapsulating drugs for posterior segment administration

1. Nanostructured Lipid Carriers (NLC)

NLC are considered to be the most effective ocular drug delivery system that can enhance the corneal absorption of drugs and achieve sustained and controlled release of drugs [14].The lipid component of NLC is derived from the lipid component of the biosome, so it has high biocompatibility and tear film biomimetic type and can interact with the outer lipid layer of tear film and increase the retention of the carrier in conjunctival sac as a drug depot [3]. Using NLC as an ocular drug delivery carrier can increase the drug half-life period by increasing permeability and slowing down metabolism, so as to improve the pharmacokinetic features of the drug in the eye [8]. Based on the above features, NLC has great potential in the development of a non-invasive posterior ocular drug delivery system. Main focus for NLC development for posterior ocular drug delivery system are: 1. Increase the corneal penetration of drugs; 2. Increase the viscosity and targeting of the carrier on the cornea; 3. Construct the targeted drug delivery system with monoclonal antibodies.

Ali.J et al. [18] designed and characterized dual-drug NLC carrying timolol maleate and brinzolamide for the treatment of glaucoma.Two drugs with different properties were encapsulated in NLC, dual-drug NLC was prepared by melt emulsification technology and feature properties such as particle size and encapsulation rate were evaluated, as well as in vitro drug release and permeation. The results showed that by optimizing the dose and excipient concentration,two drugs with different features could be successfully encapsulated in NLC, and the release pattern and penetration of two drugs from NLC were significantly enhanced in combination with the drugs in corresponding suspension. Tian et al. [28] studied the transport mechanism of NLC through corneal epithelium,fluorescent labeling molecule RhodamineB (RhB) was used to label NLC and confocal detection of intracellular fluorescence was used to evaluate the release of in vitro colloidal delivery system [28], the retention time in anterior corneal area was observed to be extended [29].The results showed that these NLCs could enhance the prolonged time of action in anterior cornea and increase corneal penetration. Esfahani.G et al. [30] studied the therapeutic effect of propranolole hydrochloride NLC on hemangioma of lagophthalmiclocal vascular network. Higuchi model showed that propranolol hydrochloride NLC significantly improved the penetration of hydrophilic drug propranolol hydrochloride into the cornea, and could further reach the local ocular vascular network to treat ocular hemangioma.

2. Liposome

Advantages of liposome as a nano-delivery carrier for ocular drugs are less immunogenicity and good biodegradability,which can achieve controlled release of drugs under the action of ocular esterases [8].Due to the amphipathic nature, liposome is used clinically as carriers for hydrophilic anti-VEGF drugs and hydrophobic corticosteroid drugs, and belongs to the common dosage form for the treatment of ocular diseases. Its small size and variable surface charge help to reach the therapeutic target site in the retina through RPE [31]. In addition, liposome can form a viscous continuous layer on ocular surface and partially protect the drug

from tear drainage and extend the retention time in the eye surface [32][33] so as to increase the bioavailability of the locally applied drug.

Feng Cao et al. [17] hybridized the liposomes containing dexamethasone disodium phosphate (DEXP) with glycylsarcosine (GS) anchored lactic dehydrogenase (LDH) to construct a new nanocomposite material (DEXP-HSPC-LDH-GS) that could more effectively deliver the drugs to posterior oculus. As a classic substrate of PepT-1, GS could be used to target PepT-1 on the ocular surface after modification of LDH;positive carrier LDH could promote anterior corneal retention through electrostatic adsorption.The study showed that DEXP-HSPC-LDH-GSnanocomposite oculus drops could be used toenhance the bioavailability of posterior ocular drug by local instillation.Irene Teresa Molina-Martínezet al. [34] preparedacetazolamide-loaded nanoliposomes and combined them with hydroxypropyl methyl cellulose (HPMC) and permeable protection media, trehalose and erythritol. The results showed that the bioavailability ofhybrid liposome-HPMC system in the posterior segment increased compared with the drug solution, and the lagophthalmos showed higher tolerance. Qu.Y et al. [35] prepared and characterized triamcinolone acetonide–chitosan coated liposome (TA-CHL) in order to increase the efficiency of triamcinolone acetonideto the posterior segment to treat macular edema. The liposome had sustained release features and good stability without obvious toxicity to cornea, conjunctiva and retina.Optical coherence tomography system was used to detect the pharmacokinetics of CHL in vivo,indicating that CHL had good drug delivery capabilities.

3. Nanocrystal

Drug nanocrystals refer to pure drug crystals or hybrid drug crystals with particle size between 1-1000nm. Compared with liposomes, nanocrystals are less involved in stability issues [15];compared with other nanocarriers, nanocrystals are pure drug particles that can be considered as having 100% drug loading [36].The reduction in the size of drug particles leads to an increase in surface area, which helps to increase the contact area of the drug with the bio-film, as well as mucoadhesive properties of the nanocrystals; a larger surface area also increases the saturated solubility of the drug and eliminates the need for high-concentration surfactants, so as to avoid the corneal toxicity due to high concentration surfactants. Based on the above features, nanocrystals have great potential in the development of posterior ocular drug delivery systems. There are currently nonanocrystal preparations on the market for ocular delivery,which may be due to patent restrictions on crystal preparation [15]. Kim et al. [37] developed a nanocrystal suspension of cyclosporin A to study the irritation of lagophthalmos and compared it with the commercially available product Restasis® (an ocular emulsion). The results showed that the tear rate of commercial product group decreased, while there was no change in tear flow rate in control group after the nanocrystal suspension was treated. Popov et al. [38] developed loteprednol etabonate (LEMPP) nanocrystals formucus penetration for ocular drug delivery. Compared with the commercially available product Lotemax®, sustained drug delivery and improved drug bioavailability were observed.

Ananosuspension was formed or the viscosity of nanosuspension was increased by preparing an in-situ gel, the time of action of nanocrystals could be further extended.

4. Microemulsions (ME)

ME is a colloidal nano-dispersion system stabilized by surfactants and auxiliary surfactants. MEs are easy to be produced and sterilized with thermodynamic stability, and have been a promising system for ocular drug delivery. There have been reports on MEs of several drugs such as of loxacin [25] and timolol [39] used for posterior ocular drug delivery, all showing sustained release and improved bioavailability. However, due to the high concentration of surfactant added in preparation process of MEs, corneal epithelial cell toxicity may be caused, which limits the further use of MEs as ocular drug carriers [16]. Sai H.S. Boddu et al. [40] studied the development and evaluation of ocular MEs of dexamethasone and tobramycin for the treatment of ocular infections. Appropriate excipients were used to bring the pH of MEs close to the physiological range, compared with control group, no toxicity was observed in cytotoxicity studies in bovine corneal endothelial cells. Anti-inflammatory studies of microglia have shown that the activity of MEs is significantly higher than that of commercially available Tobradex suspension at a concentration of 0.1%. Antibacterial studies have shown that MEs have significantly higher efficacy than commercially available suspensions. Stability studies indicate that the preparation is stable at 4°C and 25°C for 3 months. The study concludes that MEs may become a suitable substitute for Tobradex suspension. Baspinar et al. [41] prepared an ocular ME containing everolimus at 1 mg/mL. In in-vitro corneal penetration test, the concentration of everolimus in the corneal receiving cell reached 8.64 ng/mL in 30min, which was significantly higher than penetration amount in free drug group, indicating that the ME carrier could significantly increase the corneal permeability of everolimus.

5. Nanosphere

Nanosphere is a microparticle dispersion system formed by drug dispersion or adsorption in a macromolecule or polymer stroma [42]. Carrier materials mainly include natural macromolecules such as starch, albumin, gelatin and chitosan and synthetic polymers such as polylactic acid (PLA). Distribution of nanospheres in the eye is mainly affected by the particle size. Nanospheres smaller than 200 nm can be distributed to the retina,and nanoparticles with larger sizes are only distributed in tissues such as vitreous body; ultra-small particle size is not conducive to drugs reaching posterior segment, only a small amount of nanospheres smaller than 20 nm penetrate the sclera, and a very small amount reaches the choroid and retina [10]. The main reason may be clearance effects of ultra-small particle size nanoparticles by periocular circulation [42]. Since the main active enzyme system in the eye is esterase, the bio-degradation of macromolecule capsule wall materials of nanosphere in the eye limits its further development in ocular delivery [10]. García ML et al. [42] prepared pegylated-PLGA nanospheres containing Dexibuprofen to improve the biopharmaceutical features of anti-inflammatory drugs for ocular drug delivery. Dexibuprofen was the active enantiomer of ibuprofen,and lower doses could be applied to achieve the same level of treatment. The surface of nanospheres was negatively charged,the average particle size was

less than 200 nm, and had high encapsulation efficiency; X-ray, FTIR and DSC analyses confirmed that drugs were dispersed in the stroma of nanospheres. Although the in vitro release curve lasted up to 12 hours, the in vitro corneal and scleral penetration curves indicated higher drug retention and penetration in corneal tissue rather than in the sclera. Cell activity studies confirmed that pegylated-PLGA nanospheres had lower cytotoxicity than free dextrobuprofen at most tested concentrations. However, in vitro (via HET-CAM test) and in vivo (via Draize test) tolerance measurements showed that nanospheres had a certain corneal irritation. The anti-inflammatory effects of nanospheres in albino rabbits were evaluated before and after inflammation induction, and it was confirmed that the nanospheres could effectively treat and prevent ocular inflammation.

6. Dendrimer

Dendrimers are the most promising class 1 polymers in ocular drug delivery [43]. These uniquely structured polymer nanoparticles can be used as a multi-functional platform that enables complete ocular delivery [44]. The unique structure provides dendrimers with drug delivery properties that many linear polymers do not have.The clear core-shell structure and narrow polydispersity make the bio-distribution more predictable, and the modification of end groups is easier to control [45]. Moreover, drugs and other treatments can be loaded onto nanoparticles in a variety of ways, such as direct conjugation or ionic interactions [46]. Such versatility makes dendrimers a highly adaptable delivery platform. Dendrimer is still in its infancy,and the first synthetic molecule was born in the mid-1980s. Nonetheless, there are few studies on dendrimers used for ocular drug delivery ways until now, and the reason may be the biodegradation of polymers in the eye [47]. Dexamethasone (DEX) has been shown to effectively reduce inflammation after eye injury, but it is quickly cleared in the anterior chamber [48]. Yavuz et al. [49] and Soiberman et al. [50] have usedhydroxy-terminated dendrimers to achieve sustained delivery of DEX after subconjunctival drug delivery. In the former, DEX delivery is directed to the posterior oculus; in the latter, DEX is used for cornealpenetration for the treatment of corneal inflammation.Both studies have shown that DEX delivery using dendrimers is more efficient and longer acting than simple eye drops. These two studies highlight the potential of dendrimers as a promising strategy for the treatment of anterior and posterior diseases.

7. Nanomicelle

Recent studies have shown that nanomicelles may be one of the most effective nanocarriers for improving the bioavailability of hydrophobic drugs.Its amphiphilic block copolymer can form nano-aggregates with a core-shell structure, which can dissolve drugs with poor water solubility [51]. A new polymer nanomicelle, polyvinylcaprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PVCL-PVA-PEG), is an effective carrier to improve the bioavailability of cornea drugs, and also shows excellent ocular tolerance, such a nanomicelle is also very stable in storage as an ocular solution. It may also be a promising strategy for ocular drugs with high water solubility, stability and bioavailability [52]. Curcumin has been shown to inhibit the proliferation of lens epithelial cells and protect

retinal cells [50]. Xianggen Wu et al. [51] by encapsulating with PVCL-PVA-PEG nanomicelles, solubility, chemical stability and antioxidant activity of curcumin were greatly improved. Furthermore, nanomicelle curcumin ocular solution was easy to prepare and was stable to storage conditions. Also, it had good cell tolerance as well as excellent ocular tolerance in rabbits. Compared with the free curcumin solution, the use of nanomicelles significantly improved in vitro cell uptake and in vivo corneal penetration and anti-inflammatory efficacy.

8. Nanogel

Nanogel is an aqueous dispersion of nano-scale polymer particles. Its sol morphology can respond to changes in pH, temperature and ion concentration. It can form gel morphology of polymer network by physical or chemical crosslinking [53]. As an ideal drug delivery carrier, nanogels have excellent drug-carrying capacity, high stability, biological consistency, and response to various environmental stimuli. Nowadays, targeting and response, especially the multi-response of nanoscale gel system for drug delivery, has become a study focus [54]. Nanogel application studies mainly focus on anti-tumor agents and proteins. It was first used to improve the sustained release performance of injectable drugs. Injectable nanogel has good fluidity in vitro and can contain drugs in its sol state. After injection into the body, it fully fills the tissue defects and undergoes a sol-gel transition in situ to achieve targeted drug delivery, embolization, and function as a tissue scaffold [54]. Based on the property that nanogel can achieve sol-gel transition with various environmental stimuli, it has been reported that nanogel is used to develop insulin sustained release system to reduce injection frequency [55], coat enamel to inhibit dental caries induced by streptococcus mutans and construct bone morphogenetic protein 2 for bone delivery [56]. It is transforming growth factor (TGF)-β/ion corresponding gel of transforming TGF-β to promote bone regeneration, and treat bone injury such as fractures [57]. Because the nanogel combines the features of aquogel and nanoparticles and has the potential to achieve controlled delivery of specific bioactive agent sites and/or time, the use of nanogel to develop ocular drug delivery systems has attracted great attention in the past decade. Physically cross linked nanogel contains hydrophobic drugs and biomacromolecules and becomes a good sustained release platform, but their mechanical stability is poor; the nanogel formed by chemical crosslinking has better mechanical strength but also has biodegradation problems, which is difficult to be degraded by active enzymes in the eye [58]. Sheardown H et al. [59] synthesized 140 nm self-assembled nanogel by adding side chains of ceric ammonium nitrate N-tert-butylacrylamide (PNtBAm) to methyl cellulose (MC). The synthetic molecule (MC-g-PNtBAm) self-assembled in water, driven by the hydrophobic interaction of grafted side chains, to produce a colloidal solution. The sol-gel transition was completed by pH, and the charge ratio of initiator and monomer was used to synthesize materials to control the degree of hydrophobic modification. Cell activity studies confirmed the biocompatibility of MC-g-PNtBAm nanogel. The efficiency of encapsulating the model drug dexamethasone with the gel was higher than 95 %, and its release exhibited the smallest burst period; meanwhile, the diffusion of the drug

from the nanogel could be delayed by increasing the degree of crosslinking. This study showed that the release curve of embedded compound from MC-g-PNtBAm nanogel could be adjusted by simply adjusting the degree of hydrophobic modification. MC-g-PNtBAm nanogel provided a new idea for constructing ocular drug delivery systems.

Opportunities and challenges in clinical transformation

Although there have been many advances in the construction of ocular delivery systems in recent years, many achievements have not yet been successfully converted into marketed drugs. The reason is the lack of reliable animal models in the drug evaluation. Most studies entering clinical trials have shown sufficient efficacy and safety in animal models. However, it is impossible for any animal model showing diseases and conditions to replicate human physiological responses, especially for ocular diseases [58]. Although there have been studies to establish rodent models that are cost-effective and easy to operate, rodents have smaller eyes and correspondingly larger corneal surfaces than human eyes [60][61]; rabbits are often used to evaluate ophthalmic therapeutics, because they are more comparable in size to human eyes than rodents. However, compared with humans, rabbits blink less and produce more mucus and less tear [61][62]. These differences in anatomy and physiology affect the evaluation of pharmacokinetics and bring difficulties in predicting clinical effects to positive preclinical results [61]. In order to successfully carry out clinical translation, it is necessary to reliably enlarge production to minimize differences between batches. Moreover, the purity and sterilization grade of ocular drugs pose great challenges to the preparation process; the storage stability of nanomedicines as well as differences between batches may also lead to a slower clinical conversion rate [63].

Conclusions

Drug delivery to the posterior segment has obvious clinical value for the treatment of many serious ocular diseases,and its importance will only increase with population growth and aging.Non-invasive delivery systems have obvious advantages over the existing periocular injections and systemic drug delivery in terms of invasiveness and safety, which has become a popular direction of ocular drug studies. Nanomedicines, as a strategy for constructing new drug delivery systems, are revolutionizing the pharmaceutical industry.At present, a lot of achievements have been obtained in the study on tumor targeting and drug sustained and controlled release,which is expected to be a new idea for drug delivery to the posterior segment and realization of sustained and controlled drug release. There have been reports on lipid nanocarriers, nanocrystals and nanomicelles used for ocular delivery, innovations of the study focus on the optimizing the biodegradability and bio-tolerance of carriers for active enzyme systems and metabolic pathways in the eye, to achieve the control of drug release and improve the stability of the drug to ocular enzyme system.In view of the complex anatomical structure and physiological features of the eye, as well as unique tear renewal and drug delivery volume restrictions and other difficulties, it is absolutely challenging to achieve the

bio-barrier penetration, biocompatibility, sustained and controlled release, biodegradation, safety and efficiency and controlled dosage of drugs in the meanwhile for non-invasive treatment; moreover, considering that there is no mature animal model for in vivo testing of ocular drugs and ocular drugs have high sterilization and purity standards, in clinical conversion, it also puts forward requirements for the preparation process and safety evaluation of the preparation. Although such a system has not yet come out,it is a promising and creative study direction for the future.With the recent progress in the field of biological nanomaterials, the study on these non-invasive ocular delivery systems based on nanotechnology will significantly affect treatment strategies of posterior ocular diseases and bring hope to the majority of patients.

Availability of data and materials

Not applicable

Abbreviations

DR: Diabetic retinopathy
AMD: Age-related macular degeneration
NLC: Nanostructured lipid carriers
ME: Microemulsions
CNV: Choroidal neovascularization
BRB: Blood-retinal barrier
PDT: Photodynamic therapy
IVT: Intravitreous injection
VEGF: Vascular endothelial growth factor
RPE: Retinal pigment epithelium
RhB: RhodamineB
GS: Glycylsarcosine
DEXP: Dexamethasone disodium phosphate
TA-CHL: acetonide–chitosan coated liposome
LEMPP: Loteprednol etabonate
LDH: Lactic dehydrogenase
HPMC: Hydroxypropyl methyl cellulose
PLA: Polylactic acid
DEX: Dexamethasone
MC: Methylcellulose
PVCL-PVA-PEG: Polyethylene glycol graft copolymer
PNtBAm: N-tert-butylacrylamide

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