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Review

Nano-based drug delivery systems for the treatment of non-infectious uveitis

Xingdi Wu [a,b,1], Mengyuan Hu [a,b,1], Yilu Cai [c], Fan Jia [d,e], Yang Ye [a,b], Naiji Yu [a,b], Min Chen [a,b,**], Kaijun Wang [a,b,*]

[a] Department of Ophthalmology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China
[b] Zhejiang Provincial Key Lab of Ophthalmology, Hangzhou, China
[c] Zhejiang University School of Medicine, Hangzhou, China
[d] MOE Key Laboratory of Macromolecule Synthesis and Functionalization of Ministry of Education, Department of Polymer Science and Engineering, Zhejiang University, Hangzhou, China
[e] Key Laboratory of Cardiovascular Intervention and Regenerative Medicine of Zhejiang Province, Department of Cardiology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China

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ABSTRACT

Background: Uveitis is one of the most prevalent causes of global visual impairment. The current approaches to treating non-infectious uveitis (NIU) involve the utilization of corticosteroids, immunosuppressant and biologics agents. Nevertheless, the intricate ocular anatomy barriers and adverse side effects of the drugs pose significant obstacles to effective treatment outcomes.

Main text: To improve drug bioavailability and therapeutic outcomes for NIU while minimize side effects, researchers are committed to developing novel nano-based drug delivery systems (DDS), which have the capacity to achieve targeted delivery, increase bioavailability, achieve sustained release, reduce side effects and improve therapeutic effects. Thus, DDS based on nanotechnology, including liposome, dendrimer, hydrogels, nanoparticles, nanomicelles, nanosuspensions and nanoemulsions have emerged as promising alternatives to conventional ocular delivery methods for the management of NIU.

Conclusions: In this review, we summarize the current therapeutic challenges faced by NIU and describe various nano-based intraocular DDS involved in the treatment of NIU. It is concluded that nano-based DDS is an appealing approach to addressing the unmet needs for the treatment of NIU.

1. Introduction

Uveitis, marked by intraocular inflammation affecting the iris, ciliary body, and choroid, manifests with symptoms such as pain, redness, photophobia, and shed tears.[1] The estimated incidence of uveitis ranges from 17 to 52 cases per 100000 population. It is believed to account for 5%–20% of total blindness in the developed world and 25% in the developing world. The increased social morbidity of uveitis is most common in working-age adults (aged 20–59 years).[2,3] Uveitis can be categorized based on the anatomical site of inflammation as anterior, intermediate, or posterior, and can also manifest as panuveitis, involving inflammation across all 3 components of the uvea.[4] Additionally, uveitis is also classified by its etiology, such as infectious causes, non-infectious origins, and masquerade syndromes.[5] This review specifically focuses on non-infectious uveitis (NIU). Idiopathic cases, accounting for 35%–57% of uveitis cases, cannot be classified within specific ocular syndromes because of the absence of associated systemic diseases.[6] The etiology of NIU remains incompletely understood, which requires further exploration of its inflammatory mechanisms to alleviate ocular inflammation and improve treatment effectiveness. Despite the recognized ocular and systemic side effects, glucocorticoids and/or immunosuppressive agents remain the cornerstone of treatment in clinical practice.[7] The significant impact on visual function and quality of life, both from loss of vision and long-term effects of corticosteroids and immunosuppressive therapies, underscore the urgent need for safe and effective treatment strategies for NIU.[8]

Medication treatments, encompassing both topical and systemic approaches, play a crucial role in managing NIU. Systemic therapy is often

* Corresponding author. Department of Ophthalmology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China.
** Corresponding author. Department of Ophthalmology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China.
E-mail addresses: chenmineye@zju.edu.cn (M. Chen), ze_wkj@zju.edu.cn (K. Wang).
[1] These authors contributed equally to this work.

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reserved for severe cases because of its inherent side effects and limited drug accumulation at the disease site within the eye. In contrast, topical administration, particularly eye drops, is favored for most ocular conditions due to its convenience and non-invasive nature.[9] However, traditional eye drops face significant challenges, including the anatomical barriers of the eye, in which lead to short duration of drug contact on the ocular surface and limited penetration through ocular barriers. Consequently, it leads to decreased bioavailability, necessitating frequent dosing and subsequently reducing patient compliance, thereby diminishing the overall treatment efficacy compared to more invasive methods.[10,11]

Over the past few decades, researchers have made significant strides in developing safe, patient-centered formulations, delivery methods, and devices. Among these advances, nano-based DDS have emerged as a promising strategy to surmount these limitations. These systems facilitate drug penetration through ocular barriers, enhancing drug bioavailability in target tissues and thereby optimizing therapeutic outcomes. Nano-based DDS also help mitigate the potential for toxicity and adverse reactions.[12] The nanoscale characteristics of these eye drops enable reduced drug dosages and administration frequencies, significantly improving patient compliance in treating ocular diseases.[9]

In this review, we present a brief overview of the current therapeutic options for NIU and investigate the current therapeutic challenges. Besides, we summarize novel DDS based on nanotechnology such as liposome, dendrimer, hydrogels, nanoparticles, nanomicelles, nanosuspensions and nanoemulsions, and discuss the perspectives of novel DDS in advancing the future of NIU treatment.

2. Clinical treatment of NIU

The objective of treating NIU is to achieve complete remission and reduce inflammation, thus mitigating ocular complications, preventing progressive damage, and averting long-term irreversible vision impairment.[13] In the therapeutic management of NIU, treatment strategies primarily encompass local therapies, such as topical corticosteroids and regional injections or implants, and systemic therapies, including oral corticosteroids, immunosuppressive drugs, and biologics. Normally, a combination of these methods is employed to optimize patient outcomes.[14] The selection of therapy depends on the specific clinical presentation of NIU. For patients with acute uveitis, short-term treatment will be more aggressive, requiring the use of a high dose of corticosteroids, whereas chronic or recurrent forms necessitate a regimen designed for sustained inflammation control with minimal adverse effects, often involving lower drug dosages.[15]

Corticosteroids (topical, periocular or systemic) are frequently the first line of treatment because of their quick effectiveness. The choice of corticosteroid administration route is based on the specific location and activity of the uveitis. For optimal efficacy, topical corticosteroids are commonly prescribed for anterior uveitis, whereas more severe cases of intermediate or posterior uveitis may necessitate periocular corticosteroid injections.[16] When a desired response is not achieved, or disease control cannot be maintained with acceptable doses of corticosteroids, second-line immunomodulatory agents become necessary.[17] Classical immunomodulatory agents, including T cell inhibitors, alkylating agents, or antimetabolites, are often employed to manage cases with undesirable side effects and treatment resistance. In recurrent cases, a combination of corticosteroid and immunosuppressive therapy, such as methotrexate, may be considered.[18] Biologics, used as steroid-sparing agents, can be particularly useful for patients with poor tolerance to systemic steroids or in severe disease cases that threaten visual function. Adalimumab demonstrated effectiveness in treating NIU and non-anterior uveitis, and other biologics have also shown great potential in refractory cases.[19,20]

The conventional methods for administering ocular drugs include topical, systemic, intraocular, and periocular delivery routes. Drugs can reach the posterior segment of the eye primarily through topical, systemic, and intravitreal routes. Local administration of corticosteroids or immunosuppressive agents, via periocular or intravitreal injections, can mitigate systemic effects, but may also lead to local complications, including glaucoma and cataract. While systemic therapies remain a cornerstone in the treatment of NIU, they are typically prescribed in high doses with predictable and severe systemic side effects, due to low bioavailability in ocular tissues.[21] The topical administration of eye drops is the simplest and most commonly used method for ocular drug delivery.[10] However, their efficacy is constrained by the natural biological ocular barriers, rendering low penetration of drugs into the eye and diminished therapeutic effect.[22] It has been reported that the ocular bioavailability of topical administered drugs typically falls below 5%, necessitating multiple daily doses to sustain minimal therapeutic levels.[23] Therefore, DDS that can break the blockage of natural ocular barriers are always in high demand in treatment of NIU.

3. Barriers to drug delivery of the eye

As mentioned before, ocular barriers constitute great challenges for efficient drug delivery. Naturally evolved as protection of the eye, it also constitutes as a formidable barrier for drug delivery (Fig. 1). Consequently, recent research aimed at improving treatments for ophthalmic diseases has increasingly focused on overcoming these barriers. The use of nano-based DDS has emerged as a promising approach, allowing drugs to bypass the ocular barriers and improve the bioavailability of targeted tissues while prolonging their retention time.[24,25]

3.1. Tear film and nasolacrimal drainage

The tear film, a non-uniform aqueous phase covering the cornea surface, consists of three distinct layers: lipid layer, aqueous layer, and mucus layer, which serves as the initial barrier to ocular drug delivery.[26] The inner mucus layer consists mainly of proteins produced by epithelial goblet cells, which adhere to the epithelium. These mucin proteins form a web-like network through disulfide bridges, calcium crosslinking, and hydrogen bonding interactions. The resulting porous structure spatially traps foreign particles and pathogens, while negatively charged polysaccharides and hydrophobic regions repel most foreign substances and further enhance their adhesion barrier properties, as a barrier to locally administered treatments.[27] The middle aqueous layer contains a variety of water-soluble and insoluble components Some endogenous proteins, like globulins, albumin and lactoferrin, can bind and metabolize the administered drug, thereby reducing their bioavailability.[28] The primary role of the outer lipid layer is to reduce the surface tension of the tear film, preventing water evaporation while reducing drug absorption into the cornea and sclera.[29]

In addition, the continuous rapid flow of tears, accompanied by nasolacrimal duct drainage, forms an important dynamic barrier. The average volume of the tear film is about 7 μL, and after topical application, the volume increases and any excess liquid drains instantly into the nasal cavity. As a result, more than 85% of the drug dose is wasted before it reaches the corneal surface.[30,31] Additionally, the rapid turnover of the tear fluid further dilutes the residual drug, decreasing the diffusion rate and concentration gradient.[30]

3.2. Corneal

The cornea is a key pathway for drug absorption following topical application, consisting of multiple layers: the epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium. The corneal epithelium, with its surface tight and gap junctions, crucially limits transcorneal drug absorption.[32] This barrier imposes a restriction on the diffusion of macromolecules and hydrophilic molecules, and only smaller molecules are permitted to pass through as its average pore diameter is 2.0 nm. Furthermore, under physiological pH conditions, pores with negative charges create an extra barrier for charged

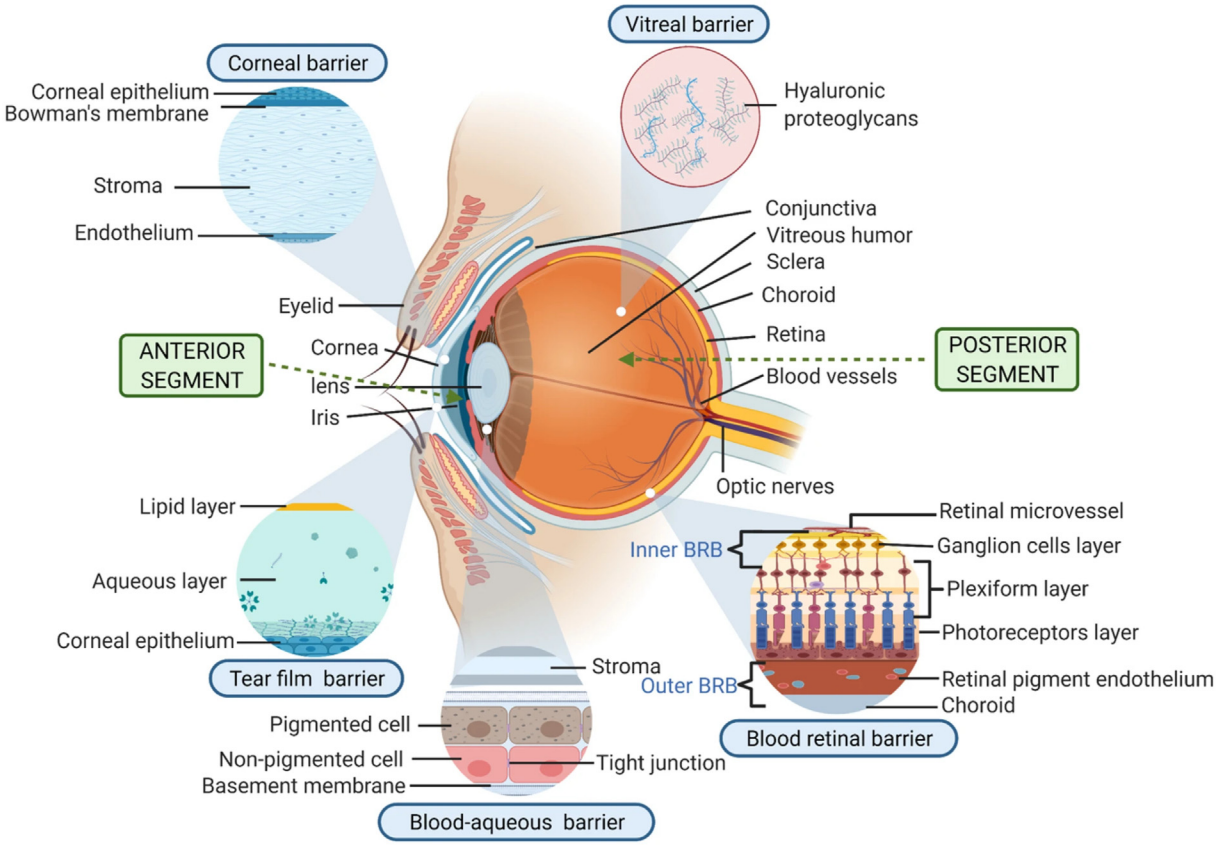

Fig. 1. Anatomical barriers in ocular drug delivery.[22] Copyright 2022, Drug Delivery and Translational Research.

molecules through ionic interaction.[33] The stroma, which constitutes the majority of corneal thickness, maintains transparency and rigidity through water retention and type I collagen composition.[34] This structure forms a barrier to lipophilic drugs and hampers the diffusion of hydrophilic macromolecules due to its collagen fiber alignment.[35] Consequently, several factors, including molecular weight, lipophilicity, charge, and the degree of drug ionization, significantly influence transcorneal drug absorption, making drug design and selection even more complicated.

3.3. Conjunctiva and sclera

The conjunctiva is a thin, highly vascularized, semi-translucent mucous membrane lining the inner surface of the upper and lower eyelids, encompassing the upper epithelium and underlying stroma.[36] Its permeability is 25 times that of the cornea, largely because of its greater surface area. The paracellular distance of conjunctival tissue is 250 times larger than that of corneal tissue, facilitating the passage of large hydrophilic molecules.[37,38] The conjunctival stroma, with its extensive blood and lymphatic supply, rapidly eliminates large quantities of therapeutic drugs through systemic circulation.[39,40]

The sclera, which serves as the eye's outermost layer, is a dense, hydrophilic, collagenous connective tissue. It comprises a cross-stacked collagen matrix interwoven with negatively charged proteoglycans.[41] Hydrophilic drugs traverse the scleral matrix more readily than lipophilic ones. The permeability through the sclera is also greatly influenced by the drug molecular radius and charge.[42]

3.4. Aqueous humor and vitreous

Pharmaceuticals are eliminated from the aqueous humor through two primary pathways: the conventional trabecular meshwork outflow and the uveoscleral outflow pathway. The trabecular meshwork pathway operates via convective flow and is independent of the drug's physicochemical properties. In contrast, the uveoscleral pathway depends on the lipophilicity of the drug for its elimination across the vessel endothelium.[33] The vitreous cavity is a semi-solid structure composed of 99% water, with the remainder being collagen and hyaluronic acid.[43] The distribution of administered drugs within the vitreous and their subsequent bioavailability in the retina are profoundly affected by the molecular weight and charge of the compounds.[37] Moreover, drugs within the vitreous are eliminated either by diffusing anteriorly into the aqueous humor or by penetrating posteriorly into the retinal vascular system.[44]

3.5. Blood-ocular barrier

The Blood-Aqueous Barrier (BAB) consists of the vasculature endothelium of the iris and ciliary muscle, as well as the posterior iris and non-pigmented ciliary epithelium. The tight junctions between cells restrict the permeability of substances with high molecular weight and highly hydrophilicity, thereby protecting the fragile, vision sensitive cells.[45]

The Blood-Retinal Barrier (BRB) comprises two primary components: the retinal pigment epithelial cells (RPEs) and the retinal capillary endothelium. Together, these structures effectively prevent drugs from entering the posterior chamber from the bloodstream.[33,46] The RPE is an epithelial layer characterized by tight junctions that hinders the passive diffusion of drugs between cells, allowing only small lipophilic molecules to diffuse through intracellular pathways.[47] The inner BRB is a robust structural barrier that prevents diffusion of molecules between retinal microvessels due to its absence of fenestrations and lack of specialized intercellular junction proteins. This barrier selectively guards the retina against foreign substances in the blood, particularly hydrophilic compounds and large molecules.[30,37]

4. Types of nano-based drug delivery systems

In ophthalmic practice, commonly used administration routes for treating the majority of ocular diseases include topical, systemic, periocular, and intraocular methods. These methods, however, are often hindered by limitations such as poor drug penetration and bioavailability, short residence time at the target site, reliance on patient compliance and tolerance, and risk of side effects from repeated administrations.[48] To address these challenges in ocular drug delivery, novel DDS have emerged as a promising solution. Development of nanocarriers offers numerous advantages, including increased transcorneal permeability, overcoming ocular barriers, prolonged drug residence time, improved patient compliance, reducing the frequency of administration, minimized drug degradation, and the achievement of sustained/controlled drug release, drug targeting and nucleotide drug delivery.[49]

Recent advances in nanotechnology have revolutionized our comprehension of disease mechanisms and driven the development and use of DDS for treating ocular diseases. In the era of nanotechnology, nano-based DDS such as liposomes, nanomicelles, hydrogels, dendrimers, nanoparticles, nanosuspensions and nanoemulsions have shown significant promise as effective carriers for ocular drug delivery (Fig. 2).[50] Table 1 summarizes the advantages and disadvantages of different types of nano-based DDS. Developing a system that meets all the required characteristics for addressing various diseases remains challenging.

4.1. Liposome

Conventional liposomes are fundamental vesicular structures consisting of a bilayer of lipids that encase an aqueous core. This distinctive architecture allows them to encapsulate hydrophilic drugs within their aqueous core and hydrophobic molecules within the lipid bilayer, respectively.[51] Their structural similarity to cell membranes renders them highly compatible with biological systems.[52] Liposomes are recognized for their ability to enhance the bioavailability of various therapeutic agents, utilizing lipids that are both biocompatible and biodegradable. In addition, liposomal surface charge can be tuned to positive, promoting interaction with the negatively charged ocular mucosa and thereby prolonging contact time and enhancing corneal permeation.[49] Over the years, numerous studies have demonstrated that liposomes formulations effectively serve as ocular DDS targeting both anterior and posterior segment diseases.[53] Liposomes offer several advantages, such as prolonged drug release, extended residence time, and

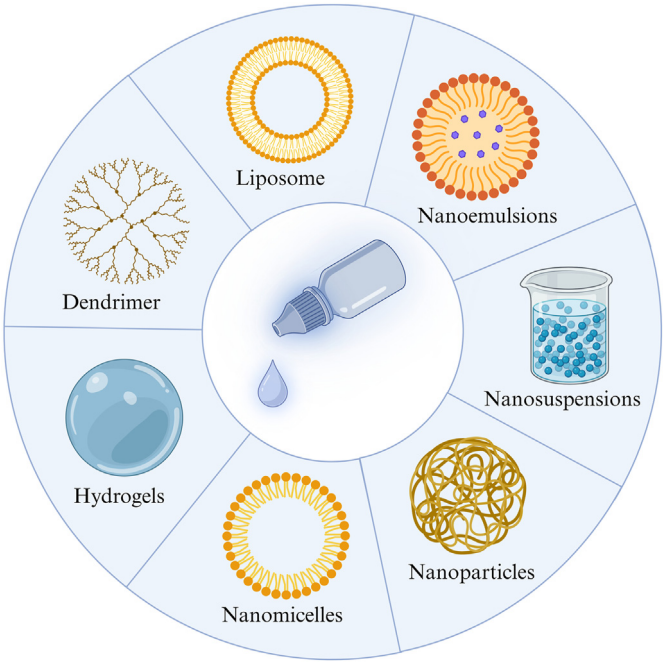

Fig. 2. Illustration of nano-based drug delivery systems for NIU.

Table 1
Types and main characteristics of Nano-Based Drug Delivery Systems.

Nano-Based Drug Delivery Systems	Advantages	Disadvantages	References
Liposome	Non-toxicity Extended residence time and improved corneal permeation Prolonged drug release Easy for surface modification Biocompatible and biodegradable	Limited drug loading capacity Short shelf life Sterilization issues	49,51,54,55
Dendrimer	High drug encapsulation Precise biodistribution Ability to functionalize surface groups	Multiple formulation procedures, Cytotoxicity Difficulties in large-scale production	49,57,58,61
Hydrogels	Excellent biocompatibility High dispersibility Extend residence time of drugs Sustained drug release Deliver multiple drugs simultaneously	Poor mechanical strength, Static property Incomplete mimicking of the native cellular microenvironments	63–68
Nanoparticles	Enhanced scalability, better absorption and intracellular penetration Reduced irritation Prolonged drug release, precise drug targeting The reduced risk of non-specific uptake and premature degradation	Inadequate drug loading Potential toxicity associated with surfactant concentrations Premature drug release during storage Uneven particle dispersion	72–75,61
Nanosuspensions	Increased drug loading with minimal toxicity Increased tissue targeting of drugs Increase the solubility Increased residence time Prolonged drug release	Physical instability	77,78
Nanoemulsions	Enhanced drug stability Reduced adverse reactions Sustained release	Eye irritation Low viscosity	54,79
Nanomicelles	Enhanced drug stability Reduced adverse reactions Sustained drug release Prolonged corneal retention time Simple and cheap fabrication	Difficulty in drug loading Lack of scalability	29,54,61

non-toxicity.[51] However, traditional liposomes have drawbacks, including limited drug loading capacity, short shelf life, and sterilization issues. To mitigate these issues, modifications can be made to liposome chemistry, size, surface charge, and lipid composition to meet specific stability and kinetic requirements.[55] For example, polyamidoamine (PAMAM)-coated compound liposomes are frequently employed to improve stability and applicability for specific use. Coatings like PAMAM have been shown to improved encapsulation efficiency, stability, permeability and bioavailability of drugs.[56]

4.2. Dendrimer

Dendrimers represent a unique class of synthetic macromolecules characterized by their highly branched, three-dimensional nanoscale architecture, and high functionality. Their sizes are parallel to native proteins, with similar narrow polydispersity. Their structural attributes allow for efficient encapsulation and precise biodistribution, positioning them a strong candidate for ocular DDS. Additionally, their versatility allows for the engineering of multifunctional biological macromolecules through surface modifications, broadening their potential applications.[49,57,58]

Since their initial synthesis by Tomalia et al. in the mid-1980s, PAMAM dendrimers have been extensively studied for their potential in delivering both hydrophilic and lipophilic drugs, nucleic acids (including DNA and miRNA/siRNA), macromolecules, and other biomedical applications.[57,59,60] Clinical translation of this system is impeded by multiple formulation procedures, difficulty in large-scale production and cytotoxicity, and therefore, further evaluation is necessary.[61,62]

4.3. Hydrogels

Hydrogels consist of a three-dimensional network of hydrophilic polymers that possess a high water retention capacity. These materials offer excellent biocompatibility, high dispersibility in aqueous environments, and can be designed to be either biodegradable or non-degradable.[63] Hydrogels can enhance therapeutic efficacy via several mechanisms: extending the residence time of drugs at the administration site, providing sustained drug release at the target location, and enabling the simultaneous delivery of multiple drugs.[64–67] However, they still have some drawbacks such as weak mechanics, static characteristics and incomplete mimicking of the native cellular microenvironments.[68] In recent years, numerous hydrogels have been created to treat various eye conditions. These advancements include in-situ gelling hydrogels, hydrogel-based contact lenses, cyclodextrin/poly (ethylene glycol)-based supramolecular hydrogels, and hydrogel-forming microneedles.[69] For instance, Fang et al. developed a polypseudorotaxane hydrogel for anterior uveitis treatment, showing improved precorneal retention, corneal permeability, intraocular bioavailability, and anti-inflammatory efficacy in a rabbit model of endotoxin induced uveitis (EIU). The hydrogel demonstrated shear-thinning behavior, sustained drug release, and good biocompatibility, making it a promising ophthalmic drug delivery system for uveitis and other eye conditions.[70]

4.4. Nanoparticles

Nanoparticles have gained significant attention as ocular DDS over the past few decades. Common materials used for nanoparticles include lipids, proteins, and biodegradable polymers, which can be synthetically derived from materials such as poly(lactide-co-glycolide) (PLGA), polylactic acid (PLA), and polycaprolactone (PCL), or they can be naturally sourced from substances like albumin, chitosan, sodium alginate, and gelatin.[71] Nanoparticles present numerous benefits, including enhanced scalability, better absorption and intracellular penetration, reduced irritation, prolonged drug release, precise drug targeting, and the reduced risk of non-specific uptake and premature degradation.[72–75] Despite the considerable promise of nanoparticles for targeted ocular drug delivery, significant limitations remain that hinder their widespread clinical use. These include inadequate drug loading, difficulty in achieving uniform particle dispersion, the risk of premature drug release during storage, and potential toxicity associated with surfactant concentrations.[61] Therefore, further research is necessary to overcome these challenges and advance the clinical translation of nanoparticle-based DDS.

4.5. Nanosuspensions and nanoemulsions

Nanosuspensions and nanoemulsions have proven to be highly effective DDS for ocular applications. These nanotechnology-based formulations offer enhanced drug solubility, stability, and bioavailability. By reducing the particle size to the nanoscale, these systems ensure better penetration and prolonged retention of therapeutic agents within ocular tissues.[76]

Nanosuspensions, which consist of submicron-sized drug particles dispersed in an aqueous medium, provide a versatile platform for delivering drugs with poor water solubility.[77] Their small particle size leads to an increased surface area, facilitating rapid drug absorption and improved therapeutic efficacy.[78] Furthermore, the controlled release properties of nanosuspensions minimize the frequent administration, thereby improving patient compliance. Although nanosuspensions have numerous advantages, the stability issue still remains unresolved.[78]

Nanoemulsions, which are spontaneous biphasic dispersions of two immiscible liquids stabilized by surfactants, offer distinct advantages in ocular drug delivery.[79] Their capacity to encapsulate both hydrophilic and lipophilic drugs broadens their applicability across various therapeutic agents.[79] Additionally, their stability in physiological conditions ensures sustained drug release, thereby reducing the frequency of administration and mitigating associated side effects.[80–82] Although nanoemulsions can be used in ocular formulations, they still have some drawbacks, such as eye irritation and low viscosity.[54]

4.6. Nanomicelles

Self-assembled nanomicelles, one of the most commonly used ophthalmic DDS for both anterior and posterior eye segments, are easily prepared using amphiphilic molecules. Their unique chemical structure allows for the internal dissolution of drugs, enhances drug stability, reduces adverse reactions, and provides sustained release, making them safe alternatives for ocular drug delivery.[54] Easy scale-up procedures and a low production cost are another major advantage of nanomicelles over other nanocarriers.[29] Nanomicelles loaded with dexamethasone (Dex) have demonstrated superior bioavailability for anterior segment delivery in vivo compared to traditional suspensions, indicating their potential an alternative delivery platform.[83] In addition, nanomicelle-based DDS have been developed to target the posterior segment of the eye, further supporting their promise for future clinical applications in ocular drug delivery.[84,85] Despite these encouraging results, the issues of difficulty in drug loading and lack of scalability remain unresolved.[61]

5. Nanotechnology for the potential clinical drug treatment of NIU

The main objectives of NIU treatment are to control inflammation, prevent visual impairment, and improve the quality of patient's life. The treatment modality of infectious uveitis is mainly through eliminating the cause. NIU, which is idiopathic and often associated with immune abnormalities, has traditionally been managed with topical or systemic corticosteroids.[86] In some clinical situations, immunosuppressive therapy is necessary to control persistent inflammation.[87] Recently, biological drugs have emerged as valuable options for various forms of NIU that are unresponsive to conventional treatments.[20]

5.1. The delivery of corticosteroids

Corticosteroids, including Dex and triamcinolone acetonide (TA) are the first-line treatment for NIU.[88] Numerous studies have explored the use of nanomaterials to target eye tissue as a DDS to achieve sustained corticosteroid release.

In an article published by Alami-Milani et al., they demonstrated that polycaprolactone-polyethylene glycol-polycaprolactone (PCL-PEG-PCL) micelles enhance the anti-inflammatory effects of Dex. The micelles showed excellent cellular compatibility and uptake. While Dex-loaded micelles alleviated uveitis symptoms over time, their efficacy did not significantly differ from commercially available Dex eye drops at 24h and 36h post-treatment. These findings indicate that PCL-PEG-PCL micelles hold potential as a viable delivery system for Dex in the treatment of anterior uveitis. However, further research is required to fully validate this approach.[89] Safwat et al. prepared micelles incorporating TA using poly (ethylene glycol)-block-poly(ε-caprolactone) (PEG-b-PCL) or poly (ethylene glycol)-block-poly (lactic acid) (PEG-b-PLA) for ocular inflammation treatment. Both micelle types exhibited high drug loading and encapsulation efficiencies, with PEG2-b-PLA1 micelles showing the highest capacity. When suspended in chitosan hydrogel, these micelles demonstrated good ocular anti-inflammatory activity in vivo, suggesting their potential as effective ocular DDS for improving TA solubility and sustained release.[90] Sabzevari et al. also utilized polymeric mucoadhesive nanoparticles to load TA. These nanoparticles, composed of poly-β amino ester (PbAE), exhibited longer residence in the precorneal area and better penetration due to ionic interactions. Notably, the nanoparticles are more effective than microparticles in treating rabbits with EIU.[91]

Recently, pharmaceutical researchers have progressively focused on developing DDS that efficiently achieve therapeutic goals while minimizing side effects. As drug-carrying microspheres or nanoparticles, PLGA vehicles have drug protection effects, increase drug solubility, improve bioavailability, and reduce toxicity or side effects. However, it is still limited due to its high hydrophobicity.[92,93] Guo et al. prepared TA-loaded methoxypoly (ethyleneglycol) (mPEG)-PLGA nanoparticles by incorporating mPEG blocks into a PLGA molecular chain, conferring them with dual properties that render them both hydrophilic and hydrophobic. The formulation was able to release TA for at least 45 days, exhibiting a slow and sustained release profile compared to TA in phosphate buffer saline (PBS). The property of gradually releasing TA from TA-loaded nanoparticles aligns with the progression of experimental autoimmune uveoretinitis (EAU), thereby exhibiting a favorable therapeutic effect on uveitis, particularly for chronic and recurrent cases in clinical practice.[92] Likewise, Luo et al. utilized divalent zinc ions to enhance the delivery of dexamethasone sodium phosphate (DSP) within PLGA nanoparticles. In the rat model of EAU, subconjunctival injection of DSP-Zn-nanoparticles demonstrated superior efficacy compared to DSP solution injection for at least 3 weeks, markedly lowering clinical scores, reducing cytokine mRNA expression, and minimizing retinal damage and inflammatory cell infiltration.[94] Additionally, Sabzevari et al. proposed TA-loaded nanoparticles using Poly (D, L-lactide-co-glycolide) (PLGA) via a modified emulsification/solvent diffusion method, which exhibited controlled release properties. Importantly, topical application of these TA nanoparticles achieved effects equivalent to TA injections in treating EIU.[95] In another article by Xing et al., TA was formulated in PLGA-chitosan (PLC) nanoparticles for the treatment of EIU. The TA-loaded PLC nanoparticles exhibited excellent anti-inflammatory activity compared to TA suspension. Besides, these designed nanocarriers demonstrated excellent biocompatibility and prolonged drug release. Pharmacokinetic analysis further confirmed the superiority of the PLC-based nanocarrier system, indicating its potential in treating ocular inflammatory diseases.[96]

Surface modification of nanocarriers can enhance the bioavailability of nanocarriers. Utilizing cationic polymer for surface modification can potentially enhance residence time and drug uptake.[97] Alkholief et al. designed HA-coated DSP-chitosan nanoparticles (CSNPs) as a sustained ocular delivery vehicle. Coating the CSNPs' surfaces with HA improves cellular targeting to promote corneal and conjunctival healing. DSP-HA-CSNPs increase transcorneal flux and permeability by around 10-fold, while uncoated CSNPs is 4.7-fold compared to the DSP-aqueous solution (DSP-AqS). Meanwhile, uncoated and HA-coated CSNPs can markedly reduce eye inflammation in EIU rabbits, as evidenced by decreasing inflammatory factors and inhibiting apoptosis. This finding suggests that the DSP-CSNPs platform enhances delivery efficacy, thereby exhibiting a strong anti-inflammatory effect in EIU rabbits.[98] Moreover, Nirbhavane et al. developed a novel TA formulation using a cationic nano lipid carrier designed to prolong the drug's residence time on the ocular surface through charge-based interactions. Ex vivo transcorneal permeation study in porcine corneal suggested that cTA-NLC is capable of penetrating the deeper layers of the eye within 2h and can remain there for up to 24h. Importantly, the formulation significantly decreases tumor necrosis factor(TNF)-α within inflammatory cells triggered by LPS, suggesting that it has potent anti-inflammatory properties.[99]

To develop a safer preparation technique for fabricating nanoparticles for drug delivery without utilizing organic solvents and surfactants, Huang et al. introduced a straightforward approach to generate high drug payloads nanoparticles by combining small molecules and polymer components to locally suppress ocular inflammation. Different from conventional nanoparticle manufacturing techniques, succinated triamcinolone acetonide (TA-SA)/poly (ethylene glycol)-poly (ε-caprolactone)-poly (ethylene glycol) (PECE) nanoparticles are produced by assembling a low molecular weight hydrogel (TA-SA hydrogel) and a polymeric hydrogel (PECE hydrogel). These nanoparticles exhibit good stability and are produced without the need for organic solvents or surfactants at any stage of the manufacturing process. In vivo studies revealed that the developed nanoparticles exhibited superior anti-inflammatory effects in EIU rabbits compared to TA suspension, by suppressing the production of proinflammatory cytokines like NO and TNF-α.[100] Yu et al. developed a Dex-peptide conjugate (Dex-SA-FFFE) to form nanoparticles with high drug payload in aqueous solution. These nanoparticles exhibited sustained release and minimal cytotoxicity, showing comparable therapeutic effects to DSP solution in a rabbit EIU model.[101]

Recently, supramolecular hydrogels, which are created through the self-assembly of small molecules, have garnered significant interest. Their appeal lies in their flexibility in designing, readiness of production, high drug payload and carrier-free characteristics. Wu et al. constructed a DSP supramolecular hydrogel using a calcium ion cross-linking strategy. In an EAU rat model, both supramolecular hydrogel and natural Dex solution exhibited a significant anti-inflammatory efficacy by down-regulating Th1 and Th17 response. Compared with Dex aqueous solution, single intravitreal injections of Dex supramolecular hydrogel up to 30μg/eye were well tolerated with no adverse effects. Based on these findings, it is suggested that the DSP supramolecular hydrogel developed may serve as an alternative treatment for NIU.[102] Chen et al. rationally designed a drug-peptide supramolecular hydrogel by incorporating motifs from anti-inflammatory drug Dex and Arg-Gly-Asp (RGD). The integration of peptides into the hydrogel significantly enhances its functionality, enabling selective targeting of specific cell receptors. This hydrogel not only shows improved performance in integrin targeting and cellular uptake, but also enhances the transcorneal permeability and pharmacological efficacy through ligand-receptor interactions when administered topically.[103] Recent studies increasingly underscore the critical role of oxidative stress in the pathogenesis of uveitis, suggesting that combined antioxidant and anti-inflammatory therapies might led to a favorable prognosis.[104] Liu et al. designed multifunctional hydrogel eye drops (DCFH) for the noninvasive treatment of uveitis. The DCFH consists of the anti-inflammatory agent DSP and the reactive oxygen species (ROS) scavenger cerium-based metal−organic frameworks (Ce-MOFs) incorporated into the thermosensitive triblock copolymer F127. Ce-MOFs

exhibited ROS-scavenging properties and a porous structure with a high specific surface area, enabling efficient DSP loading and release. Additionally, Pluronic F127 contributes to the system by forming a transparent hydrogel at physiological temperatures, improving drug retention and sustained release in the eye. In therapeutic terms, DCFH shows notable efficacy in treating EIU via reducing ocular inflammatory response, inhibiting inflammatory cytokines and downregulating the expression of NLPR3 and iNOS, highlighting its potential as a significant excipient in ophthalmic anti-inflammatory treatments.[105]

5.2. The delivery of immunosuppressants

Alternatively, immunosuppressive therapy is recommended as a second-line choice of NIU treatment. Immunomodulatory agents such as cyclosporine-A, rapamycin (sirolimus), and tacrolimus can mitigate steroid-induced side effects, including glaucoma, cataracts, vascular occlusion, proliferative vitreoretinopathy, cystoid macular edema, and blindness.[106,107] Cyclosporine A (CyA) is a potent immunomodulatory drug that suppresses T lymphocytes activation by preventing transcription of cytokine genes.[108] However, its application in ocular treatments is restricted by its high molecular weight and limited permeability across biological barriers.

In an experiment by Kasper et al., CyA-loaded methoxy-poly(-ethylene-glycol)-hexyl substituted poly-(lactic acid) (mPEGhexPLA) nanocarriers were applied topically to a mouse model of EAU. With repeated topical applications of the nanocarrier, it was well-tolerated and demonstrated non-toxicity. After administration, the drug mainly accumulated in the cornea, sclera-choroidal tissue, and lymph nodes, along with a significantly reduction in EAU severity compared to the untreated controls. Furthermore, this therapeutic effect was accompanied by a reduction in T-cell count, reduced T-cell proliferation, and diminished interleukin (IL)-2 secretion in the lymph nodes of the treated eye. Thus, topical application of CyA-containing nanocarriers proved to be an effective treatment for EAU.[109] Similarly, Shen et al. synthesized thiolated NLC nanocarrier for local ocular delivery of CyA. The formulation exhibited a good ocular tolerance and exhibit a sustained drug release in vitro. It was found that thiolated NLC extended the precorneal residence time and delivered high levels of CyA to the anterior chamber. These findings indicate that thiolated NLCs hold promise as a therapeutic strategy for anterior segment inflammatory diseases due to their bio-adhesive properties and sustained release characteristics.[110] Additionally, Ghezzi et al. prepared a tocopherol polyethylene glycol succinate (TPGS) micellar formulation capable of dissolving large amounts of CyA and facilitating its transport across ocular barriers. TPGS micelles, being a water-based formulation with good biocompatibility, effectively promoted drug retention and penetration within the cornea and sclera. Moreover, they formed a drug reservoir within the tissue, sustaining drug release into deeper tissues over an extended period.[111]

Rapamycin, a well-established inhibitor of the mammalian target of rapamycin (mTOR), plays a crucial role in regulating immune responses, T-cell proliferation, and proinflammatory cytokine production. Inhibiting mTOR thus offers a promising approach for treating uveitis.[112,113] To deliver rapamycin locally to the eye, Badr et al. formulated a nanoparticle-based eye drop, Molecular Envelope Technology-Rapamycin, which successfully controlled the progression of EAU with comparable efficacy to Dex eye drops.[114] Similarly, Cholkar et al. formulated rapamycin-loaded mixed nanomicellar formulations (MNFs) for targeted delivery to the posterior segment of the eye. Their optimized rapamycin-loaed MNF (0.2%), formulated with a polymeric matrix comprising vitamin E TPGS and octoxynol-40 (Oc-40), exhibited superior rapamycin entrapment and loading efficiency. In vivo studies revealed high concentrations of rapamycin in the retina-choroid (362.35 $\pm$ 56.17 ng/g tissue), significantly exceeding therapeutic levels with a single topical application, while no detectable rapamycin in vitreous body. These findings underscore the formulation's potential for targeted drug delivery in uveitis treatment.[115]

Everolimus, a rapamycin derivative, is a potent immunosuppressive agent with higher bioavailability, shorter half-life and quicker reach to "steady-state" level compared to rapamycin.[116] Kasper et al. investigated the therapeutic effects of topically delivery of everolimus on EAU using a novel aqueous methoxy poly(ethylene-glycol)-hexyl substituted poly (lactic acid) (mPEGhexPLA) -based nanocarrier formulation. A single-eye topical application of a 0.5% everolimu/mPEGhexPLA formulation led to a marked reduction in the severity of EAU compared to mice treated with PBS. Remarkably, improvement was also observed in the contralateral eyes, possibly due to systemic immunosuppressive effects influencing several systemic cellular immune responses.[116] Mehra et al. prepared the everolimus loaded nanomicelles (Evr-NMs) using Soluplus®, a grafted polymer of polyvinyl caprolactam-polyvinylalcohol-polyethyleneglycol (PVCL-PVA-PEG). The resulting nanomicelles demonstrated high encapsulation efficiency and stability, remaining viable for at least three months when stored at 4 °C. In addition, the Evr-NMs provided sustained drug release and significantly improved permeability of everolimus in goat cornea compared to everolimus suspension. With demonstrated stability and no ocular toxicity, Evr-NMs DDS present a promising nanocarrier for topical drug delivery in uveitis treatment.[117]

Similar to rapamycin, tacrolimus (TAC or FK506) has demonstrated comparable efficacy in treating ocular inflammation when combined with nanomaterials. Rebibo et al. designed and optimized nonirritant and stable tacrolimus PLGA nanocapsules (TAC-loaded PLGA nanocapsules) using the solvent displacement method. The optimized formulation, featuring a particle size of 143.9 $\pm$ 15 nm and a PDI of 0.8, exhibited uniform particle size and high encapsulation efficiency. TAC-loaded PLGA nanocapsules enhanced drug retention in the cornea while facilitating deeper ocular penetration. These promising findings indicate that this formulation could potentially eliminate the necessity for intravitreal injections or systemic treating, thereby reducing severe side effects.[118]

The PD-1 pathway is essential in the pathogenesis of autoimmunity and auto-inflammation.[119] Therefore, Liu et al. proposed a strategy combining PD-1 receptor targeting and glycolysis inhibition to specifically suppress T cells. They synthesized a novel nanoplatform TPP, in which TEPP-46 was encapsulated in PLGA-PEG nanoparticles and the surface of nanoparticles was modified with PD-1 antibody. TPP demonstrated good stability, high biocompatibility, and biosafety. More importantly, TPP efficiently targeted PD-1$^+$ lymphocytes via PD-1 antibody modification. Meanwhile, TEPP-46 specifically targeted and inhibited the activation and proliferation of effector T cells, effectively suppressing EAU activity in association with a substantial decrease in Th1 and Th17 cells.[120]

5.3. The delivery of protein based biological agents

TNF-α is a multifunctional cytokine primarily secreted by macrophages, natural killer cells and T lymphocytes. It plays a critical role in the pathogenesis of various inflammatory ocular diseases, including scleritis, uveitis, and dry eye disease.[121] Therefore, targeting TNF-α represents a promising therapeutic strategy for managing ocular inflammatory diseases. Infliximab, a human-mouse chimeric IgG1 antibody, neutralizes soluble TNF-α and has proven effective in treating refractory uveitis.[122] Zhang et al. utilized liposomes as a sustained-release delivery system for infliximab, achieving sustained low concentrations in the vitreous and retina-choroid, potentially enhancing safety and tolerability. In an EAU model, intravitreal injection of infliximab or infliximab-liposome significantly diminished intraocular inflammation. The manifestations of EAU were markedly improved, with infliximab providing immediate relief and infliximab-liposome offering prolonged effects. The liposomal infliximab exhibited long-term stability and may represent a promising candidate for ocular diseases treatment.[123]

Adalimumab (ADA), a fully human monoclonal antibody, specifically targets TNF-α, counteracting its biological activity. Chen et al. designed a chitosan-based hydrogel eye drop as a delivery system for ADA,

composed by low-deacetylated chitosan and β-glycerophosphate(β-GP). Compared with free drug administration, the hydrogel eye drops demonstrated great biocompatibility, controlled ADA release, increased permeation and enhanced drug loading efficacy both in vitro and in vivo studies. After instilling low-deacetylated chitosan/β-GP-ADA, ADA signal was detected in the iris and ciliary body, even reaching the deeper retina. More importantly, compared with free ADA, the ADA-loaded hydrogel eye drops dramatically suppressed EIU and inflammation by reducing IL-6 and TNF-a levels.[124]

5.4. The delivery of other agents with anti-inflammatory properties

Curcumin is a natural polyphenol compound have been wildly applied in treating various diseases, including autoimmune disorders, cancer, metabolism and infectious diseases.[125] Jiang et al. designed Fe-curcumin nanozymes by coordinating natural antioxidants with Fe3+, creating highly soluble nanoparticles that target anti-inflammatory and ROS scavenging effects for EAU treatment. The experiments revealed that the inflammatory response and ROS levels in the Fe-curcumin nanozymes treatment group were reduced compared with the normal saline group, as evidenced by the downregulation of key inflammatory cytokines, reduced H_2O_2 release; inhibition of Th1 and Th17 cell proliferation; and attenuation of ocular pathologies. In addition, drug concentrations do not produce cytotoxicity within a certain range, suggesting its potential as a prospective therapeutic option for clinical application.[126] Receptor-mediated drug delivery has recently been used for post-operative uveitis treatment. Ganugula et al. successfully developed a formulation by encapsulating curcumin in double-headed polyester nanoparticles, using gambogic acid (GA) as a coupling agent and PLGA as the polymer. Oral administration of this nanoparticles led to a notable increase in curcumin levels in the aqueous humor, producing clinical effects comparable to conventional anti-inflammatory agents in canine models of lens-induced uveitis. This innovative nanoparticle delivery system could improve curcumin's bioavailability while also minimize the common side effects linked to topical corticosteroids or NSAIDs.[127]

Flurbiprofen, a poorly water soluble anti-inflammatory drugs, has been shown to effective suppress intraocular inflammation while avoiding many adverse effects of corticosteroid.[128] Fang et al. developed polypseudorotaxane hydrogels combining Soluplus micelles with cyclodextrins, which exhibited enhanced transcorneal permeability (P_{app}, 1.84 folds), longer precorneal retention (AUC, 21.2 folds), and increased intraocular bioavailability ($AUC_{Aqueous\ humor}$, 17.8 folds) compared to drug solutions. Importantly, the hydrogels effectively reduced inflammation in the EIU rabbit model with fewer administrations and proved safe in cytotoxicity and ocular irritation assessments.[70]

Antioxidants, particularly copper-zinc superoxide dismutase (SOD1), have the potential to act as powerful ROS scavengers, offering protective effects against oxidative stress in various pathological conditions. An et al. developed a new therapeutic modality for ocular use based on multilayer polyion complex nanoparticles of SOD1 (Nano-SOD1). This formulation demonstrates adequate storage stability and is non-irritating to the eye. In comparison to the native enzyme, Nano-SOD1 exhibits better corneal retention, more effective penetration into deeper ocular tissues, and prolonged enzyme activity within the eye. In rabbits with immunogenic uveitis, nano-SOD1 treatment significantly outperformed the native enzyme in reducing inflammation, resulting in reduced manifestations of uveitis and decreased levels of inflammatory factors and proteins in the anterior chamber. Additionally, Nano-SOD1 demonstrated superior efficacy in restoring antioxidant capacity within ocular tissues compared to the native enzyme.[129]

6. Conclusions

Uveitis is a vision-threatening inflammatory disorder, which is one of the leading causes of visual loss worldwide. The advent of nano-based DDS offers promising solutions to the challenges posed by impediments to the route of administration and side effects of the drugs themselves in the treatment of NIU, both in the anterior and posterior segment of the eye. Nano-based DDS strategies are particularly advantageous due to their ability to achieve targeted delivery, increased bioavailability, sustained release, reduced side effects, and improved therapeutic efficacy. Despite the obvious advantages over conventional therapies, there are still many issues that need to be addressed before clinical translation, such as large-scale manufacturing and late-phase clinical trials. Future efforts should focus on developing novel non-invasive DDS with satisfactory bioavailability, dose accuracy, and sustainable release, all while minimizing cellular or tissue toxicity. In addition, optimizing the safety, stability, size, pH, surface tension, refractive index, osmotic pressure and zeta potential of nanocarriers is crucial. For clinical translation, batch stability and formula design are also critical factors that should be considered carefully. At the same time, extensive in vitro and in vivo experiments are necessary, and animal models that more closely resemble human eye diseases should be established. Long-term safety and stability of delivery vectors in human eyes must also be thoroughly evaluated.

In conclusion, advancements in nanotechnology have opened new avenues in the treatment of NIU. By addressing the limitations of current treatment regimens, nano-based DDS offer the potential for more effective, safer, and patient-friendly therapies. Ongoing research and clinical trials are essential to fully realize the benefits of these innovative approaches and integrate them into mainstream clinical practice. As research progresses, these innovative DDS are expected to revolutionize present clinical practices in future.

Study approval

Not Applicable.

Author contributions

The authors confirm contribution to the paper as follows: conceived and designed the review: XDW, FJ, MC, KJW; searched and selected references of the review: XDW, MYH, Drafting the manuscript: XDW, MYH; YLC, FJ. All authors reviewed and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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