Review

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Drug delivery methods based on nanotechnology for the treatment of eye diseases

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Abstract

One of the most difficult tasks among the numerous medication delivery methods is ocular drug delivery. Despite having effective medications for treating ocular illness, we have not yet managed to develop an appropriate drug delivery strategy with the fewest side effects. Nanotechnology has the potential to significantly address the drawbacks of current ocular delivery systems, such as their insufficient therapeutic effectiveness and unfavourable side effects from invasive surgery or systemic exposure. The objective of the current research is to highlight and update the most recent developments in nano-based technologies for the detection and treatment of ocular diseases. Even if more work has to be done, the advancements shown here might lead to brand-new, very practical ocular nanomedicines.

Keywords: drug delivery systems, nanocarriers, nanotechnology, ocular barriers, ocular diseases, treatment

Introduction

According to World Health Organization (WHO) research from 2015, there are about 217 million adults worldwide who are 18 years of age or older who have ocular conditions that might damage their vision and ultimately render them permanently blind[1]. Numerous preclinical and clinical research have been conducted over the last 10 years to discover therapies for various ocular conditions, including uveitis, age-related macular degeneration, diabetic retinopathy, glaucoma, and cataracts[2]. Innovations in ocular pathological processes and the treatment of eye diseases have made significant progress. However, because of the particular anatomical and physiological characteristics of the eye, it is difficult to diagnose and treat these disorders. Rarely were serious ocular problems diagnosed early on using the standard treatment procedures, and neither could vision loss[3]. Thus, better diagnostic and treatment techniques that are developing for eye illnesses have drawn a lot of interest. The present hot issue and high-potential technology known as nanotechnology has a significant impact on a number of sectors related to engineering, chemistry, medicine, and biology. This technique has garnered significant scientific interest during the last 10 years[4,5]. Nanoscience is the study of physical, chemical, and biological characteristics of nanoscale materials. The creation and use of materials having at least one dimension on the nanoscale scale constitutes nanotechnology[6]. Some materials with a nanoscale structure exhibit extraordinary mechanical, optical, electrical, chemical, and magnetic properties. Drugs and drug delivery systems' physicochemical and biological qualities may be improved by using these attributes[7–9]. Rapid advancements have also been achieved in the use of nanotechnology for the detection and treatment of eye diseases (Fig. 1).

The most popular nanotechnology-based ocular delivery systems (NODS) are nanocapsules, nanoliposomes, niosomes, nanohydrogels, cubosomes, nanomicelles, and nanoparticles (NPs), which have certain advantages over existing diagnostic and therapeutic methods[10–12]. Nanomaterials were created to revolutionise the diagnosis and treatment of various illnesses due to their unique properties and potential applications in biology and medicine[13,14]. NPs are now often used to deliver various medicines, peptides, vaccines, and other substances

HIGHLIGHTS

- The bone-targeting medication delivery systems is one of the creative ways to improve eye diseases treatment.
- Methods of using nanoparticles to create drugs for the treatment of eye diseases.
- It is proven that the use of nanomaterials significantly enhances the treatment of eye diseases.

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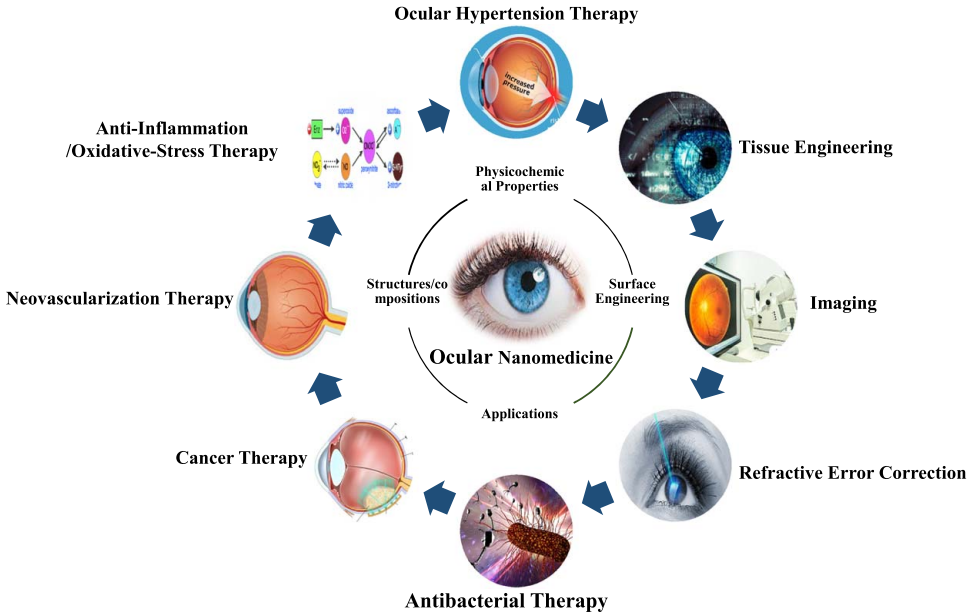

Figure 1. Schematic presentation of ocular nanomedicine for use in ophthalmology with diverse biological applications.

successfully[15]. Due to their regulated release, appropriate therapeutic toxicity, and nanometre-scale dimensions, NPs exhibit fewer side effects than traditional chemotherapeutic medications and show positive benefits even at low doses[16]. The application of NPs in nanostructured devices, films for ocular medication delivery, and contact lens implants that incorporate NPs is thus more appealing[3].

This review delves into the evolving landscape of drug delivery methods based on nanotechnology, exploring their potential in addressing various eye diseases. Through a comprehensive review of materials, procedures, and characterisation techniques, as well as insights from clinical studies, biosafety profiles, and challenges in development, this article seeks to shed light on the transformative impact of nanotechnology in ocular medicine. By elucidating the advantages and challenges associated with nano-based medication delivery devices, this article aims to provide a holistic perspective on the current state and future possibilities in treating anterior eye illnesses.

Delivery methods based on nanotechnology

Micelles, nanoemulsions, nanosuspensions, NPs, niosomes, dendrimers, liposomes, nanowafers, and cubosomes are a few of the nanocarriers that have been produced for anterior segment eye diseases (ASEDs). The current state of ocular medication delivery systems is anticipated to change, particularly for ASEDs, thanks to nanotechnology delivery methods. Nano-ocular delivery systems provide a number of benefits, one of which is increased bioavailability. To achieve the intended effectiveness and safety, however, the formulation of nano-ocular delivery systems requires rigorous development methods and careful selection of excipients/materials. Nanotechnology-based drug delivery offers several advantages over conventional therapies for ophthalmic diseases, primarily due to their ability to provide targeted, sustained, and controlled drug release.

Materials and procedures for medication delivery systems based on nanotechnology

The pharmaceutically effective substances (phytochemicals, genes, peptides, and drugs), polymers, stabilisers, and lipids are the main components of nanocarriers employed as a vehicle for ocular administration. Table 1 lists these ingredients for formulation.

Polymers

When creating ocular nanocarriers, synthetic, semi-synthetic, and natural polymers are all used. Chitosan, gellan gum, alginate, hyaluronic acid, albumin, and gelatin are among the natural polymers that are often utilised[17,18]. They benefit from being both biocompatible and biodegradable. A biocompatible positively charged polymer called chitosan is created when chitin undergoes a deacetylation process. In addition to serving as a mucoadhesive polymer, it improves ocular medication penetration by reversibly loosening corneal epithelial intercellular tight junctions[19]. Chitosan has been frequently used in NODS to treat ASEDs in order to enhance the mucoadhesive characteristics of the system, despite the fact that its utilisation is limited by poor water solubility at physiological pH[20,21]. Since chitosan is hydrophilic and does not effectively encapsulate hydrophobic drugs, it is frequently modified and grafted with artificial polymers. Galactosylated chitosan, glycol chitosan, and *N*-trimethyl chitosan are only a few examples of chitosan derivatives with increased water solubility and ease of functionalisation that are employed in ocular drug administration[22,23].

In certain ocular tissues, such as the aqueous humour and cornea, hyaluronic acid is an endogenous hydrophilic, biodegradable polysaccharide, and biocompatible[24]. Hyaluronic acid

Table 1

Ocular delivery systems based on nanotechnology often include the following active components and excipients.

Drug/Excipients	Example
Surfactants	Polysorbate (Tween), Transcutol P, vitamin E TPGS (D-α-tocopherol polyethylene glycol 1000 succinate), sorbitan esters (Span), oleylamine, tyloxapol, polyoxyl 40 hydrogenated castor oil (Cremophor RH-40), poloxamers (Pluronic, Lutrol), Solutol HS 15 (Kolliphor HS 15)
	Glycerol, ethanol, co-surfactants – propylene glycol
Lipids	Lecithin, phospholipids – phosphatidylcholine (PC), phosphatidylglycerol, distearoylphosphatidylcholine (DSPC), dioleoyl phosphatidylcholine (DOPC), dipalmitoyl phosphatidylcholine, 1,2 dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE)
	Fatty acid – stearic acid
	Castor oil, liquid lipids – oleic acid, squalene, coconut oil, olive oil, palmitic oil, glyceryl tricarylate (Miglyol 812), soybean oil
	Wax – cholesterol
	Polyethylene glycol monosterate (Gelucire), partial Glyceride – glyceryl tribehenate (Compritol), glyceryl palmitostearate (Precirol)
	Triglycerides – trilaurin, tripalmitin, trimyristin, and tristearin (Dynasan 112, 114, 116, 118, respectively)
Polymers	Synthetic – poly (ethylene glycolpolycaprolactone, poly (glycolic acid), polyvinyl alcohol, polylactic acid, poly (lactic-co-glycolic acid), methacrylic acid-methyl acrylate copolymer (Eudragit), poly (acrylic acid), poly(amidoamine), carbosilane
	Hydroxypropyl methylcellulose, semi-synthetic – sodium carboxymethylcellulose
	Alginate, natural – chitosan, albumin, gelatin, hyaluronic acid, gellan gum
Active pharmaceutical ingredient	Phytochemicals – naringenin, epigallocatechin gallate and myricetin, resveratrol, hesperetin, glycyrrhizin, curcumin,
	Plasma DNA, genes – transcription factor, monoclonal antibody
	Octreotide, proteins, and peptides – lactoferrin, catalase, protamine
	Tramcinolone, immunosuppressant- dexamethasone, cyclosporine A, tacrolimus,
	Ganciclovir, antiviral – acyclovir
	Natamycin, antifungal – amphotericin B, voriconazole
	Flurbiprofen, anti-inflammatory drugs – diclofenac, pranoprofen

promotes ocular retention of nanoformulations by binding to CD44 (cluster of differentiation 44) receptors on corneal epithelial cells[25]. It is used as a lubricant in eye drops to alleviate the symptoms of dry eye disease (DED). Hyaluronic acid is often employed as a coating material for nanocarriers, similar to how chitosan is[26]. Alginate is a crucial natural polymer in NODS[27]. Alginate has effective mucoadhesive qualities. For instance, utilising three techniques (electrospraying, emulsification, and their combination), Kianersi and colleagues reported the synthesis of alginate-based NPs containing encapsulated betamethasone sodium phosphate[27]. Additionally, coated with gelatin and chitosan, these NPs were tested for ocular administration.

In most nanotechnology-based delivery systems, matrix-forming and viscosity-enhancing materials such as sodium carboxyl methylcellulose, methylcellulose, hydroxypropyl methylcellulose, and carboxymethyl cellulose are used[28]. Additionally, a number of synthetic polymers have been used in ASED treatment nanocarriers. They consist of poly (ethylene glycol) (PEG), poly-caprolactone, poly (lactic-co-glycolic acid) (PLGA), poly (glycolic acid), poly (acrylic acid), poly (vinyl alcohol), and polyamidoamine (PAMAM). PEG is often used in NODS as a coating material for the delivery of drugs, genes, and peptides. It is a stealthy water-soluble polymer that shields the coated nanocarrier from opsonisation and phagocytosis[29]. Hydrophobic medications have been delivered using poly (lactic acid) (PLA), a hydrophobic polyester. Its weak degradability restricts its usage in ophthalmology. To get around this, lactic acid and glycolic acid are often copolymerised to create PLGA, a more biodegradable copolymer[24].

In nanocarriers such as polymeric micelles, block and graft copolymers mixing hydrophilic and hydrophobic polymers are often used. PEG is often the hydrophilic element. Examples of copolymers used in the creation of micelles are 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[amino (polyethylene glycol)-2000] (ammonium salt) and methoxy-poly (ethylene glycol)–poly (lactic acid)[30].

Emerging ocular delivery techniques use polymeric dendrimers. With a stable hydrophilic structure that is simple to functionalise for targeted drug administration, PAMAM is the first commercialised and most widely used dendrimer in drug delivery. Poly (propylene imine), polyether-copolyester, peptide dendrimers, and PEGylated are further dendrimers[31].

Pharmaceutical active compounds

Anti-inflammatory, antibacterial, immunosuppressive, and anti-glaucoma medications are only a few of the pharmacological groups represented among the active pharmaceutical substances used in NODS[32]. For the treatment and prevention of DED, conjunctiva fibrosis, cataract, and other ocular diseases[33–36], NODS have also been used to target peptides and genes in ocular tissues. Additionally, the delivery of phytochemicals to the anterior segment of the eye using NODS has been studied[37,38]; examples include naringenin, myricetin, resveratrol, glycyrrhizin, hesperetin, curcumin, and epigallocatechin gallate.

Lipids

To create lipid NPs, lipids such as partial glycerides, triglycerides, fatty acids, waxes, and steroids are used[39]. Monoglyceride, diglyceride, and triglyceride combinations make up partial glycerides. Better drug loading and the avoidance of drug ejection brought on by lipid recrystallisation are two benefits they provide[40].

In particular, nanostructured lipid carriers made from liquid lipids are used to create nanocarriers. To get over the issues with solid lipids' poor drug loading and drug ejection, they are combined with lipids in a nanostructured lipid carrier that are solid. Oleic acid, soybean oil, castor oil, and medium chain triglycerides (such as Miglyol and Labrafac) are some of them[41,42]. They are often used in the formulation of ocular gene delivery to aid in the negatively charged gene material's adherence to the nanocarrier[43,44]. The binding of the

nanocarriers on the negatively charged ocular surface is further made easier by cationic lipids[43].

When creating liposomes, niosomes, lipid polymer NPs, and nanoemulsions, phospholipids like phosphatidylglycerol, phosphatidylcholine, phosphatidylethanolamine, and their derivatives are used[45]. Their amphiphilic properties encourage the development of lipid bilayers that resemble cell membranes, which improves drug encapsulation and stability.

Surfactants or stabilisers

Due to their amphiphilic nature, surfactants serve as formulation stabilisers. They play a crucial role in the physicochemical and biocompatibility of systems based on ocular nanotechnology[46]. Non-ionic surfactants like sorbitan esters or polysorbates are preferred in ocular nanocarriers due to their lower toxicity. Nevertheless, topical ophthalmic preparations frequently contain the cationic surfactant benzalkonium chloride as a preservative. Surfactants used often in ophthalmology include polysorbate, kolliphor, poloxamers, sorbitan esters, tyloxapol, cremophors, Transcutol P, and vitamin E TPGS (D-α-tocopherol polyethylene glycol 1000 succinate)[47].

Characterisation of medication delivery systems based on nanotechnology for the eyes

It is crucial for ocular drug delivery to characterise the distribution, particle size, encapsulation efficiency, surface charge, drug release, drug loading, stability, absorption, and safety/toxicity of the nanocarrier. Characterising the distribution, particle size, encapsulation effectiveness, surface charge, drug release, drug loading, stability, uptake, and safety/toxicity of the nanocarrier are important for ocular drug delivery. Additionally, additional ocular-specific needs, including sterility, pH, osmolality, surface tension, and viscosity, must be met by the delivery mechanism.

Particle size

The physical stability of nanocarriers is mostly determined by the particle size and polydispersity index, which are important features of nanocarriers. By using dynamic light scattering and photon correlation spectroscopy, these characteristics are often examined[48]. This approach is sensitive, rapid, and simple to utilise.

Particle size and dispersion in liquid-based formulations intended for ocular application should be optimised. Particles larger than 10nm should typically not be included in formulations intended for ocular administration[49]. Smaller, monodispersed NPs are often favoured because of their improved biodistribution profile and stability. By avoiding creaming, coalescence, Ostwald ripening, flocculation, and sedimentation during storage, they boost the stability of the nanoformulation[50]. Additionally, smaller particles enter the tear film's inner mucin layer more quickly than bigger ones. Additionally, they are more readily absorbed by ocular epithelial cells and produce less irritation[51]. Smaller NPs showed more aqueous humour absorption than larger ones, but they were also eliminated from the tear fluid more quickly[52]. Higher small particle dissolution in the tear fluid was thought to be the cause of the quick clearance. The type, concentration, and formulation techniques of excipients may all affect the particle size of nanoformulations[53].

Zeta potential

Another crucial aspect of nanoformulations is zeta potential. Due to its effect on the interaction and stability of nanocarriers with biological systems, it is one of the most investigated characteristics. Electrostatic repulsion may stabilise nanoformulations at high zeta potential levels (>30 mV). The electrostatic contact with the negatively charged ocular surface is improved by positively charged particles, however. It is important to remember that sterically stabilising particles with zeta potential values lower than 30 mV are also possible[54,55].

Surface morphology

The biodistribution, toxicity, and cellular uptake of NPs are all influenced by their surface shape[56]. NPs may take the form of spheres, cubes, or rods, among other forms. NPs with a spherical shape are preferable for enhancing medication performance[57].

The investigation of the structure of NPs often makes use of scanning electron microscopy (SEM) and transmission electron microscopy (TEM)[48,58]. While TEM displays the internal structure, size, and shape of particles, SEM displays the morphology and surface structure of the particles.

Lipid crystallinity

Differential scanning calorimetry may be used to examine the crystallinity and thermal behaviour of lipid nanoformulations[59]. Another method that is often used to examine the crystal structure of nanocarriers is powder X-ray diffractometry (PXRD)[20]. Lipid NPs' crystallinity may have an impact on their stability, release, and drug loading[59,60]. When extremely crystalline lipids are used in nanoformulations, instability problems such as drug ejection during storage result. In order to generate a less crystalline structure with greater stability and drug loading capability, a mixture of lipids is utilised[61].

Effectiveness of entrapment and drug loading

To prevent drug waste during formulation, a high drug payload is needed for nanocarriers. In order to test the effectiveness of entrapment in a nanoformulation, the unentrapped drug and the entrapped drug are typically separated using centrifugation at 10 000–20 000 rpm for 10–30 min. The drug concentration is subsequently measured spectrophotometrically or by high-performance liquid chromatography[29,62].

Drug release is sustained in nanocarriers with great entrapment efficiency. Additionally, the medication is shielded from premature metabolism and deterioration. Additionally, the ratio of drug to excipient concentration is higher, allowing for the creation of high-dose formulation[63]. Additionally, using a formulation with a high dose per unit volume helps prevent the significant alteration in the fluid dynamics of the eye caused by injecting a large volume of ocular formulation. High medication loading hence enhances biocompatibility. Medication solubility is the main factor that affects medication loading.

Drug release/permeability studies

To maintain therapeutic medication concentration and prevent toxicological consequences, drug release must be controlled in the ocular system. To achieve regulated and sustained medication release, nanocarriers are being developed and optimised[61].

Franz diffusion cells are often used in nanoformulation investigations for ex-vivo permeation and in-vitro drug release. The release medium is a phosphate buffer solution (pH 7.4), simulated or artificial tear fluid, glutathione bicarbonate Ringer's solution, human cornea construct, excised cornea (rabbit, porcine, or bovine), or whole bovine eye. The barrier membrane is a dialysis membrane (12–14 kDa as the molecular weight cut-off)[61,64]. To mimic the biological environment, the setup is continuously stirred and kept at a temperature of 37°C. By examining the concentration of medication that passed through the barrier membrane and into the receptor compartment of the release device, one may determine the total quantity penetrated per unit area. The apparent permeability coefficient and steady-state flux (Js), two additional permeability parameters, are also calculated[64].

Due to the rabbit eye's near resemblance to the human eye in terms of structure and composition of tears, in-vivo release experiments are typically conducted using rabbits[65]. One eye receives treatment with the nanoformulation, while the other acts as a control and receives treatment with regular saline. The aqueous humour is removed and its drug content is examined[66]. Other pharmacokinetic parameters are calculated[66], including the maximum drug concentration (C_{max}), the time it takes to reach the C_{max} (t_{max}), and the area under the concentration–time curve (AUC0-t).

Mucoadhesion and ocular retention

An efficient topical ocular administration method must have ocular retention or mucoadhesiveness since it significantly increases the bioavailability of medications in the eye. Researchers use fluorescence imaging, gamma scintigraphy, and surface plasmon resonance spectroscopy to evaluate the ocular retention of topically administered nanoformulations in vivo[67,68].

Stability research

When creating nanocarriers, stability problems like Ostwald ripening, flocculation, creaming, coalescence, and sedimentation are major concerns. Physical instability may be caused by lipid alteration brought on by a shift in the crystallinity of the lipids in lipid nanoformulations[69]. Analysing changes in particle size, entrapment effectiveness, and zeta potential during storage may be used to track these instability issues[69].

Toxicity research

The assessment of a new drug delivery system's biocompatibility and safety profile is crucial throughout development. Surfactants and cationic lipids are used in the formation of nanoformulations, which raises the majority of safety issues[70]. On long-term usage, several cationic lipids that are widely employed in nanoformulations might kill corneal epithelial cells[71].

Draize's test, Schimer's test, HET-CAM (method for evaluating the eye irritation properties) test, permeability and bovine opacity test, cell viability research, and histopathology investigations are only a few of the tests that have been used to look into the security of nanoformulations for ocular administration[72,73]. Inflammation, ocular heat, redness, irritation, conjunctival chemosis, and corneal opacity are symptoms of ocular intolerance and toxicity. An infrared camera may be used to evaluate an inflammatory process if the temperature of the ocular surface increases[74]. Ocular toxicity is detected in the HET-CAM test by irritation, haemorrhage, and coagulation in the chorio-allantoic membrane of a fertilised chicken egg[72]. In a cell viability research, human corneal epithelial cells are incubated with the test formulation for a period of time, following which the proportion of viable cells is counted. The cytotoxicity of nanoformulations intended for ocular use has been widely studied using this approach[41,75]. Surface tension, sterility, pH, viscosity, and other formulation requirements for eyes should all be optimised.

Clinical studies for medication delivery systems based on nanotechnology for treating illnesses of the anterior eye

Scientists working in the pharmaceutical and medication delivery fields have developed ocular nanoformulations that are now through different phases of clinical testing. Table 2 lists the nanotech medication delivery technologies for anterior eye disorders now undergoing clinical trials. A urea-loaded nanoparticulate system used as an eye drop is the subject of the Phase II clinical research known as NCT03001466[76], which is intended to cure cataracts. Polymeric NPs made of Pluronic F-127 copolymer were used to improve the effectiveness of urea. The effectiveness of urea-loaded NPs was compared to a placebo eye drop in a salt solution that was balanced. Patients in each group received one drop of eye drop five times a day for 8 weeks while receiving either urea NPs or a balanced salt solution. The difference in the patients' visual acuity scores at 6 months was then assessed.

In a clinical experiment (NCT02420834) conducted at Aston University in the United Kingdom, additional artificial tears, such as a phospholipid liposomal spray, were utilised to treat dry eyes[77]. Patients received these artificial tears as well as the liposomal spray for a month as needed after a brief wash-out time. After 4 months, symptoms were evaluated using the Ocular Surface Disease Index, a brief questionnaire. Non-invasive break-up time, parallel conjunctival folds on the lids, tear meniscus height, Phenol Red Test, and Ocular Surface Staining were also assessed as outcomes.

In November 2021, a more recent Phase III clinical study (NCT02845674) evaluating the use of 0.09% cyclosporine micellar solution to treat dry eyes was completed[78]. There were 258 participants in the research who were 18 years of age or older and of both sexes. Another clinical study for an omega-3-fatty acid-containing microemulsion to treat dry eyes is NCT02908282[79]. While Systane, a nanoemulsion based on propylene glycol, is now undergoing a Phase IV clinical study to treat dry eye condition. It is suggested that Systane will make up for any deficits in the tear film's lipid and aqueous layers. A Systane clinical research that is presently enroling volunteers intends to show that Systane Hydration lubricant eye drops minimise corneal staining in DED patients having lens replacement surgery[80]. In addition to receiving the usual post-operative care, participants will receive Systane Hydration lubricant eye drops four times per day for 2 weeks before and 4 weeks after surgery. Instead of receiving Systane Hydration lubricating eye drops, the control group will get the post-operative standard of care as determined by the investigator.

Table 2

Trials of nanomedicines in treating anterior ocular disorders are presently being conducted.

Drug/Product	Formulation	Disease	Phase	Identifier
Phospholipid	Liposome	Dry eye disease	NA	NCT02420834
Latanoprost (POLAT-001)	Liposome	Glaucoma	II	NCT02466399
Dexamethasone (OCS-01)	Nanoparticle	Inflammation, post-operative corneal pain	II	NCT04130802
Urea	Nanoparticle	Cataract	II	NCT03001466
Cyclosporine OTX-101	Nanomicelle	Dry eye disease	III	NCT02845674
Omega-3 fatty acids (Remogen Omega)	Microemulsion	Dry eye	NA	NCT02908282

On ClinicalTrials.gov, POLAT-001 and latanoprost ophthalmic solution were compared in a clinical Phase II study for patients with open-angle glaucoma and ocular hypertension (NCT02466399). There were 80 participants in this clinical experiment. After 3 months of therapy, the intraocular pressure difference between subconjunctival liposomal latanoprost (POLAT-001) and latanoprost ophthalmic solution was assessed to compare the effectiveness and safety of the two treatments.

More people are interested in creating new nanoformulations as a result of recent developments and the success of some nanomedicines for ocular diseases. However, more work has to be done to speed up the release of these nanomedicines on the market at reasonable prices.

Nano-based materials' biosafety profiles and toxicity for use in ocular medication delivery applications

Although there is a lot of information available on characterisation, ophthalmic drug delivery, formulation, and NPs targeting, there is little information available on the safety and toxicity of the materials and aforementioned systems. Prior to the licencing of ocular products for clinical research, toxicity and safety are crucial issues that are always of concern[81]. Recently, many studies in this area have been conducted. It was recommended to provide ibuprofen as an anti-inflammatory medicine by ocular injection together with NLC (nanostructured lipid carrier) and a thermoresponsive gel. For ocular administration, this nanoformulation demonstrated high biosafety, stability, and a prolonged ibuprofen release profile[82]. In a different investigation, the efficacy of administering liposome-encapsulated infliximab intravitreally to rat models of autoimmune uveoretinitis was examined. The drug's stability in the vitreous was discovered to be increased by liposomes, which also showed acceptable biosafety and a considerable therapeutic benefit in experimental autoimmune uveoretinitis (EAU)[83].

Tan *et al*.[84] also showed that chitosan-coated liposomes had higher penetrability and bioavailability (3.9 and 2 times, respectively) compared to uncoated liposomes containing merely a timolol maleate solution. Additionally, for 4 and 2 h, respectively, unmodified and chitosan-modified liposomes continuously release drugs into the eye tissues, which has a greater effect on lowering IOP. Lipid-based nanocarriers including nanoemulsions and liposomes were shown to be more biocompatible and safer to interact with biomembranes than other nanomaterials, and they demonstrated their presence in the market[2]. The safety and efficacy of Cequa in treating dry eye syndrome have been investigated. A total of 744 participants participated in phase III clinical studies with Cequa, and the research design included two randomised, vehicle-controlled, 12-week trials.

The results revealed a significantly improved Schirmer score compared to the vehicle with Cequa when two doses were taken in a day. Additionally, more than 5% of patients reported experiencing negative consequences[2]. Tacrolimus-loaded NPs based on Eudragit RL 100 was obtained for local ocular usage. Analysis of the in-vivo safety study's histopathological and ophthalmological samples revealed no evidence of eye discomfort. This research revealed slower tacrolimus release from the particles and better tacrolimus-loaded NPs reaching the eye than the solution medication[85].

A dispersion of the resolvin E1 prodrug's aqueous micelle is known as RX-10045. After cataract surgery, RX-10045 was compared to a placebo in a Phase II clinical research to assess its efficacy and safety in treating ocular inflammation and discomfort. The primary goal of clearing anterior inflammation 8 days following cataract surgery was not substantially attained with either RX-10045 formulation compared to the placebo group[86].

Using HET-CAM, Draize, and MTT (cell viability assay) analyses, fluconazole nanoemulsion in-situ gel formulation was evaluated by Samimi *et al*.[87] for its toxicity and ability to irritate retinal cells. The fluconazole in-situ gel formulation was nontoxic and may be used in the ocular tissue at the 0.1% and 0.5% doses, according to the viability test on retinal cells. Fluconazole optimised formulation was shown to be well-tolerated and non-irritating for ocular usage according to Draize and HET-CAM testing. An evaluation of the topical nanomicellar immunosuppressant formulation everolimus revealed comparable effectiveness and safety. In this research, everolimus-loaded positively charged Soluplus was used to boost ocular bioavailability for the treatment of uveitis by improving penetrability through eye epithelia with no or moderate irritation[88].

In conclusion, the safety of nanocarriers before use by patients is of great concern because of the ocular sensitivity and toxicity of the nanocarriers. The nanocarriers suitability for various clinical needs in the anterior section should still be further explored in terms of biodegradability, burst release or sustained, and patient convenience. Additionally, the biological interactions and surface chemistry of nanocarriers need to be taken into account in order to fully understand their biosafety profile[89].

Challenges in developing nano-based medication delivery devices for eye illnesses for clinical use

Drug distribution is exceedingly difficult due to the complex and diverse physiological barriers in the eye, which has led to the creation of multiple innovative delivery mechanisms. Only a very small number of these new delivery systems have been successfully marketed as nano-based drug delivery systems, despite the

numerous studies on them for the treatment of various ocular diseases[90]. Given that these nano-based delivery systems are more complicated than traditional delivery systems, the sluggish translation of NODS may be due to the lengthier, more stringent, and more costly clearance procedure[90]. The fact that animal models cannot accurately replicate human physiological characteristics is yet another significant factor in the poor clinical translation of these nanosystems[91]. Because they are simple to handle and relatively inexpensive, rodents, particularly mice, rabbits, and rats, have been widely used in many preclinical studies. The pharmacokinetic properties of these formulations have, however, been observed to significantly vary due to changes in ocular anatomy and physiology. For instance, rats' eyes are smaller than ours, and their lens-to-cornea ratio is higher.

Rabbits also produce more mucus, blink less often, and are more likely to experience ocular discomfort[3]. Additionally, the immunological makeup of the human retina differs significantly from that of the majority of preclinical studies' use of rodents. Predicting the effectiveness of clinical research based on animal-based preclinical testing is particularly difficult as a result of all of them[92].

The clinical translation of several of these medicines has also been reported to be hampered by the scaling up of the nano-based delivery systems from laboratory to big industrial scale. Scaling up nano-based delivery systems, such as NPs created using low-energy techniques like phase inversion composition, phase inversion temperature, and emulsion inversion point techniques, has been reported to result in a variety of changes to the particles' properties, particularly their physicochemical properties[2]. As a consequence, a number of high-energy techniques were developed to address the drawbacks of these low-energy processes. However, it has been noted that the formulation of NPs using high-energy techniques like ultrasonication and hot homogenisation leads to recoalescence, which in turn makes the entire system thermodynamically unstable[2]. Additionally, studies indicate that numerous techniques for creating these nano-based systems typically entail difficult multi-step processes. These techniques have extremely low repeatability and inadequate consistency. As a result, manufacturing nano-based systems is particularly difficult since doing so results in issues such as batch-to-batch fluctuations and dispersion stability, which in turn make quality control exceedingly complex[93]. According to reports, minute adjustments in a few process variables may have a big impact on the yield percentage and particle size. These variables have been shown to significantly impact the rate of drug release, the effectiveness of the system, and the pharmacological and pharmacokinetic characteristics of the active components[94]. Nano-based delivery methods are continually being developed using fresh materials that are being found. This makes it exceedingly difficult to evaluate and characterise the systems properly, which may restrict their ability to be used in clinical settings[90]. When compared to equivalent materials in the macro size range, nano-based systems' characteristics are fundamentally different due to their particle size. Therefore, the difficulty to accurately evaluate these systems' long-term safety profiles represents a significant barrier to the clinical approval of these formulations[90]. Safety testing is crucial since these devices must be nontoxic and biocompatible to the ocular system. Additionally, they must be simple to metabolise and should not build up in the eye[93]. The easy transfer from the preclinical stage to clinical trials has, however, been hampered by the complexity of nanosystems and the lack of adequate information to completely prove their biosafety and nontoxicity.

Although there are obstacles in the way of the successful clinical translation of nanotechnology-based drug carriers for ophthalmology, there is hope that many nanotechnology products will soon be approved.

A comparison between drug delivery methods based on nanotechnology and traditional delivery methods

Precision and targeting

Nanotechnology demonstrates superior performance in the realm of targeted drug administration, effectively reducing the impact on healthy tissues, a capability that is typically absent in conventional approaches[95].

Dosage and frequency

Nanotechnology has the potential to offer prolonged release capabilities, hence decreasing the need for frequent administration. This attribute can be especially advantageous in the treatment of chronic illnesses. Conventional approaches may necessitate a higher frequency of administration. The user's text is already academic and does not require any rewriting[95].

Bioavailability

Nanotechnology has been found to improve the solubility and permeability of drugs, hence resulting in enhanced bioavailability when compared to conventional approaches such as oral medications[95].

Side effects

The utilisation of nanotechnology has been found to effectively decrease systemic exposure and mitigate the occurrence of side effects in other bodily regions, in contrast to conventional approaches, which may result in more widespread side effects[95].

Complexity and cost

The use of nanotechnology-based approaches may entail greater intricacy in terms of development and production, hence potentially resulting in elevated prices when juxtaposed with conventional methods such as eye drops.

Invasiveness

The invasiveness of traditional medical procedures, such as injections and operations, tends to be greater and associated with increased hazards as compared to non-invasive techniques utilising nanotechnology.

Flexibility

Nanotechnology provides a versatile platform for the integration of pharmaceuticals and therapeutic agents, a task that may present difficulties when employing conventional approaches.

Nevertheless, the use of this technology presents some difficulties pertaining to the intricacy of its creation, its compatibility with biological systems, and the need for regulatory authorisation. Traditional therapies are often used and well recognised; however, they may not possess the same level of accuracy and

Table 3

Advantages and disadvantages of drug delivery methods based on nanotechnology and traditional delivery methods for treating eye diseases.

	Advantages	Disadvantages
Nanotechnology-based drug delivery	*Targeted Delivery*: Nanoparticles can be engineered to target specific cells or tissues within the eye, minimising off-target effects and reducing systemic exposure. *Sustained Release*: Nanoparticles allow for controlled and sustained release of therapeutic agents, reducing the need for frequent administrations. *Enhanced Bioavailability*: Nanoparticles can improve the solubility and stability of drugs, increasing their bioavailability and effectiveness. *Reduced Side Effects*: Targeted delivery reduces exposure of healthy tissues to the drug, minimising side effects. *Customisation*: Nanoparticles can be designed to carry a variety of drugs, including small molecules, proteins, and genetic material.	*Complex Development*: Designing and manufacturing nanoparticles for ocular delivery can be technically challenging and expensive. *Biocompatibility Concerns*: Nanoparticles need to be biocompatible to avoid adverse reactions in the eye. *Regulatory Hurdles*: Gaining regulatory approval for new nanoparticle-based treatments requires extensive testing and validation.
Conventional eye disease treatments	*Established Methods*: Conventional treatments like eye drops, ointments, and injections are well-established and widely used. *Immediate Effects*: Some treatments provide rapid relief from symptoms or halt disease progression. *Familiarity*: Healthcare providers and patients are more familiar with traditional treatment methods. *Lower Cost*: Conventional treatments are often less expensive compared to developing and producing nanotechnology-based therapies.	*Limited Targeting*: Conventional treatments might not effectively target specific cells or tissues, leading to potential side effects and reduced efficacy. *Frequent Administration*: Some treatments require frequent administrations due to short duration of effect, leading to patient inconvenience and non-compliance. *Systemic Exposure*: Drugs delivered via conventional methods can enter the systemic circulation, causing systemic side effects. *Low Bioavailability*: Poor drug solubility and rapid clearance from the eye can lead to low drug bioavailability.

effectiveness as methods based on nanotechnology[96]. The selection between the two methodologies frequently relies on the particular ocular ailment, the intended treatment result, and the trade-off between advantages and probable consequences. Table 3 illustrates the merits and demerits of medication delivery techniques based on nanotechnology in comparison to conventional administration methods in the context of treating ocular ailments.

In summary, the utilisation of nanotechnology in medicine delivery for the treatment of ocular ailments has several advantages, including heightened accuracy, focused administration, diminished adverse effects, and the possibility of increased therapeutic results. Nevertheless, it is plausible that the development of these procedures might entail greater intricacy and financial investment when juxtaposed with conventional approaches. The selection between the two methodologies is contingent upon the particular ailment, the pharmaceutical agent employed, and the equilibrium between accuracy and feasibility.

Complications of nanotechnology-based drug delivery for the treatment of eye diseases

The use of nanotechnology in drug delivery exhibits significant potential in the management of diverse ocular ailments, owing to its capacity to provide precise and regulated administration of therapeutic substances. Nevertheless, similar to every medical intervention, there exist possible problems and obstacles linked to this particular method. Several challenges arise when considering the application of nanotechnology-based medication delivery systems for the treatment of ocular disorders, including[97,98].

Biocompatibility and toxicity

Biocompatibility and toxicity are critical considerations in the field of nanotechnology, particularly in relation to the materials employed, such as NPs, liposomes, and dendrimers. It is imperative that these materials exhibit biocompatibility and do not have any deleterious effects on ocular tissues. The presence of any possible toxicity within the ocular environment has the potential to induce inflammation, cause damage to cells, or result in other unfavourable outcomes. The user's text is already academic and does not require any rewriting[99].

Immunogenicity

The introduction of NPs into the ocular region has the potential to elicit an immunological response, so instigating inflammation and posing a risk of detrimental effects on the adjacent tissues. The potential consequences of this situation may undermine the efficacy of the treatment and give rise to undesired adverse reactions. The user has provided a numerical reference without any accompanying text or context[100].

Accumulation and clearance

The potential for NPs to amass in the eye over time is contingent upon their clearance efficiency. The persistence of accumulation over an extended period may lead to adverse consequences, including elevated intraocular pressure or compromised visual function[101].

Retinal detachment

Retinal detachment may occur as a consequence of introducing NPs or other delivery methods into the eye, resulting in the separation of the retina from the underlying tissue layers. The aforementioned condition may lead to a loss of visual acuity and necessitates prompt medical attention.

Barrier penetration

The human eye possesses inherent physiological barriers that serve to impede the entry of exogenous agents, such as the blood–retinal barrier and the corneal epithelial barrier. The problem lies in ensuring the effective penetration of NPs through these obstacles in order to reach the desired target spot.

Unintended effects on healthy tissues

NPs have the potential to mistakenly impact healthy tissues located inside the ocular region, resulting in unforeseen ramifications. For instance, the use of NPs engineered to selectively target particular cells may inadvertently affect neighbouring cells and surrounding tissues.

Dosage regulation

The regulation of dose is of utmost importance in ensuring the optimal administration of therapeutic agents by NPs. Excessive dosage may result in harmful effects, whilst insufficient dosage may fail to yield the intended therapeutic outcome.

Patient variability

The efficacy and safety of nanotechnology-based medication delivery can be influenced by patient variability, which encompasses individual differences in ocular architecture, physiology, and health. The feasibility of finding a solution that is universally applicable may be limited.

Long-term effects

The comprehensive understanding of the long-term consequences associated with the introduction of NPs into the ocular region remains incomplete. It is important to do research on the effects of long-term exposure and extended treatment protocols in order to evaluate possible hazards.

Regulatory approval

The process of introducing nanotechnology-based medication delivery systems to the market necessitates thorough examination and adherence to regulatory protocols. The process of establishing safety and efficacy through clinical trials may be intricate and time-intensive.

Cost and accessibility

The cost and accessibility of nanotechnology-based medicines pose significant challenges, particularly in places with low resources, as their development and production might incur substantial expenses.

The potential of nanotechnology-based drug delivery in the treatment of eye diseases is promising. However, the successful management of potential complications associated with this approach necessitates comprehensive research, rigorous testing, and close collaboration among researchers, clinicians, and regulatory agencies. These measures are crucial to guarantee the safety and efficacy of treatments for patients.

The use of nanotechnology in drug delivery systems has considerable potential in the management of ocular disorders, as it offers the ability to augment therapeutic effectiveness, mitigate adverse reactions, and boost patient adherence. Nevertheless, there exist many obstacles that must be overcome in the advancement and execution of nanotechnology-driven medication delivery systems for ocular ailments. These hurdles include concerns pertaining to safety, regulatory clearance, scalability, and cost-efficiency. However, continuous research and improvements in this particular subject present great opportunities for enhancing the management and treatment results of diverse ocular conditions.

Conclusions and outlook for the future

Effective treatment of anterior ocular degeneration remains challenging due to limitations in the anterior eye region. To address this issue, research should focus on developing safer, less toxic, stable, and effective nanoformulations for drug delivery to the anterior eye segment. These formulations should deliver small molecules and biologics with better pharmacokinetic and pharmacodynamic properties. Combining ocular active drugs with enzyme inhibitors can improve ocular absorption and bioavailability. NPs should be able to deliver medications to various eye tissues while maintaining biodegradation and patient comfort. Further research should focus on the role of viscosity and permeability enhancers in increasing ocular bioavailability. Emerging technologies like hydrogel template technology, mucus-penetrating particles, and particle replication in non-wetting templates can improve the overall efficacy of ocular medications. Future research should consider all potential applications for nanoformulations and address stability problems like particle growth.

Ethical approval

This paper has not been published anywhere else, and no under journals are considering publishing it. The writers affirm that there are no moral problems with the manuscript's publishing.

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Author contribution

M.T.O.K.: conceptualisation, data curation, and writing – original draft preparation, reviewing, and editing; Z.A.: writing – reviewing and editing, visualisation, and supervision; I.B.A.: writing – reviewing and editing, visualisation, supervision, and preparation; S.Z.: data curation, writing – original draft preparation, reviewing, and editing; A.B.A.: data curation, writing – original draft preparation, reviewing, and editing; H.H.: writing – reviewing and editing, visualisation, and supervision; A.A.A.: data curation, writing – original draft. The study's inception and design included contributions from all authors. All authors evaluated and approved the final draft.

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