



# Hopes and hurdles of nanogels in the treatment of ocular diseases

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## ABSTRACT

Drug delivery to the eye faces various challenges in the form of physiological (blinking, nasolacrimal drainage), anatomical (static and dynamic), and metabolic barriers. Drugs injected systemically are not able to cross the blood-retinal barrier into the retina. Nanocarrier-loaded *in situ* gels have gained popularity in the drug delivery system for their targeted administration and stimuli-responsive behavior. Nanogels emerged as an innovative approach over the conventional treatment for ocular drug delivery, by providing dual benefits of hydrogels and nanoparticles (NPs) in one dosage form. Nanogels are polymer-based 3-D hydrogel materials. Nanogels can be designed in the form of *in-situ* nanogels to exhibit sensitivity toward internal and external stimuli, such as light, temperature, pH, redox, and ionic strength, for controlled drug release. In addition, the incorporation of NPs in the gel decreases the burst release issues associated with NPs. *In-situ* gels are liquid during administration to the eye and get rapidly converted in the *cul-de-sac* of the eye into a gel form that releases the drug gradually. This article is going to review *in-situ* nanogels and their applications in the treatment of ocular diseases. In addition, the challenges as well as the progress made by nanogels in ocular delivery are also reviewed in detail.

## INTRODUCTION

The human eye is a complex organ with a unique structure and physiology that prevents medications from reaching specific ophthalmic areas. The challenging task is to increase medication residence time and ensure proper ocular penetration [1]. The issues with conventional ocular drug delivery include short contact times of the drug in the eye and poor ocular bioavailability (BA) as a result of solution drainage, tears turnover, and dilution or lacrimation [2]. Due to different anatomical and physiological barriers, only 1% or even less of the administered dose of the drug reaches the intraocular tissues, which lowers the absorption of the drugs. Topical dosage forms need to maintain a balance between lipophilicity and hydrophilicity as well as longer contact times for better therapeutic outcomes [3]. All these drawbacks of conventional methods can be overcome by nanotechnology.

By delivering precise medications to specified locations and targets, nanotechnology provides numerous advantages in the treatment of chronic human diseases [4]. The emergence of nanoformulation results in the ability to surpass ocular barriers, improve drug residence time on the cornea surface, boost permeability and BA of the medication, reduce degradation of unstable drugs, and be well tolerated by the patient compared to the conventional drug [5]. With a compound annual growth rate of 6.9% from 2023 to 2030, the market for ocular drug delivery in India is expected to increase from its estimated value of 0.9 billion USD in 2022 to 1.5 billion USD by 2030 [6]. It has been established that nanosized formulations can improve medication retention/permeation and extend drug release in ocular tissue [7]. Some common eye ailments or diseases include glaucoma, cataracts, ocular surface infections, inflammation, dry eye syndrome, diabetic retinopathy (DR), diabetic macular edema, age-related macular degeneration (AMD), and retinal vein occlusion [8]. Ocular drug delivery systems are employed to administer drugs to the eyes for the treatment of various disorders that affect vision [9,10]. Various dosage forms for ophthalmic preparations include liquid, semi-solid, or solid for example eye drops, suspensions, ointments, creams, emulsions, contact lenses, and ocular inserts. The anterior region of the eye

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absorbs medication through eye drops, but short residence time prevents the proper absorption of drugs from eye drops [11]. The ocular residence time can be greatly improved by the creams and ointments (semi-solid), however, they may cause blurred vision [12]. Ocular gels are one technique to extend the residence time of drugs at the precorneal level and, their BA. Ocular gels are formed of a 3-D cross-linked polymer or a colloidal network submerged in a fluid [13]. The *in-situ* gelling system is among the most intriguing methods for lengthening the period that medications remain on the surface of the eye [14]. Temperature, pH, and ions are some examples of internal stimuli that can trigger gelation [15]. The easy method of preparation, simple administration, and exact dose distribution are some advantages of the *in-situ* gelling system [16]. Drugs can be delivered to ocular targets using nanoparticulate drug delivery devices [17]. The current study focuses on the applications of nanogels in the treatment of various ocular diseases. It provided a thorough description of nanogels from various angles, including ideal characteristics, approaches, applications, upcoming trends, formulation challenges, and future prospects.

#### **Ideal characteristic of *in-situ* gels for ocular drug delivery**

The successful treatment of a disease depends on the ideal requirement from the formulation. A perfect *in-situ* gelling drug delivery formulation should meet the requirements listed below. Some crucial factors that must be required in ocular drug delivery are discussed here [18,19].

#### ***Gelation (transition of phase from sol-gel)***

Under physiological circumstances or in the presence of the trigger for gelation, the formulation should be supplied as a solution that is converted immediately into a gel to avoid precorneal drainage [18].

#### ***Optimal pH***

The pH of the formulation should be the same as that of eye pH, i.e., formulations that have slight changes in pH either acidic or alkaline can irritate or harm ocular tissues [20].

#### ***Clarity***

The formulation must be transparent, clear, and colorless. Normal vision should not be hampered by it. Any contaminant, such as particles, ought to be absent because they could irritate the ocular tissues [21].

#### ***Adhesiveness***

The formulation must adhere to the eye's precorneal surface to provide longer residence time and absorption [22].

#### ***Isotonicity***

Isotonicity should be maintained to avoid eye discomfort or tissue damage [22].

#### ***Ocular tolerance***

The polymers in the formulation should be well-tolerated and biocompatible with the ocular tissues. There should not be any tissue damage brought on by the formulation,

including inflammation, redness, edema, or any other unfavorable side effects [23].

#### ***Reproducibility***

The formulation must exhibit the same characteristics on repeated preparation and massive manufacturing. An *in-situ* gelling device is best for consistent administration when it is a free-flowing liquid [23].

#### ***Rheological properties***

The two most important requirements for an *in-situ* gelling system are viscosity and gel strength. The formulation must have the right amount of viscosity for convenient administration and a fast transition from sol to gel. In addition, the gel that is produced must reside over time without disintegrating or degrading. *In-situ* gels usually show pseudoplastic flow. It is preferable to utilize viscoelastic fluids with high viscosities at low shear rates and low viscosities under high shear rates because certain areas endure extremely high shear rates and tissue movement [23].

#### ***Drug content***

The formulation must have high drug content without any chemical degradation or unfavorable interactions with the polymers or other excipients [22].

#### ***Sustained drug release***

The *in-situ* gelling system should release the drug over extended periods to generate the best BA with the fewest side effects [22,23].

### **OCULAR GELS**

Ocular gels are simple viscous dosage forms that remain unchanged after injection. They can reside for a longer time in the eye in comparison to normal liquid eye drops. However, they are difficult to administer and can result in vision impairment, crusting on the eyelids, and tearing while preventing accurate and reproducible drug delivery [24]. Therefore, ocular gels are primarily used as tear substitutes in the treatment of dry eye [25]. The designing of a novel strategy for safe, easy, and efficient ocular drug delivery is a serious matter that necessitates innovative approaches [26]. In recent years, several novel techniques utilizing various tactics have been created to enhance the ocular delivery system [27]. The ocular *in-situ* gel has drawn the most attention over the past few years. The *in-situ* gel system is designed as a liquid preparation that can be injected into the eyes and, when exposed to the physiologic environment of the body, transforms into an *in-situ* gel [28]. This increases the precorneal residence time of the formulation and improves the ocular BA of the drug [29]. Table 1 highlighted some ocular liquid gels.

### **IN-SITU OCULAR GELS**

Drug delivery systems known as *in-situ gels* undergo *in-situ* gelation after being injected into the body and release the drug over a prolonged or regulated period [30]. This gelation is caused by stimuli like temperature, pH, and other factors [18]. *In-situ*, ocular gels are low-viscosity liquids that transform into viscoelastic

**Table 1.** List of ocular hydrogels.

Brand	Therapeutic agent	Gelling agent	Application	Company	Market status	Reference
ReSure® Sealant	Phosphate and borate salt solutions	Polyethylene glycol	Cataract surgery	Ocular Therapeutix	Marketed	[75]
Lumecare®	Sodium hyaluronate	Carbomer 980	Dry eye syndrome	Medicom	Marketed	[76]
Viscotears® liquid gel	-	Carbomer 980	Dry eye syndrome	Bausch and Lomb UK Limited	Marketed	[77]
Xailin Gel®	Hyaluronate de sodium	Carbomer 980	Dry eye syndrome	VISU Farma	Marketed	[78]
Clinitas Gel®	Cetrimide	Carbomer 980	Dry eye syndrome	Altacor	Marketed	[79]
GelTears®	-	Carbomer 980	Dry eye syndrome	Bausch & Lomb	Marketed	[80]
Liquivisc®	-	Carbomer 974P	Dry eye syndrome	Laboratoires Thea	Marketed	[81]
Tiopex®	Timolol Maleate	Carbomer 974P	Glaucoma	Laboratoires THEA	Marketed	[82]
Timoptic® GFS	Timolol maleate	Xanthan gum	Glaucoma	Falcon	Marketed	[83]
Timoptic-XE®	Timolol maleate	Gellan gum	Glaucoma	Merck	Marketed	[84]
Pilopine HS®	Pilocarpine hydrochloride	Carbopol 940	Glaucoma	Alcon Laboratories	Marketed	[85]
AktenTM®	Lidocaine hydrochloride	Hypromellose	Ocular anesthesia	Akten	Marketed	[86]
Zirgan®	Ganciclovir	Carbomer 974P	Acute herpetic keratitis	Sirion Therapeutics	Marketed	[87]
OTX-TKI	Axitinib	PEG	AMD	Ocular Therapeutix	Phase I clinical trial	[88]
OTX-IVT	Aflibercept	PEG	AMD, DME, and RVO	Ocular Therapeutix	Preclinical	[89]
Dextenza®	Dexamethasone	4-Arm PEG N-hydroxy succinimidyl glutarate (20 K)	Post-surgical ocular inflammation and pain	Ocular Therapeutix	Marketed	[90]
DuraSite®/Azasite®	Azithromycin	Poloxamer 407, polycarophil	Bacterial conjunctivitis	Inspire Pharmaceuticals	Marketed	[91]
Virgan®	Ganciclovir	Carbomer 974P	Acute herpetic keratitis	Laboratoires THEA	Marketed	[92]
ACUVUE® Theravision™ with Ketotifen	Ketotifen	Etafilcon A	Vision correction and allergic eye itch	REGENERON Johnson & Johnson Vision	Approved	[93]

gels in the conjunctival *cul-de-sac* as a result of conformational changes in polymers in reaction to the physiological environment [31]. *In-situ* gels are liquids in the rest and get converted quickly into the gel in the eye's *cul-de-sac* in reaction to environmental changes to generate viscoelastic gels [32]. The fluid system of the eye creates a solution or weak gel before instillation in the eye and before a strong gel forms, therefore, the rate at which *in-situ* gel develops is essential [17]. *In-situ* gels can be formulated using both natural and artificial polymers [33]. A wide variety of drug molecules and materials of therapeutic advantages such as antibiotics (ofloxacin, ciprofloxacin, and gatifloxacin), beta-blockers (timolol and carteolol), Non-steroidal anti-inflammatory drugs (NSAIDs) (ketorolac tromethamine and indomethacin), pilocarpine hydrochloride, puerarin, recombinant Recombinant Human Epidermal Growth Factor (rhEGF), and antivirals (acyclovir) has been delivered through *in-situ* gelling systems. Table 2 summarizes some marketed ocular *in-situ* gels and their applications.

#### Approaches of *in-situ* gelling system

The *in-situ* gelling system works on the stimuli response [19]. The major stimuli for *in-situ* gels are temperature, pH, and ions.

#### Temperature-induced gelling system

Temperature-induced *in-situ* gels are liquid at room temperature (20°C–25°C) and get converted to the gel due to the higher temperature (35°C–37°C), at the application location. At a critical temperature, such as the lower critical solution temperature or upper critical solution temperature, temperature-sensitive hydrogels either go through a volume phase transition or a sol-gel phase transition. The polymer gradually dissolves and micellar aggregation increases, at high temperatures to give sol-to-gel transformation (the entanglement of the polymeric network) [34,35].

#### pH-induced gelling system

pH-induced *in-situ* gels are polymeric dispersions in aqueous systems that spontaneously gel after application at the target site in response to a change in pH [36]. The polymer undergoes inter-diffusion due to electrostatic, hydrophobic, and hydrogen bonding interactions at a particular pH [37]. The phase transition of the carbopol solution occurs at a pH range of 4.0–7.4 due to the ionization of the carbopol polymer.

#### Ion-activated gelling system

The sol-to-gel transition is triggered in this form of *in-situ* hydrogel by the presence of monovalent or divalent cations such

**Table 2.** List of approved ocular *in-situ* gels.

Marketed formulation	Drug	Polymer	Application	Type	Company	Reference
Virgan	Ganciclovir	Carbopol® 974	Viral infection	pH-triggered	Laboratoires THEA-France	[47]
Timoptol-LA	Timolol maleate	Gellan gum	Glaucoma	Ion-activated	Laboratories Merck Sharp and Dohme	[47]
AzaSite	Azithromycin	Poloxamer 407	Bacterial infection	Temperature-triggered	InSite Vision	[94]
Akten®	Lidocaine hydrochloride	HPMC	Local anaesthetic	Temperature-triggered	Akorn Inc., Lake Forest, IL	[86]
Pilopine HS®	Pilocarpine hydrochloride	Carbopol 940	Glaucoma and reduced intraocular pressure	pH-triggered	Alcon laboratories, inc. USA	[85]
Timoptic-XE®	Timoptic-XE® (Timolol maleate)	Gellan gum	Ocular hypertension	Ion-induced	Merck Pharmaceuticals, USA	[95]
Cytoryn	Interleukin-2 (IL-2)	Triblock copolymer	Peritumoral	Regel system (diffusion)	Macromed	[96]

as Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, and Mg<sup>2+</sup> ions. The formulation is administered as a liquid solution into the *cul-de-sac*, and the electrolytes of the tear fluid, particularly Na<sup>+</sup>, Ca<sup>2+</sup>, and Mg<sup>2+</sup> cations, induce gelation of the polymer. Cross-linking occurs between cations and negatively charged polysaccharides [38].

## OCULAR NANOGELS

Compared to pure gel, nanogels combine the properties of nanoparticles (NPs) and gel to provide high adhesiveness and BA [39]. Various drugs have been incorporated into gels for ocular administration as given in Table 3. NPs are nanosized particles of biodegradable components. Nanogels can be created using a variety of synthetic and natural polymers, including Poly Lactic Acid (PLA) and poly(lactic-co-glycolic acid (PLGA), as well as natural polymers such as chitosan and alginate [40]. Both hydrophilic and hydrophobic drugs, as well as charged solutes and other diagnostic tools, can be administered using nanogels. The drug loading in nanogels is relatively high because of the functional groups present in the polymeric network. The drug may be integrated into the matrix or bonded to the surface. For a decade, nanotechnology has demonstrated promising outcomes for the delivery of ocular medications [41]. The minute size of NPs is a very positive trait for their potential to reduce irritation in ocular tissue and to sustain drug delivery without needing repeated doses [42]. The size and surface characteristics of NPs are the primary factors influencing the penetration of NPs into the eye [33]. The capacity of modern nanotechnology-based carriers to entrap both hydrophilic and lipophilic medicines, good ocular permeability, prolonged residence time, good drug stability, and high BA are some key advantages to adopting this technique for ocular delivery [43,44].

NPs with a size between 200 and 2,000 nm are capable of being taken up effectively and kept by the tissues where they have been kept for up to 2 months [24]. The incorporation of NPs with hydrogel provides the desired drug levels at the retina [45].

## IN-SITU OCULAR NANOGEL

The term “nanoparticle-loaded *in-situ* gel” refers to the combination of two drug delivery techniques, namely NPs and *in-situ* gel [4]. Both integrating the drug during NP creation

or adsorbing the drug after NP formation by incubating them in drug solution are effective ways to achieve drug loading in NPs [46]. The incorporation strategy is more effective than the latter one since it traps a significant amount of the medication. For ocular administration, drug-loaded NPs are added to the gels [47]. The transport of drugs into the eye is limited by the blood–retinal barrier, corneal barrier, and tear film barrier [48]. It is significantly more difficult to deliver drugs to the posterior segment because of the shape and complicated physiology of the eye. Typical ophthalmic formulations cannot give and maintain an acceptable drug concentration in the retina [21]. *In-situ*, gelling systems are gels that are administered as a solution and change into gels at the ocular surface. *In-situ* gelling systems often experience reversible sol-gel phase transitions [22]. The idea of a NP has significantly grown in popularity during the past few decades. Recently, there has been an increase in interest in producing nanogels, which provide researchers with vast and new prospects for a variety of biological and pharmacological applications by fusing the benefits of NPs and hydrogels [49]. One might achieve optimal drug loading and controlled release for effective peroral, rectal, vaginal, ophthalmic, and transdermal drug administration by modifying a biodegradable nano gel technology and fine-tuning its composition [50]. Also, the basic components can be easily purchased and the nanogels can be generated on an industrial scale, offering a high cost-benefit ratio. Most importantly, to lessen the undesirable toxicity, nano gel particles can be quickly eliminated from the body after therapy by renal excretion and/or enzymatic destruction. Nano-gelling systems are excellent at speeding up corneal penetration and increasing ocular BA. These nanogels are replete with NPs [51]. Various research focused on NPs-loaded ocular *in-situ* gels has been given in Table 4. The limitations of nanotechnology include large-scale manufacturing, and limiting the dosages of medications [52].

## Application of *in-situ* nanogels in ocular drug delivery

### NPs loaded *in-situ* gels for bacterial keratitis

Antibiotics administered topically can cure ophthalmic infections more effectively. Various strategies, such as

microparticles, gels, micelles, liposomes, gel-forming solutions, NPs, and nanoemulsions (NEs), have been used to extend the stay of drugs in the cornea. Reducing nasolacrimal drainage is one of the most promising methods for lengthening the residence time at the ocular surface [53]. Often, this is accomplished by raising the vehicle's viscosity. Moreover, ocular inserts may offer improved drug residency at the ocular surface. However, the foreign body experience from the ocular implants results in low patient compliance [54]. As an alternative, *in-situ*, gel-forming solutions have emerged as one of the most promising methods for lengthening the period that drugs remain in the eye without having any negative side effects [11]. When applied in the form of solutions, *in-situ* gel-forming substances go through a sol-to-gel transition once they reach the eye. Several mechanisms, such as changes in pH (pH-sensitive gel), changes in temperature (thermosensitive gel), and ionic strength, can cause the gel to develop (ionic gelation) as shown in Figure 1 [55]. Polymeric solutions that transform from a solution to a gel when subjected to temperature variations are known as thermoresponsive gelling systems. At body temperature, some organic and synthetic polymers exhibit thermoresponsive gelling characteristics. In a research chitosan-based thermoresponsive hydrogels were introduced into rabbit eyes for the sustained administration of latanoprost and ferulic acid [56].

Hydrocortisone-loaded PLGA NPs included in thermoresponsive *in-situ* gel showed increased ocular BA [57]. Increased precorneal residence duration and enhanced ocular BA were found for sparflaxacin-loaded PLGA-NPs integrated with pH-sensitive *in-situ* gel [35]. Ganciclovir prodrug-loaded PLGA-NPs in thermoresponsive PLGA-PEG *in-situ* gel showed improved efficacy for corneal keratitis [58]. Polyacrylic acid (PAA) is a frequently used safe and mucoadhesive ocular polymer because of its nonabrasive and flexible nature. Poloxamers are biocompatible synthetic amphiphilic polymers

with good thermoresponsive properties [59]. Furthermore, poloxamer solutions can create transparent gels that do not hinder normal eyesight. The Food and Drug Administration (FDA) has authorized the use of poloxamer 407 as an "inactive ingredient" in a variety of products, including intravenous, solutions, suspensions, inhalation, and ophthalmic formulations [60].

#### *NPs loaded in-situ gels for the treatment of cataract*

Cataract is the most common ocular condition and the major cause of blindness in people worldwide. In cataracts excessive lens and tissue collapse are caused by crystallin aggregation. Genetic predisposition, aging, toxic chemicals, exposure to UV light, oxidative stress, metabolic problems, hereditary mutations, and diabetes are some risk factors for the development of cataracts. Surgery is the most effective method of cataract prevention in clinical settings because there are currently no anti-cataract medications on the market. However, recent studies have shown that lanosterol (Lan), a crucial early rate-limiting step in the biosynthesis of cholesterol, interfered with the aggregation of D-crystalline by interacting with the hydrophobic dimerization interface in individuals and it was a significant factor in the prevention of cataract development in animal models [61]. The application of drugs in the form of *in situ* nanogels would be a promising approach for the treatment of cataracts.

#### *NPs loaded in-situ gels for the treatment of glaucoma*

Retinal ganglion cells loss, excavation of the optic disc, and progressive visual field loss are symptoms of glaucoma, an age-related optic neuropathy [3]. The primary risk factor for the onset and progression of glaucoma is intraocular pressure. Although all medical and surgical treatments lower intraocular pressure. However, in certain glaucoma patients, uncontrollable intraocular pressure (IOP) continues to cause rapid vision loss

**Table 3.** Nanogel for ocular delivery.

Excipients	Therapeutic agent	Type of formulation	Preparation method	Application	Key findings	References
Cyclodextrin	Dexamethasone	Nanogel	Emulsion-solvent evaporation	Ocular infections	Increased the ocular BA and gave high dexamethasone concentrations in the aqueous humor for at least 3 hours after administration of the eye drops.	[97]
Chitosan, poly (HEMA)	Timolol maleate	Diamond nano gel	Spontaneous cluster formation	Glaucoma	Showed sustained drug release, biocompatible and stable, retention of NDs	[98]
Carbopol 934, Pluronic F127, HPMC and Benzalkonium Chloride	Flurbiprofen	Thermosensitive <i>in-situ</i> nanogel	Anti-solvent precipitation method	Miosis	Good stability revealed that <i>in situ</i> gels comprehend the combination of Pluronic-F127 (14%) and carbopol (0.3%) polymer enhance the precorneal resident time.	[99]
Chitin	Fluconazole	Nanogel	Controlled regeneration chemistry method	Corneal fungal infection	<i>Ex-vivo</i> corneal permeation studies showed effective penetration and retention of the fluconazole nanogels to the deeper sections of the cornea.	[100]
Polyvinylpyrrolidone and acrylic acid	Pilocarpine	Nanogel	$\gamma$ radiation-induced polymerization	Open-angle and chronic glaucoma	Showed improved stability and BA of pilocarpine	[40]

**Table 4.** List of NPs loaded ocular *in-situ* gels.

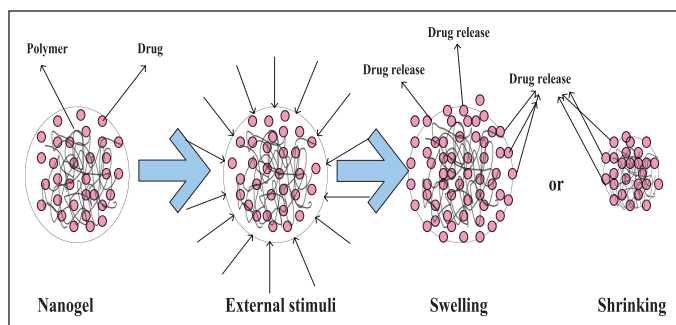
Drug	Formulation	Excipients	Method of preparation	Application	Key findings	References
Oxytetracycline-HCl	NPs integrated thermoresponsive <i>in-situ</i> gel	Poloxamer-N407, PAA, gelatin type B, polyvinyl alcohol (PVA)	Cold method	Bacterial keratitis	Increased poloxamer concentration resulted in a viscous and stable gel	[53]
Sparfloxacin	NPs loaded <i>in-situ</i> gels	PLGA, PVA, chitosan	Nanoprecipitation technique	Bacterial conjunctivitis	Showed extended-release with better tolerability, and prolonged retention at the corneal site	[101]
Ganciclovir	Prodrug-loaded PLGA-NPs thermosensitive <i>in-situ</i> gels	PLGA, PEG	Emulsion solvent evaporation method	Corneal keratitis	Longer residence time and <i>in vitro</i> , release of prodrugs from NP showed a biphasic release	[102]
Lanosterol	Thermosensitive <i>in-situ</i> gels	Lan powder, 2-hydroxypropyl- $\beta$ -cyclodextrin, 0.5% MC	Bead mill method	Cataract	Increased ocular residence time	[103]
Dorzolamide	<i>In-situ</i> gel of chitosan NP	Chitosan, sodium alginate, mannuronic, guluronic acid	Iontropic gelation method	Glaucoma	Showed sustained release of drug with good gelling properties	[64]
Triamcinolone acetonide (TA)	Solid lipid NPs	Glyceryl behenate, glyceryl monostearate, Pluronic® F-68, Tween® 80, gellan gum	Hot homogenization and ultrasonication method	Diabetic macular edema	Showed improved permeability and stability	[104]
Lutein	NE <i>in-situ</i> gel	Gellan-gum, Lipoid E80, Medium chain triglyceride, Poloxham 188, Glycerol,	Solvent evaporation method	AMD	Prolonged retention time	[67]
Fluorometholone	(Thermosensitive gels) Polymeric PLGA-loaded NPs in <i>in-situ</i> gels	Poloxamer 188, MC, benzalkonium chloride, sodium alginate, guluronic and mannuronic acid	Solvent displacement method	Anti-inflammatory	Improved the precorneal residence time reflected in the ocular BA	[105]
Moxifloxacin	Nanostructured lipid carrier enriched <i>in-situ</i> gel	Poloxamer-188, glyceryl monostearate, Capmul mixture	Hot homogenization ultrasonication method	Endophthalmitis	Showed increased corneal residence time, as well as improved therapeutic activity.	[106]
Brinzolamide	NE	Poloxamer 407, poloxamer 188, glycerol triacetate	Emulsification method (low energy method)	Glaucoma	Showed good gelation capacity and adequate spreadability	[107]
DIS	NPs	Mannitol, MC	Dispersion method	DR	Showed good solubility of DIS by the reduction in particle size and improved viscosity	[69]

even after therapeutic IOP reduction [62]. Innovative drug delivery techniques, such as *in-situ* gels filled with NPs, have greatly increased the medication's ocular BA [63]. *In-situ*, gel-containing NPs loaded with dorzolamide hydrochloride offered a more intensive glaucoma treatment and higher patient compliance because it requires fewer applications daily than traditional eye drops [64].

#### **NP-loaded *in-situ* gel for the treatment of AMD**

AMD, the world's leading cause of blindness, affects millions of people over 65. As the population ages, it is predicted that this degenerative sickness will become more common, creating an unmet medical need [65]. Although the pathogenic mechanism underlying AMD is not yet fully understood, oxidative stress is known to play a substantial role in AMD

pathology. The retina uses a lot of oxygen, making it vulnerable to damage from oxidative stress [66]. Lutein is a carotenoid with a molecular weight of 568.85. It is soluble in organic solvents and has high lipophilicity despite having a low solubility in water (0.000732 mg/ml, log P 7.8). Because of its ability to quench singlet oxygen and eliminate free radicals, lutein is commonly used as an antioxidant to protect the retina from harm caused by oxidative stress. In addition, lutein can filter out UV and blue rays, which are harmful to the retina. Furthermore, the amount of lutein in the macular region is related to the pathogenesis of AMD since it is the main component of human retinal macular pigment. The optical density of the macular pigment can be increased in patients' retinas to prevent and treat AMD. Lutein, in general, can treat AMD either by reducing reactive oxygen species, increasing the optical density of the macular pigment,



**Figure 1.** Mechanism of stimuli-responsive nanogel.

and/or reducing the quantity of damaging light that enters the retina. To reduce the precorneal loss caused by the medication, an *in-situ* gel was created [67]. Cell-penetrating peptides are short, less than 30 amino acid peptides that quickly and without the need for receptors bind to cells. A homologous domain generates penetratin, a peptide that enters cells. According to studies, it has a strong ability to enter the eye and can carry medications to the retina. Stearyl penetratin (ste-penetratin) was added to the NE to boost penetration using a noninvasive delivery approach. To increase the period of corneal retention and let the penetratin work to its full potential, an ion-responsive *in-situ* gel of penetratin-NE was developed [67].

#### ***NPs loaded in-situ gel for the treatment of DR***

Major global public health concerns today include the treatment and prevention of diabetes mellitus (DM), which is predicted to affect 4.4% of patients by 2030. Prothrombotic conditions with poor coagulation, platelet dysfunction, and endothelial dysfunction develop in DM patients. Nephropathy, neuropathy, and microvascular issues are the early signs of diabetes complications. DM is characterized by DR. DR is one of the most prevalent microvascular issues in persons with diabetes [68]. It is distinguished by retinal capillary cell death, malfunction of the glia and neurons, artery blockage, vascular leakage, and visual loss that may result in blindness. The alcoholic syndrome is treated with disulfiram (DIS), a dimer of diethyldithiocarbamate. The administration of DIS to the retina has been demonstrated to be effective in treating DR's retinal impairment. To further enhance the ocular BA, NPs and an *in-situ* gelling method were combined. It was found that increased the ocular BA by using methylcellulose (MC) as the *in-situ* gelling agent. These high ocular BAs enable medicines to reach the retina [69].

#### ***Retinoblastoma***

The most frequent primary malignant intraocular tumor in children, retinal blastoma (Rb), arises from retinal stem cells. Most children survive Rb with the help of systemic chemotherapy, but they frequently lose their vision or require ocular enucleation [70]. The administration of local anticancer drugs would be helpful to raise the local drug concentration and reduce chemotherapy's negative side effects concerning the pure availability of the target tumor by systemic chemotherapy [70]. The current study describes a novel hydrogel implant that can deliver low molecular weight hydrophilic anticancer medicines

topotecan and vincristine at therapeutically effective quantities. The proposed hydrogel implant consists of two layers: an inner hydrophilic layer made of 2-hydroxyethyl methacrylate (HEMA) that acts as a reservoir for the chemotherapy agent and an outer hydrophobic layer made of 2-ethoxy ethyl methacrylate (EOEMA) that serves as a barrier to guard the surrounding vascularized tissue from the cytotoxicity of the chemotherapy agents that are being delivered. Studies conducted on enucleated pig eyes showed that the medicines may diffuse past the sclera and enter the vitreous humor. The sorption, release, and transport characteristics of HEMA-based hydrogels were investigated, demonstrating the possibility of modifying the drug loading capacity and diffusion by the level of crosslinking. The gels made from EOEMA turned out to be impervious to drug sorption and diffusion. Unloaded hydrogels had excellent biocompatibility according to a chorioallantoic membrane assay. *In vitro* tests revealed considerable cytotoxicity of drug-loaded hydrogels against an Rb cell line after 2 days for topotecan-loaded hydrogels and at least 6 days for vincristine-loaded hydrogels. For the local administration of active drugs to the eyeball for the treatment of Rb and other ocular illnesses, the bi-layered hydrogel implant can be viewed as promising.

#### **UPCOMING TRENDS IN NANOGELS**

In various biomedical applications, from cancer to neurological illnesses, nanogels constitute an innovative system for adjustable drug release and targeted therapy. To improve the processes and provide advanced nanomaterials, researchers have spent a lot of time investigating the design of these nanocarriers [71]. These NPs' swelling behavior is what sets them apart. The hydrophilic characteristic of the finished nanonetwork, which can incorporate a large quantity of water or biological fluids while preserving its structural integrity, is largely due to the polymers utilized in Nanogel production, which absorb water. However, nanogels have recently been investigated for use in a variety of sectors besides healthcare. The potential use of nanogels as catalysts, adsorbents, or sensing materials for environmental applications serves as a clear instance of this. Nanogels have been proven to be particularly helpful in environmental applications for the removal of organic contaminants, due to their huge surface area, porosity, and encapsulating capabilities [72]. Nanogels have sparked a lot of interest in targeted drug delivery. Targeting cancer cells in the body with effective formulation and functionalization of the particles helps prevent numerous negative effects of other treatments [57]. Cardiovascular disorders can also be treated with nanogel compositions [73].

#### **CHALLENGES AND FUTURE PROSPECTIVE OF OCULAR NANOGELS**

Nanogels are emerging as a promising approach to treating various ocular diseases. Table 5 highlights some patents on this emerging drug delivery system. The eye is a very sensitive and very useful part of the human body. Therefore, attention should be given to the safety of any dosage form administered to the eye. The unreacted monomers or remaining surfactants in the nano gel preparation could be hazardous. Researchers need to assess the possible toxicity of nanogels and the materials utilized to prepare

**Table 5.** Patents on ocular *in-situ* gel.

Title	Year	Patent Number	Gelling Agents	References
Reversible gelling system for ocular drug delivery	2002	US 2002/0114778A1	A block copolymer of propylene oxide and ethylene oxide with HPMC	[108]
Ophthalmic drug delivery formulations and methods for preparing the same	2003	US 6511660B1	Carbopol and Pluronic	[109]
Reversible gelling system for ocular drug delivery	2004	US 6703039B2	A block copolymer of propylene oxide and ethylene oxide with HPMC	[108]
<i>In-situ</i> gel-forming solution for ocular drug delivery	2011	WO 2011018800A3	A combination of natural polysaccharide and thermoreversible polymer	[110]
<i>In-situ</i> gel ophthalmic drug delivery system of estradiol or other estrogens for prevention of cataracts	2011	US 2011/0082128A1	Deacetylated gellan gum	[32]
Nanoparticulate <i>in-situ</i> gels of TPGS, gellan and PVA as vitreous humour substitutes	2013	US 8343471B2	Gellan with PVA	[111]
Hydrogels used to deliver medicaments to the eye for the treatment of posterior segment diseases	2005	US 20050208102A1	A tetrapolymer of hydroxymethyl methacrylate, ethylene glycol, dimethylmethacrylate, and methacrylic acid.	[112]
Ophthalmic gel compositions	2013	WO2013043387A1	Lightly cross-linked carboxy-containing polymer	[113]

nanogels during repeated and prolonged application in the eye before their clinical use and commercial production. Most of the biocompatibility and safety studies of nanogels are performed on animal eyes. However, the structure of animal eyes is quite different from human eyes. Unfortunately, the results of these preclinical studies are sometimes not validated in humans. Most preclinical findings concluded no signs of toxicity and altered pharmacological effects of nanogels in the eyes. Nanogels have a great ability to get stimulated by external stimuli such as pH, light, enzymes, redox reactions, temperature, enzymes. However, the stimuli-responsive characteristics can cause significant problems if the drug does not deliver to the site of action. There are possibilities that nanogels may degrade in an undesired area before reaching their target site. This can cause off-target delivery of drugs. Nanogels are known to give prolonged drug release; therefore, this off-target drug delivery may cause significant adverse effects. Besides the toxicity issues the particle size and polydispersity of nanocarriers, as well as problems with polymer degradation, are additional drawbacks of nanogels. The problems associated with the handling and storage of nanogels are one significant challenge. It is a major problem, particularly for temperature-responsive nanogels with gelation temperatures lower than 37°C. The nano gel can get converted from sol-to-gel state in the needle or syringe making the administration difficult. The instability of nanogels can affect the shelf life of the formulation.

Nanogels are frequently prepared using organic/inorganic solvents and synthetic polymers. Therefore, toxic solvents must be fully eliminated from the formulation. Special attention must be paid to the toxicity of the degraded polymers in the eyes. The polymers should be modified for ideal characteristics such as bioadhesion, biocompatibility, and biodegradability. It is also preferable to carefully plan the nanogel formulations to reduce any hazardous effects brought on by the degradation of polymers of nanogels. The ideal feature of nanogels includes the ability to load multiple therapeutic

moieties and the controlled release of the therapeutic agents. The rheology of nanogels must be ideal for handling and storage. The prolonged retention of nanogels in the patient's body, and storage stability are other crucial properties required from nanogels. Particle sizes of 50–200 nm and polydispersity index of NPs below 0.7 are additional requirements [23,74].

## CONCLUSION

The combined benefits of hydrogels and NPs to increase ocular BA and therapeutic efficacy and lessen systemic absorption and toxicity, are seen *in-situ* nanogels. Traditional ophthalmic formulations have faced various difficulties with topical medication administration because of the anatomical and physiological barriers of the eye. Nevertheless, a lot of work has been put into finding safer and more efficient therapeutic agents up to this point, and new ocular drug delivery techniques are constantly being investigated. The release of ocular medications can be prolonged and the frequency of administration is reduced by encapsulating them in nanogels, which improves patient compliance. The safety, efficacy, stability, and patient acceptance of the formulation greatly depend on the quality control testing of the formulation. Ocular problems such as glaucoma, retinoblastoma, cataracts, AMD, dry eye syndrome, DR, and bacterial keratitis may eventually lead to vision loss or blindness if they are not properly treated. The limitations of conventional ocular delivery systems, such as their low therapeutic efficacy and unfavorable side effects from invasive surgery or systemic exposure, can be greatly overcome by nanotechnology. However, the challenges associated with the scale-up of NPs from laboratory to large-scale production, and their ocular safety need to be addressed.

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#### AUTHOR CONTRIBUTIONS

The investigation, conceptualization, and writing of Shalu Verma; Nidhi Nainwal. Review and editing, Shalu Verma. Supervision, Nidhi Nainwal. All the authors have contributed to the preparation of the manuscript, accepted the entire content, and approved its submission. All authors have read and agreed to the published version of the manuscript.

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The authors report no financial or any other conflicts of interest in this work.

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This study does not involve experiments on animals or human subjects.

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All the data is available with the authors and shall be provided upon request.

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