Review Article

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Smart Ocular Drug Delivery Systems: Design Principles and Recent Advances

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ABSTRACT

The effective treatment of ocular diseases is confronted by various factors, including ocular barriers, limited drug bioavailability, invasive procedures, and low patient compliance. Moreover, new ocular delivery systems have only overcome these problems to a certain extent. In response, smart ocular drug delivery systems have gained attention due to their ability to enable modified drug release along with the additional features they provide to the delivery system, the drug, and the treatment. Smart materials (endogenous and exogenous stimuli responsive) allow the carrier systems to exhibit a variety of properties. Studies on smart ocular drug delivery systems are relatively new and the interest in exogenous stimuli sensitive smart materials has increased in recent years. Therefore, in this review we focused on scientific advancements of these technologies to present a clear understanding of design principles which is key to developing more efficient and reliable ocular drug delivery systems. This review covers ocular barriers, diseases, drug delivery routes, conventional and novel ocular delivery systems along with a focus on the achievements of the smart ocular drug delivery systems developed in recent years. Special emphasis was given to the improved, reduced, or enabled properties of these drug delivery systems.

Keywords: Endogenous stimuli, Exogenous stimuli, Ocular delivery, Smart materials

1. Introduction

The increasing incidence of ocular diseases and the associated rising costs suggest that effective treatments need to be developed [1]. However, the isolated nature of the eye, surrounded by barriers, is one of the most challenging factors in developing effective treatments [2]. For instance, topical applications are removed from the ocular surface in few minutes, while systemic applications do not deliver sufficient amount of drug to the eye and intraocular injections are invasive and may cause severe complications. Moreover, such methods have low bioavailability and require repeated doses, resulting in lower patient compliance and treatment efficacy. In addition, these issues cannot be addressed with current treatments based on conventional ocular drug delivery systems (ODDSs), as they also have limitations [3]. On the other hand, although new ODDSs improve the low bioavailability of drugs, they have still not been able to overcome some challenges [4]. Thus, in addition to the development of novel ODDSs, it is necessary to adopt new approaches to ocular drug delivery, such as the development of implants, inserts, microneedles, gene delivery, and therapeutic contact lenses, or the use of iontophoresis, bioadhesive polymers, and smart materials [1,5]. As many studies aim to develop ODDSs with controlled release, smart drug delivery systems may have the potential to overcome the drawbacks, as well as offer various advantages [1]. In this review, as illustrated in Figure 1, the initial objective is to present the relevant background information on ocular anatomy, barriers, drug delivery routes, and the associated diseases. Subsequently, the focus will shift to ocular delivery systems and stimuli responsive systems.

2. Ocular Anatomy and Barriers

The human eye has a complex and highly sensitive structure. It consists of two main parts: anterior segment and posterior segment. The anterior segment includes the tear film, cornea, pupil, lens and ciliary body, while the posterior segment includes the conjunctiva, sclera, choroid, retina, vitreous humor and optic nerves [6,7]. Moreover, it is surrounded by both active and passive barriers such as the tear cycle, blinking, nasolacrimal drainage, eyelid, conjunctiva, corneal epithelium and blood-ocular barriers. These can protect the ocular surface and restrict the passage of substances [8]. All these factors constitute a considerable limitation in the treatment of prevalent diseases, particularly those affecting the posterior segment of the eye, which can lead to vision loss if left untreated [2].

3. Ocular Diseases

Ocular diseases affect millions of people worldwide and often require long-term treatment [1]. Furthermore, increasing amounts of dust and allergens cause a rise in diseases such as allergic conjunctivitis, retinopathy, dry eye and even glaucoma, leading to annual economic costs [9]. Current treatments strategies of ocular diseases need improvements due to their limitations such as side effects, low efficacy or low patient compliance. Dry eye treatments include artificial tears, local secretagogues, corticosteroids and immunosuppressants but these methods have some side effects such as ocular discomfort, low patient compliance, high intraocular pressure (IOP) and glaucoma [10]. In glaucoma patients, treatments with anti - glaucoma eye drops or hypotensive topical drugs often fail due to low drug bioavailability [8,9]. Conjunctivitis is the most common ocular complication [11] and its treatments include use of eye drops and ointments, which may also be in need of improvement [12]. Age related macular degeneration (AMD) is a leading cause of vision loss [11]. High-dose zinc, antioxidants, and vitamins may slow the progression of AMD, and intravitreal injections, although invasive, may be effective [8]. Ocular bacterial infections pose a serious threat to visual well-being [13] and in some cases, drugs may be ineffective as a result of drug-resistant bacteria, potentially leading to treatment failure and necessitating corneal surgery [11]. Diabetic retinopathy (DR) treatments include laser therapy to restore retinal circulation and intravitreal injections for macular edema [8]. Retinoblastoma is the most common malignant tumor in children, especially in those under the age of five and intravitreal chemotherapy was found in many cases [14].

4. Routes of Ocular Drug Administration

Topical, periocular, intraocular and systemic routes are preferred for ocular drug delivery. Although the primary ocular barrier for the routes varies, each route has pros and cons depending on the technical requirements and degree of invasiveness [4,15]. Nev-

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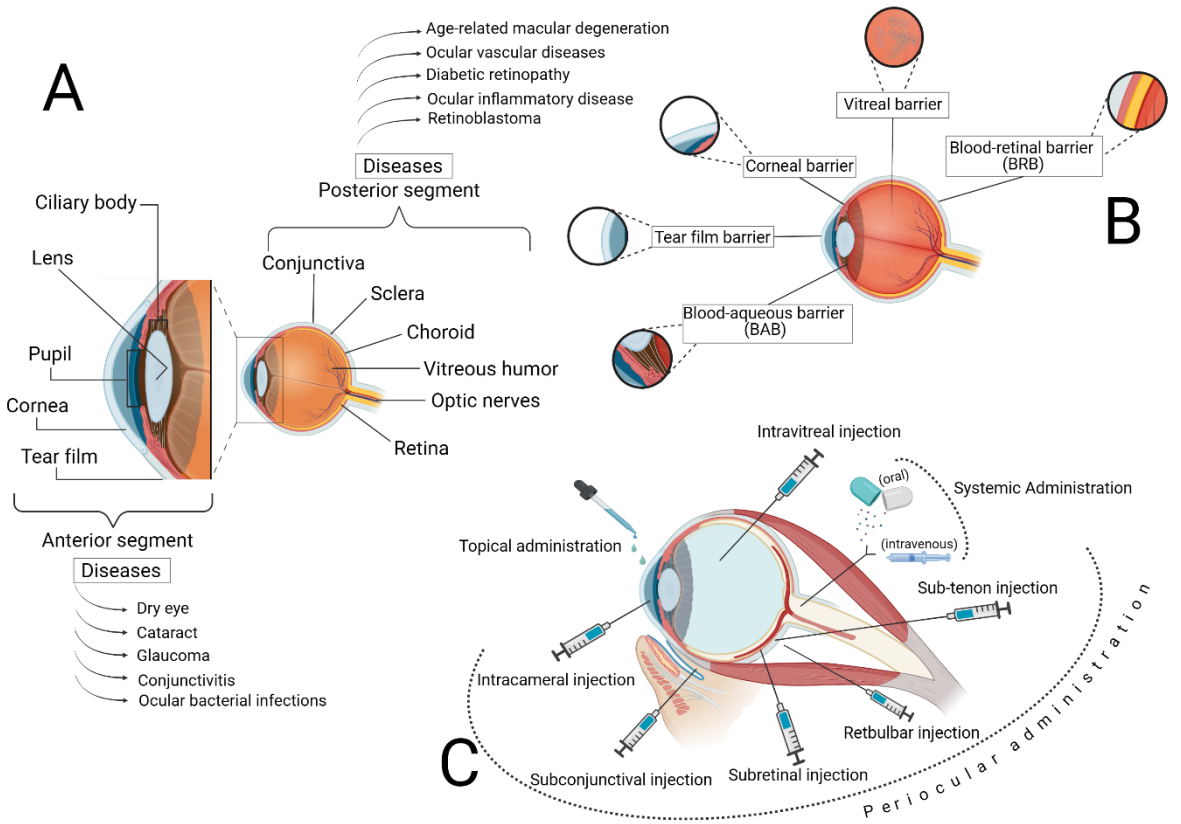

Figure 1. (A) Ocular anatomy and posterior and anterior segment diseases - some diseases may affect both segments, (B) potential ocular barriers, and (C) ocular administration routes.

ertheless, the primary drawback of these pathways is their poor drug bioavailability at the intended site [7]. Topical administration is the most preferred route of administration for ocular drug delivery, as it offers a non-invasive strategy. Although it accounts for more than 95% of the ocular products on the market, drugs administered by this route exhibit low bioavailability [1,11]. Systemic administration is usually used for the treatment of posterior segment eye diseases. However, by this route, the drug is greatly diluted in the blood and the blood-ocular barrier prevents it from reaching the eye [15]. Periocular administration covers a range of application types that can release ophthalmic formulations into the gaps between the layers of ocular tissues, providing extended drug release and enabling formulations with low water solubility to overcome precorneal barriers [7,16]. However, as these methods are invasive, pose a risk of hemorrhage, and have the problem of drug clearance from the periocular space, their use in clinics is generally not preferred [8,17]. By intravitreal administration, drug is injected using a needle into the vitreous cavity. Once the drug is injected, it disperses and reaches the posterior segment of the eye [4]. Although it is more invasive than periocular administration, it is usually considered the only option in the treatment of posterior segment eye diseases [15,18]. However, the invasive nature of this administration, especially in chronic diseases, can result in low patient compliance [18].

5. Conventional Ocular Drug Delivery Systems

A series of topical ophthalmic dosage forms such as eye drops, ointments, gels, suspensions, emulsions have been developed to prolong the retention time of drugs on the ocular surface [6,8]. These systems are easily administrable and non-invasive. [11,22]. While eye drops are easily produced and most popular, ocular ointments and gels are also preferred due to improvement of ocular contact time and bioavaila-

bility. Ocular suspensions which are not easily diluted by tears, are also utilized to prolong ocular contact time [3,11] and emulsions have the advantage of enabling sustained drug release [23]. However, because of elimination and dilution caused by the tear cycle and nasolacrimal drainage [19,20] conventional systems have low bioavailability (1-5%) [9] and some requirements, such as the shaking of the dosage form, can reduce the effectiveness of the treatment in the case of low patient compliance [3,21].

6. Novel Ocular Drug Delivery Systems

New ODDSs, as shown in Figure 2., aim to increase drug stability and retention time by overcoming ocular barriers, enhance treatment efficacy by reducing dosing frequency and side effects, and increase patient compliance by allowing multiple drug combinations [8,10]. However, although these systems have significantly improved ocular bioavailability, they have not fully overcome certain drawbacks, such as drug loss through the conjunctiva, rapid release, low stability, and difficulty in scaling up [4].

6.1. In situ gelling systems

They are low viscosity polymeric solutions that can undergo phase transition into a gel (sol-gel) depending on their chemical composition when being exposed to certain physiological conditions such as pH, ion and temperature [20,21]. Ocular *in situ* gelling systems can transform into pseudo-plastic gels when in contact with tear fluid. Thus, by increasing ocular contact time, they can improve the bioavailability of many ocular drugs [6,11,24]. Furthermore, these systems offer several benefits, such as ensuring accurate and repeatable drug doses, improving patient compliance, and reducing the frequency of drug administration [20].

6.2. Therapeutic contact lenses

They are non-invasive systems that can release drugs at sustained release manner between the cornea and the lens [7]. This close contact can significantly increase drug bioavailability, patient compliance and the delivery of many ocular drugs. They also could reduce drug dosage, dosing frequency and systemic drug absorption. However, since contact lenses loaded with nanoparticles may exhibit altered mechanical properties, it may affect their drug loading capacity [4,9].

6.3. Liposomes

They are biocompatible and biodegradable spherical carriers with a water-based core and phospholipid layers [3]. Due to these properties, they can carry lipophilic drugs in the lipid area and hydrophilic drugs in the interior part [11]. However, liposomes tend to be unstable, and when they are stored or administered, they may aggregate and fuse, which could cause the leakage of the drug [3].

6.4. Nanomicelles

By assembling various surfactants spontaneously, they can be prepared to carry many drugs in their lipophilic core and hydrophilic outer shell [8,11]. In addition to their simple preparation, reduced toxicity, increased bioavailability, high stability and improved permeability, they can efficiently deliver drugs to both the anterior and posterior segments of the eye [8]. However, hydrophilic drugs loaded nanomicelles tend to be unstable and have a short release time, which limits their applicability [3].

6.5. Polymeric nanoparticles

They are colloidal drug carrier systems classified into nanospheres and nanocapsules based on their struc-

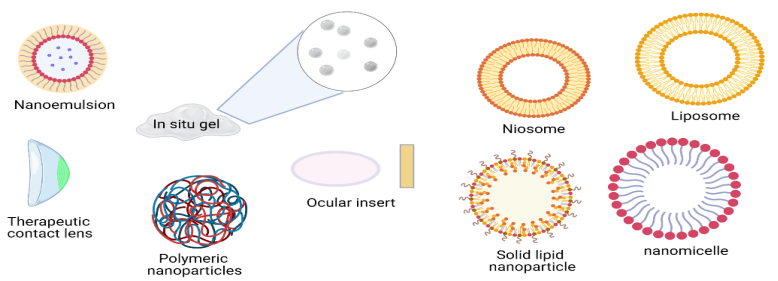

Figure 2. Novel ODDSs.

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ture and preparation method. Generally, nanoparticles containing natural and synthetic polymers such as sodium alginate, chitosan, polylactic-co-glycolic acid (PLGA) and polylactic acid (PLA) are widely used in ocular preparations. They have a great intracellular penetration, as well as being smaller and less irritating. Through providing sustained drug release and better drug absorption, they can avoid repeated doses [8,11].

7. Smart Ocular Drug Delivery Systems

Smart materials change drug-release behaviors in a reversible manner in response to pH, temperature, ionic strength, light, ultrasound, or external fields [25]. Owing to these unique properties, they have become an essential part of medical technology [26]. Nowadays, a variety of smart drug delivery systems for ocular diseases are being designed using various stimuli responsive factors [1], which are illustrated in Figure 3. Among them, polymeric materials that have high water absorption ability, stability, adhesive properties and biodegradability are widely preferred [16].

There are some important properties that smart ocular formulations must meet, as shown in schematically in Figure 4. Among these properties sterility and clarity are the most important requirements. Non-clear formulations an cause corneal abrasion as they may contain suspended particles. Also, the osmolarity of the formulation should be similar to the tear fluid [7,19]. Moreover, the viscosity of the formulation is another important factor, as high viscosity can cause residues around the eyelid [27].

7.1. Endogenous stimuli responsive ocular drug delivery systems

These systems can be endogenously stimulated and release drugs in the presence of pH, temperature, ion, enzyme and redox changes. They could improve the ocular contact time and penetration of topical applications and enhance the durability of the carrier system. However, there are also some limitations. For pH-sensitive ODDSs, the pH may vary from patient to patient or in certain diseases [16,28]. For thermosensitive ODDSs, the formulations may contain high polymer concentrations, which may lead to undesirable reactions in the long terms [23]. For ion sensitive ODDSs, the relatively small number of ion-sensitive polymers has limited the development of these systems. Despite these drawbacks, these systems can offer important outcomes, as presented in Table 1. In addition to these outcomes, the possibility of personalized treatment, the advantages of working in small laboratory settings, the wide variety of endogenous smart materials available—especially for thermosensitive systems [16,19,22,27]—make these systems attractive to researchers.

7.1.1. pH-sensitive ocular drug delivery systems

These are the systems that contain components with weak acidic or basic groups which donate or accept protons in response to changes in the ambient pH [16]. A healthy eye has a pH of 7.4 and this value may vary in certain diseases. Therefore, developing pH-sensitive ODDSs may be a useful approach. In particular, formulations with a pH between 6.5 and 8.5 are well tolerated by the eye, while those outside this range may cause discomfort and irritation. Among pH-sensitive materials, Carbopol® is widely preferred in ODDSs [16,19].

7.1.2. Thermosensitive ocular drug delivery systems

Thermosensitive smart materials are particularly preferred within *in situ* gelling systems and when these systems are heated, changes in their structure and viscosity cause a sol-gel phase transition. Moreover, the availability of many safe and biocompatible thermosensitive polymers and their rapid gelation at body temperature make them highly outstanding [19,22]. Chitosan-based thermosensitive polymers have good biocompatibility, acrylamide-based polymers can be easily adjusted to the intended temperature, and poloxamer-based polymers exhibit high biocompatibility and inert properties, while also creating transparent gels and enabling sustained drug release [27]. Furthermore, studies have suggested that thermosensitive ODDSs can overcome some ocular barriers such as blinking, lacrimation and nasolacrimal drainage [22].

7.1.3. Ion-sensitive ocular drug delivery systems

Since various cations such as Na^+, Mg^{2+} and Ca^{2+} are abundant in tear fluid, ion-sensitive formulations can easily turn into gels when in contact with the ocular surface. For ion-sensitive ODDSs, gellan gum and xanthan gum are the most preferred polymers [16,29]. Furthermore, in comparison to thermal and pH-sensitive *in situ* gelling systems, ion-sensitive systems have several advantages such as lower polymer concentrations, ideal pH and reduced eye irritation [23]. They also have a potential for large-scale

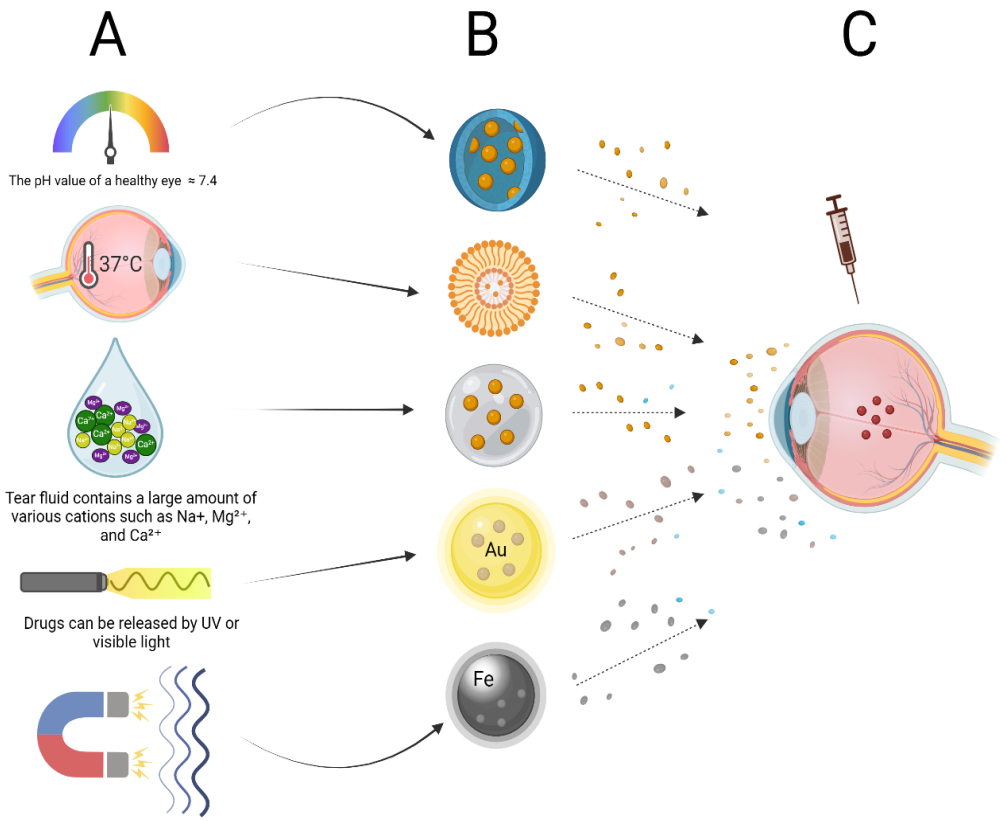

Figure 3. Modified drug release triggered by endogenous or exogenous factors. (A) triggers, (B) drug carrier systems that deliver the drug in a controlled manner, (C) improved ocular properties.

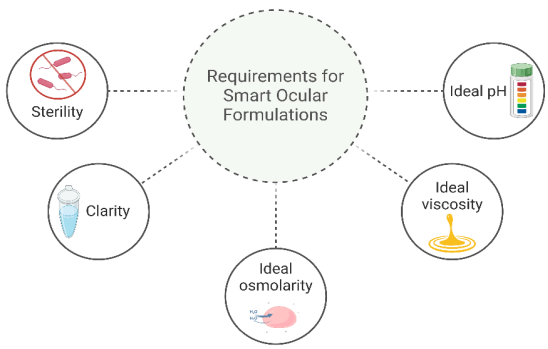

Figure 4. Key factors to develop an efficient smart ODDSs.

production without being directly affected by changes in endogenous parameters [23,28].

7.2. Exogenous and dual stimuli responsive ocular drug delivery systems

Exogenous systems, can release drugs in the presence of light, ultrasound, magnetic and electric field. These systems could offer several important advantages that endogenous sensitive systems cannot provide. Among these, the ability to provide on-demand tunable drug release and improved non-invasiveness for many strategies are the most promising ones. However, these systems also have some disadvantages. For light-sensitive ODDSs, the synthesis of photoreactive nanoparticles and phototherapy applications play a crucial role in their development, which necessitate technical knowledge and expertise

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Table 1. Improved, reduced and enabled properties of endogenous stimuli responsive ODDSs along with the role of some excipients.

Stimuli	Drugs and Diseases	Delivery Systems	Smart Materials and Excipients*	Outcomes*	Ref.
pH	Betaxolol Glaucoma	In situ gels Niosomes	Carbopol®	↑ Ocular contact time ↑ Drug release	[30]
pH	Ketotifen Allergic conjunctivitis	In situ gels	Carbopol® ↑ Viscosity ↓ pH Gellan gum and xanthan gum ↑ Gelation capacity ↑ Viscosity ↓ Drug release	↑ Ocular contact time ↑ Drug release (8 hours)	[20]
pH	Cetirizine Allergic conjunctivitis	In situ gels	Carbopol® ↑ Viscosity (non-linear) HPMC** ↑ viscosity (linear)	↑ Ocular contact time ↑ Drug release (5 hours)	[24]
pH	Cyclosporine A Dry eye	TCL**	Cellulose acetate phthalate	↑ Ocular contact time Controlled drug release (24 hours) ↑ Tear volume	[10]
pH	Panax natoginseng saponins DR**	In situ gels	Carbopol® ↓ pH	↑ Ocular penetration Sustained drug release	[6]
pH	siRNA Corneal vascularization	Vesicular system	Synthesized polymer	↑ Ocular penetration Effectively gene silencing	[31]
pH	Moxifloxacin	In situ gels	Terminalia arjuna resin ↓ pH Sodium alginate ↑ Viscosity	↑ Ocular contact time ↑ Ocular penetration Sustained drug release (12 hours)	[32]
pH	Cyclosporin A	In situ gels Nanomicelles	Gellan gum ↑ Gelation capacity	↑ Ocular contact time ↑ Ocular penetration ↓ Toxicity	[33]
pH	Timolol Brimonidine Glaucoma	TCL** (drug-eluting)	Silica nanoparticles	↑ Drug loading capacity ↓ Drug leakage Sustained drug release	[9]
Thermal	Flurbiprofen	In situ gels Nanosuspensions	Pluronic® Carbopol® ↑ Short-term bioadhesive effects ↑ Gelling capacity.	↑ Ocular contact time ↑ Drug release (6 hours)	[34]
Thermal	Oxytetracycline Ocular bacterial infections	In situ gels polymeric nanoparticles	Pluronic® F127 ↑ Viscosity ↓ Gelation temperature	↑ Ocular contact time Sustained drug release	[19]

Stimuli	Drugs and Diseases	Delivery Systems	Smart Materials and Excipients*	Outcomes*	Ref.
Thermal	Dexamethasone	In situ gels Cyclodextrin	Pluronic® F127 ↓ Gelation temperature Chitosan	↑ Ocular contact time ↑ Drug release (6 hours)	[27]
Thermal	Prednisolone Ocular inflammatory disease	In situ gels Microemulsions	Pluronic® F68 ↑ Clarity Pluronic® F127 ↓ Gelation temperature	↑ Ocular contact time Sustained drug release (16 – 24 hours)	[13]
Thermal	Resveratrol Dry eye	In situ gels PLGA** nanoparticles	Pluronic® F127	↑ Ocular contact time Controlled drug release (3 days)	[22]
Thermal	Diclofenac sodium	In situ gels Carbon dots	Pluronic® F127 Pluronic® F68 Carboxymethyl chitosan Hyaluronic acid	↑ Ocular contact time ↑ Drug release	[35]
Thermal	Itraconazole Fungal keratitis	In situ gels Nanocrystals	Pluronic® F127 Pluronic® F68 HPMC**	↑ Ocular contact time Potent antibacterial activity	[36]
Thermal	Dexamethasone Anti-VEGF** Glaucoma	In situ gels	Synthesized copolymers	↑ Ocular contact time ↑ Release of dexamethasone (35 days) ↑ Release of Anti-VEGF** (13 days)	[21]
Thermal	Ketotifen Allergic conjunctivitis	Hydrogel	pNIPAAm** Chitosan Adjustable LCST**	↑ Carrier durability ↑ Drug release (linear)	[12]
Thermal	Dexamethasone	Injectable in situ gels	Isopropylacrylamide Cystamine	↑ Carrier durability ↑ Drug release (430 days) ↓ Degradation of products	[18]
Ion	Acetazolamide Glaucoma	In situ gels Nanoemulsions	Gellan and xanthan gum ↑ Stability HPMC Carbopol® (excluded)*** Ø Gelation	↑ Ocular contact time	[37]
Ion	Brimonidine Glaucoma	In situ gels	Sodium alginate HPMC ↑ Drug release	↑ Ocular contact time Sustained drug release (8 hours)	[38]

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Stimuli	Drugs and Diseases	Delivery Systems	Smart Materials and Excipients*	Outcomes*	Ref.
Ion	Brimonidine Glaucoma	In situ gels	Gellan gum HPMC** (excluded)*** ↑ Gel strength Ø viscosity	↑ Ocular contact time Rapid and sustained drug release	[23]
Ion	Ketoconazole Fungal keratis	In situ gels Inclusion complex	Sodium alginate Cyclodextrin derivatives	↑ Ocular contact time	[39]
Ion	Betaxolol Glaucoma	TCL**	Cellulose Acetate (inner layer) Silicone Hydrogel (outer layer)	↓ Drug leakage ↓ Drug loss (30 days) Sustained drug release (168 hours)	[29]

*These symbols ↑, ↓, Ø represent an increase, a reduction, or no impact on the formulation properties, respectively.
**These abbreviations stand for: HPMC – hydroxypropyl methylcellulose, PLGA – poly(lactic-co-glycolic) acid. pNIPAAm – poly(N-isopropylacrylamide), TCL – therapeutic contact lens, DR – diabetic retinopathy, and Anti-VEGF – anti-vascular endothelial growth factor- LCST – lower critical solution temperature.
*** This excipient(s) was not included in the resulting formulation.

[40,41]. For magnetic field-sensitive ODDSs, their recent use outside clinical settings has resulted in insufficient understanding of certain distribution mechanisms [42]. Despite these drawbacks, these systems can offer important outcomes. On the other hand, some researchers have developed dual or multi responsive ODDSs by combining both endogenous and exogenous sensitive systems, as presented in Table 2. Such systems offer more stable solutions with increased ocular contact time and penetration, along with enhanced controlled drug release.

7.2.1. Light-sensitive ocular drug delivery systems

Typically prepared by adding a photoreactive group, these systems can release drugs through degradation stimulated by UV or visible light [28,41]. Since the eye is an organ that can be directly treated with light, the use of such materials in ODDSs could significantly improve the treatment efficacy by boosting targeted and controlled drug release [40]. In addition, the fact that they are not directly affected by endogenous parameters provides them an advantage over pH, thermal or ion-sensitive ODDSs [16,23,28].

7.2.2. Magnetic field-sensitive ocular drug delivery systems

Through the effect of an externally applied magnetic field, these systems can release drugs after reaching the targeted area. Due to this feature, they are generally preferred in the clinic especially for magnetic resonance imaging and theragnostic purposes [41,42]. Magnetic field-sensitive ODDSs can release drugs and improve drug permeability without damaging ocular tissues when a magnet placed on the ocular surface [42].

8. Conclusion

Choosing the most appropriate smart delivery system is a key consideration to achieve the desired outcome. As presented in this review, the majority of recent studies have focused primarily on specific desired outcomes, namely increasing ocular contact time, improving drug penetration, and enabling modified drug release. Some studies have also achieved other important outcomes, such as improved safety, reduced invasiveness, increased drug loading capacity, minimized drug leakage, controllable accumulation properties, and on-demand drug release. As these latter outcomes have been less studied, further research targeting these properties is needed. It is also important to note that some of these studies have limitations, such as being conducted with small groups of animals, being evaluated only *in vitro*, lacking optimization, or long-term biosafety and toxicity data for the materials used. Therefore, further

Table 2. Improved, reduced and enabled properties of exogenous and dual stimuli responsive ODDSs along with the role of excipients.

Stimuli	Drugs and Diseases	Delivery Systems	Smart Materials and Excipients*	Outcomes*	Ref.
Light (NIR**)	Bevacizumab AMD**	Agarose hydrogels	Gold nanoparticles	↓ Invasiveness	[43]
Light (NIR**)	Genistein	Hybrid nanoplatform Liposomes	Upconverting nanoparticles Bismuth nanoparticles	↓ Invasiveness Controlled drug release	[44]
Light (Green)	Doxorubicin Retinoblastoma	Synthesized nanoparticles	Green light sensitive nanoparticles	↓ Invasiveness Sustained drug release	[45]
Light	Bevacizumab AMD**	Micelles	Copolymers	On-demand drug release Stable ≥21 days Triggered drug release in 20 minutes.	[28]
Magnetic field	Diclofenac sodium	Nanoparticles	Iron oxide nanoparticles Sodium alginate Calcium chloride	↓ Drug clearance ↑ Scleral penetration (≈70%)	[17]
Magnetic field	Valproic acid Guanabenz	Nanoparticles	Iron oxide nanoparticles	↓ Invasiveness	[42]
Magnetic field	Dexamethasone Glaucoma	Nanoparticles	Iron-based nanoparticles	↓ Drug accumulation ↑ Ocular contact time Controlled drug release	[46]
Magnetic field	Anti-VEGF	Micropump system Gold complexes	Cylindrical nanoparticle block	On-demand drug release	[47]
Dual Thermal Light	Nitric oxide Ocular bacterial infections	NO photodonor	Pluronic® P123 Pluronic® F127	↑ Ocular contact time Controlled drug release	[48]
Dual Thermal pH	Dexamethasone	Nanogel	Heparin and chondroitin-based copolymers	↑ Ocular contact time Controlled drug release	[49]
Dual Thermal Ion	Pranoprofen	Gel	Pluronic® 407 Pluronic® 188 Gellan gum	↑ Ocular contact time ↓ Drug loss Controlled drug release	[50]
Dual Thermal Light (NIR*)	Gene-targeted drug Uveal melanoma	Nanofiber hydrogel	Gold nanorods ↑ mechanical strength Chitosan Puerarin	↑ Drug accumulation On-demand drug release	[51]
Multi Thermal pH Light	Photothermal therapy platform (low temperature)	nanoparticles	Photothermal platform Phenothiazinium nanoparticles	↓ Laser dose Effectively bacterial elimination	[52]

*These symbols ↑, ↓, ≥, ≈ represent an increase, a reduction, a value greater than or equal to, and an approximation of the formulation properties, respectively.
**These abbreviations stand for: NIR– near infrared light, AMD– Age related macular degeneration.

studies to address these weaknesses are essential to advance the next generation of ODDSs and their application in the clinic.

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During the preparation of this work, the authors used ChatGPT to improve the readability and language of a very small portion of the manuscript. BioRender was used to create the figures After using these

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tools, the authors reviewed and edited the content as needed and takes full responsibility for the content of the published article.

Conflict of Interest

The author/editor has no conflicts of interest, financial or otherwise, to declare.

Statement of Contribution of Researchers

Concept – B.E.Ç., N.Ö.; Design – B.E.Ç., F.S.; Supervision – N.Ö.; Data Collection – B.E.Ç.; Literature Search – B.E.Ç., F.S.; Writing – B.E.Ç., F.S.; Critical Reviews – B.E.Ç.; F.S.; N.Ö.

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