




Review

Contact Lenses as Drug Delivery System for Glaucoma: A Review

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Abstract: Glaucoma is an optical neuropathy associated to a progressive degeneration of retinal ganglion cells with visual field loss and is the main cause of irreversible blindness in the world. The treatment has the aim to reduce intraocular pressure. The first therapy option is to instill drugs on the ocular surface. The main limitation of this is the reduced time of the drug staying on the cornea. This means that high doses are required to ensure its therapeutic effect. A drug-loaded contact lens can diffuse into the post lens tear film in a constant and prolonged flow, resulting in an increased retention of the drug on the surface of the cornea for up to 30 min and thus providing a higher drug bioavailability, increasing the therapeutic efficacy, reducing the amount of administered drug, and thereby provoking fewer adverse events. Several different systems of drug delivery have been studied in recent decades; ranging from more simple methods of impregnating the lenses, such as soaking, to more complex ones, such as molecular imprinting have been proposed. Moreover, different drugs, from those already commercially available to new substances such as melatonin have been studied to improve the glaucoma treatment efficacy. This review describes the role of contact lenses as an innovative drug delivery system to treat glaucoma.

Keywords: glaucoma; contact lenses; drug delivery

1. Introduction

Glaucoma covers a group of multifactorial optical neuropathies associated to a progressive degeneration of retinal ganglion cells that leads to a characteristic visual field loss pattern [1]. These cells are central nervous system neurons with their cell bodies in the inner retina and the axons in the optic nerve, whose degeneration results in the cupping distinctive appearance of the optic disc and visual loss [2]. Although there is a consensus that the increase of the intraocular pressure (IOP) is the essential factor in the appearance and development of this pathology, it is not the only factor [3]. The biological basis of glaucoma is not well understood and the factors contributing to its progression have not been fully characterized [4]. From a therapeutic point of view, IOP reduction is a constant in the treatment of glaucoma [5–8].

Glaucoma is the leading cause of irreversible blindness in the world. In 2020, about 79.6 million people worldwide aged 40–80 years will have glaucoma and more than 11 million will have bilateral blindness. Because of this [9], in 2040, about 112 million people will be affected [10]. One of the main problems of this pathology is that, most of the time, it remains asymptomatic until it is severe,

which means that many of the patients who suffer from it are diagnosed late and are not properly accounted for [11,12].

There are several types of glaucoma, but the most common forms are primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG), the first being about seven times more frequent than the second in the United States and Europe [9]. If this glaucoma is not treated, the course of the pathology is chronic, progressive and results in an irreversible loss of visual field that progresses in the form of tunnel vision and finally central vision is lost. The prevalence and risk of blindness from glaucoma are higher in developing countries [9].

1.1. Physiology and Pathophysiology of Glaucoma

Intraocular pressure is regulated by the inflow and outflow of the aqueous humor in the eye. The aqueous humor is produced by the epithelium of the ciliary body and contains electrolytes, proteins, cytokines, organic solutes and growth factors that nourish the avascular tissue of the anterior chamber [13]. The rate of aqueous humor turnover has been estimated to be $2.4 \pm 0.6 \mu\text{L}/\text{min}$ in the adult eye [14]. The aqueous humor reaches the posterior chamber through the tissue components of the ciliary processes, then flows around the lens and through the pupil it enters into the anterior chamber [15] and a temperature gradient within the anterior chamber creates a convective flow towards the cornea [16]. The main drainage pathway for the aqueous humor out of the eye is the trabecular meshwork into the Schlemm's canal [17]. The trabecular meshwork is porous and acts as a filter that drains aqueous humor passively when a certain IOP value is reached [17]. There is another route of drainage known as unconventional or uveoscleral outflow pathway involving the ciliary body. Unlike the conventional pathway, the uveoscleral route is independent of the IOP values [18]. Recently, lymphatic channels have been identified by immunofluorescence and confocal microscopy in the human ciliary body which suggests a uveolymphatic pathway for the outflow of the aqueous humor [19].

1.2. Primary Open-Angle Glaucoma

The angle of the eye is the junction of the iris and the cornea, where the trabecular meshwork drains the aqueous humor from the anterior chamber of the eye. In patients with POAG the angle remains open but there is an increased resistance to aqueous outflow through the trabecular meshwork. IOP can cause a mechanical stress and strain to the axons of retinal ganglion cells at the optic nerve causing cell death [20]. The main concern with this type of glaucoma is that 50% of the patients who suffer from it have IOP values between 10 and 21 mm Hg at diagnosis, which is considered a normal range [6] and only after 30% of retinal ganglion cells have been lost do visual field defects not appear on perimetric testing [21,22]. Hispanic and blacks have an increased prevalence of POAG [9,23–25].

1.3. Primary Angle-Closure Glaucoma

In this type of glaucoma, the site of normal aqueous outflow is obstructed by the peripheral iris, resulting in an anatomically closed angle [26]. Pupillary blockage is the most common cause of angle closure. This is generally caused by the resistance of the aqueous humor to move from the posterior to the anterior chamber. As already discussed in the POAG, PACG is an asymptomatic disorder where individuals suffering from it, do not notice the disorder until a loss of visual field has already occurred [26]. Small eyes with narrow anterior chambers have a higher risk of suffering from this type of glaucoma [27]. PACG is more prevalent in Chinese and in Asian Indian race [9,24].

1.4. Diagnosis

For the diagnosis of glaucoma there is no single reference standard, but different tests are available which provide relevant information on the status and development of glaucoma. Among these tests are tonometry, visual field testing, ophthalmoscopy, gonioscopy, and optic nerve imaging. The evaluation and monitoring of the structural damage of the optic nerve is a critical item of the diagnosis of the disease [28]. Although this evaluation can be performed using an ophthalmoscope or obtaining

optic nerve head photographs, the recent development of several laser scanning imaging techniques provide more information about the amount of optic nerve fiber loss, such as confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography which have improved the identification of early disease, as well as the observation of progressive optic nerve fiber loss [29–32].

1.5. Pharmacological Treatment

IOP reduction is the only effective treatment to manage and prevent the development of glaucoma progression [5,6]. Drugs can modify IOP by reducing the production of the aqueous humour from the ciliary processes, by increasing the rate of filtration of aqueous humour through the trabecular-meshwork or uveoscleral pathways or by the combination of both. They are included in five different groups: parasymphomimetics such as pilocarpine, alpha2-agonists such as brimonidine, beta-blockers such as timolol, carbonic anhydrase inhibitors such as dorzolamide, and prostaglandins analogues such as latanoprost. Although all of them reduce IOP, none are exempt from side effects like blurred vision, tachycardia, or arrhythmia [33,34]. These side effects are shown in Table 1.

Table 1. Common adverse effects associated to glaucoma drugs.

Glaucoma Medication	Name	Local Adverse Effects	Systemic Adverse Effects
Prostaglandin analogues	Latanoprost, travoprost, brimatoprost	Conjunctival hyperemia, lengthening of eyelashes, change of iris color, uveitis, macular edema, keratitis	Systemic effects related to headaches
α -adrenergic agonist	Brimonidine, apraclonidine	Ocular irritation, Dry eyes, ocular allergy	Hypotension, irregular heart rate, bitter taste, dry mouth, renal or hepatic failure, respiratory arrest in young children
β -adrenergic blockers	Timolol, levubonol, betaxolol	Ocular irritation, Dry eyes	Bradycardia, bronchospasm, depression, fatigue, respiratory effects
Carbonic anhydrase inhibitors	Dorzolamide, brinzolamide, acetazolamide	Ocular irritation, Dry eyes, burning sensation with topical agents	Topical form: minimal systemic effects Oral form: paresthesia, nausea, diarrhea, loss of appetite and taste, lassitude, renal stones
Cholinergic agonists	Pilocarpine, carbachol	Ocular irritation, induced myopia, decreased vision due to ciliary spasm	Ciliary spasms carry headaches in young patients

Many new compounds, apart from those already commercially available, have appeared, attempting to provide effective treatments to stop ocular hypertension and glaucoma progression [26]. One of the emerging group is melatonin and its analogues, which clearly present ocular hypotensive effects [35–38] as well as potentially interesting neuroprotective actions which need to be confirmed [39,40].

Melatonin is a neurohormone which is not only produced by the pineal gland but is also synthesized and released by some ocular structures such as the retina, ciliary body or the lens [41]. It is naturally present in the aqueous humor and is involved in the control of the aqueous humour dynamics [15]. In this sense, studies performed show that melatonin and its analogues can reduce IOP in normotensive and hypertensive conditions [42,43], which has revealed the potential use of this compound and its analogues for the treatment of ocular hypertension and glaucoma [44].

Among other new potential substances to treat the elevation in IOP associated with glaucoma are nucleotides, which are seen to be interesting molecules since they could also modify the dynamic of aqueous humour [45]. Between these nucleotides, dinucleoside polyphosphates are a family of compounds formed by two nucleotides linked by a variable number of phosphates (from 2 to 7), which have revealed their key role in reducing IOP [46].

However, apart from the toxicity, the active compounds have per se, additional problems which can arise with topical antiglaucoma drugs when preservatives are added [47] or with the poor bioavailability they present. Because of this, there is a search for alternative sustained delivery approaches including nanoparticle-based topical formulations, bio adhesive matrix polymers, ocular inserts, surgical implanted drug reservoirs or contact lens-based delivery [48]. These sustained release methods may reduce the

problem of a patient's adherence to prescribed medication, improve the bioavailability of the drug, and reduce the adverse effects on the ocular surface.

The ocular surface is the place of choice for the application of drugs that treat eye diseases [49]. The most common form of application of ophthalmic formulations are eye drops [49]. However, the main problem they present is the short residence time in the cornea, only 2–3 min [50], due to the dilutive effect of the tear film and its rapid clearance [51,52] and that between 50% and 100% of the eye drop is drained through the nasolacrimal duct which can cause systemic alterations [53]. This means that the application of high doses is required for the drug to have its therapeutic effect. Another important concern is that topical eye drop therapy remains one of the toughest challenges in the management of glaucoma, as usually occurs in the treatment of all chronic relatively asymptomatic conditions. There are multiple reasons for reduced treatment adherence, including medical side effects, poor understanding of treatment aims, poor installation techniques due to dexterity issues, conditions affecting mental ability or physical barriers like arthritis and tremor, and cost [54]. In a study in which patients knew they were being monitored with an electronic device; they did not consistently take their drops in 45% of cases [55]. A major challenge when adding multiple drops is compliance. It has been demonstrated that increasing the number of drop bottles to a patient's treatment regimen negatively affects patient adherence [56]. To improve patient adherence and reduce exposure to preservatives, fixed combination therapies have been developed. Preservative-free eye drop formulations have helped patients with glaucoma, who frequently have concurrent dry eye and ocular surface disruption, as patient discomfort is reduced and their quality of life improves [57].

Within the sustained release systems, the contact lens has the essential characteristic of being placed on the ocular surface to compensate the user's ametropia during long periods of time throughout the day. This permits the contact lens to be the element that most favours the sustained release of the drug into the eye without the risk of compromising its optical function [49]. In addition to this, its hydrogel nature makes the contact lens a good candidate for drug reservoirs which are released over a longer duration from a polymeric network [49]. Drugs loaded into the contact lens diffuse into the post lens tear film in a constant and prolonged flow resulting in an increased retention of the drug on the surface of the cornea for up to 30 min [58] and providing a potential of 50% drug bioavailability [59]. Although a lot of work needs to be done in relation to the possible side effects of the residues of the remaining drug inside the contact lens, a study by Ciolino et al. reported that the contact lenses appeared safe in cell culture and in rabbit eyes [60]. Contact lens eluted products did not demonstrate any evidence of toxicity either in the human corneal-limbal epithelial cells over 24 h or in the New Zealand white rabbits. The rabbit eyes did not develop any signs of toxicity, such as conjunctival redness. Consequently, this sustained release system increases therapeutic efficacy, reduces the drug fluctuation on the corneal surface, reduces the amount of administered drug [59] and, in addition, reduces the need to add preservatives which may cause ocular irritation [61,62].

In this review, the therapeutic benefits of contact lenses in the application of drugs for the treatment of glaucoma are analyzed.

2. Drug Delivery Systems with Contact Lenses

Contact lenses are divided into two main groups according to their material: soft contact lenses, which are composed of hydrogel or silicone-hydrogel polymers, or rigid gas permeable (RGP) contact lenses. Soft materials are of more interest to be used as drug delivery systems due to their hydrophilic properties, biocompatibility, and comfort [63,64]. Furthermore, soft contact lenses represent 87% of fits in clinical practice, as opposed to 13% of RGP contact lenses [65,66].

2-Hydroxyethyl methacrylate (HEMA) is the most common monomer used to manufacture soft contact lenses, together with N-Vinylpyrrolidone (NVP) in second place, among others. These monomers show suitable properties to be safely used over the ocular surface, such as oxygen permeability, water content, and wettability [63,64]. Also, their mechanical properties allow soft contact

lenses to fit well to the shape of the eye [67]. Other monomers can be incorporated into the matrix of contact lenses to improve these mentioned properties.

Based on the water content and ionicity of hydrogels, the Food and Drug Administration (FDA) classifies soft contact lens materials into five groups, which are summarized in Table 2. Hydrogel materials are in groups I, II, III, and IV, while silicone-hydrogels are in group V.

Table 2. Food and Drug Administration (FDA) classification of soft contact lens materials.

FDA Group	Water Content (Percentage)	Ionicity *
I	<50%	Nonionic
II	>50%	Nonionic
III	<50%	Ionic
IV	>50%	Ionic
V	-	-

* Being ionic in pH range from 6.0 to 8.0.

In 1965, Sedláček [68] used soft contact lenses as drug delivery systems for the first time. These contact lenses were soaked in a solution containing 1% homatropine, which increased the pupil size of participants compared to a single topical instillation of the solution. In the following decade, different studies imitated this technique to enhance the effect of pilocarpine for acute glaucoma treatment [69–72]. By soaking soft contact lenses in drug solutions, their residence time over the ocular surface depends on the exchange between these solutions and tears. In this sense, Mcnamara et al. [73] determined that tear exchange while wearing soft contact lenses was around 30 min, compared to 5 min with no lens.

Because the molecular interaction between commercial hydrogels and drugs is not specific, the retention time of drug-soaked contact lenses is limited by their physical properties, mainly ionicity and water content [58]. Moreover, the drug pH should be kept between 6.6 to 9.0 to diminish ocular irritation and to control the dissolution of the drug at pH 7.4 to improve its diffusion through the cornea [74]. To improve both residence time and bioavailability of drugs, other specific methods to load drugs into contact lenses have been developed, such as functional monomers, molecular imprinting, colloidal nanoparticles, drug–polymer film embedding, and supercritical fluid, which will be detailed below.

Maintaining the physical properties of polymers is very important for the manufacturing of soft contact lenses as drug delivery systems. The incorporation of functionalized compounds to hydrogels alters their oxygen permeability, water content, wettability, rigidity, flexibility, glass transition temperature, and light transmittance [58]. These parameters are critical because they affect comfort and visual quality during contact lens wear, compromising its safety and efficacy [75]. As an example of how physical properties can be altered, El Shaer et al. [76] found that the incorporation of nanocapsules of prednisolone into soft contact lenses decreased their water content (between 4.7% and 5.5%), wettability (between 4.3° to 12.7° in terms of contact angle), rigidity (between 0.007 Mpa to 0.028 Mpa in terms of Young's modulus), and light transmittance (between 8.3% and 11.4%). These alterations were directly proportional to the concentration of nanoparticles for some parameters, while for others there were no changes. From a research commercialization viewpoint, the main consideration when developing contact lenses for drug delivery is that their physical properties must be acceptable according to regulatory standards and they have to offer comfort and visual quality to be well tolerated by users [77,78].

On the other hand, from a clinical perspective, contact lens contraindications must be seriously taken into account when considering these drug delivery systems in patients with previous ocular diseases. Contact lens wear affects different structures of the ocular surface, which play a crucial role in the pathophysiology of some ocular diseases that are susceptible to be treated via soft contact lenses [79]. Among the most relevant complications are corneal neovascularization, superficial punctate keratitis, and giant papillary conjunctivitis. Additionally, wearing soft contact lenses increases the risk of ocular infections, such as microbial (bacterial, fungal, and acanthamoeba) keratitis or keratoconjunctivitis

caused by adenoviruses [80]. The use of lens care solutions for disinfection is fundamental in order to prevent these ocular infections [81], which implies the possibility that their compounds alter the properties of functionalized monomers for drug delivery. Therefore, it is important to ensure the physical compatibility between functionalized contact lenses and commercial lens care solutions to maintain their efficacy for drug release [78]. Finally, considering that some commercial drugs incorporate preservative agents into their formulations, which produce ocular toxicity [82], soft contact lenses could aggravate the side effects of preservatives because they increase their residence time over the ocular surface. In clinical practice, to prevent the undesirable side effects of active or additive compounds over the ocular surface or at the systemic level, contact lenses would have to be replaced daily. The reason for this replacement is to avoid the accumulation of these compounds into the matrix of hydrogel overnight, which could increase their concentration regarding toxicity values.

Different systems of drug delivery have been studied in recent decades. Elaborating on more simple methods of impregnating the lenses, such as soaking, more complex and complicated systems such as molecular imprinting have been proposed. The following paragraphs describe the different methods to improve the drug release from contact lenses.

2.1. Soaking

Soaking soft contact lenses in a drug solution is the simplest method to load drugs into their hydrogel matrix (Figure 1a). The main advantage of this method is that commercial contact lenses containing HEMA can be used [64]. However, it has the disadvantage that the drug release occurs very quickly because the drug loading is limited by the ionicity and water content of contact lens materials [83,84], in addition to the concentration of drug solution and its molecular weight. As mentioned previously, the soaking method was the first to be proposed for drug delivery in 1965 [68]. Since then, many studies have used this method to incorporate ophthalmic drugs, such as antibiotics [85], antihistamines [86], nonsteroidal anti-inflammatories, corticosteroids [87], tear secretagogues [83,84], or glaucoma medication [88]. Despite the fact that most of the studies in the literature were done *in vitro*, some authors evaluated both the retention time and efficacy of different drugs under *in vivo* conditions, showing better results with soaked-contact lenses compared to the topical instillation of eye drops [83,84,86–90].

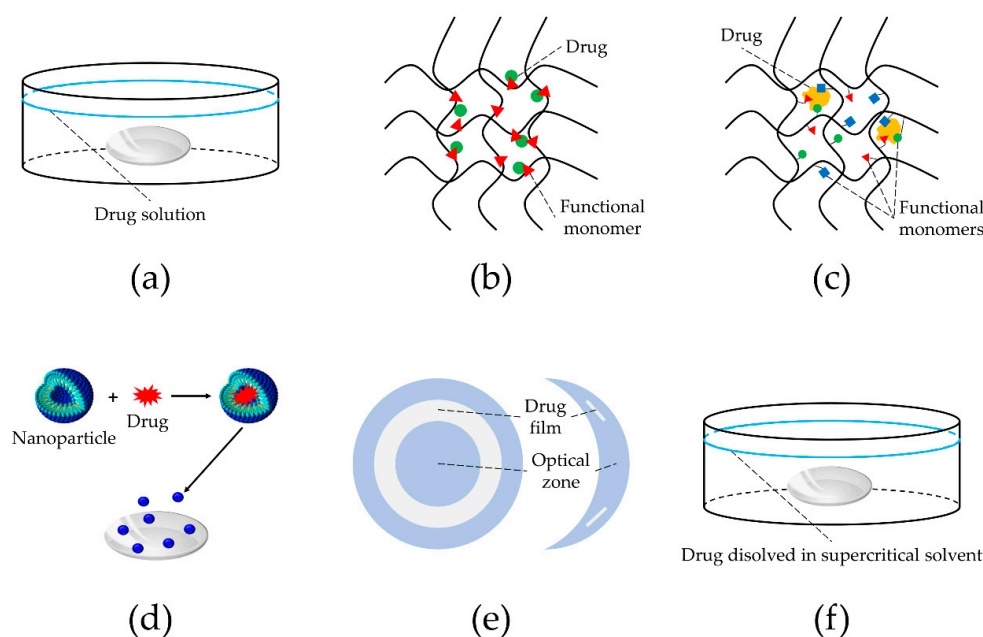


Figure 1. Representative image of the different methods to load drugs into soft contact lenses: soaking (a), functional monomers (b), molecular imprinting (c), colloidal nanoparticles (d), drug-polymer film embedded (e), and supercritical fluid (f). Each method is explained in sections from 2.1 to 2.6.

As an alternative to improving the soaking method, the previous incorporation of vitamin E into the matrix of hydrogel creates a diffusion barrier that extends the drug release over time. For example, Hsu et al. [91] increased the retention time of timolol in a pHEMA-based contact lens from 1 h (without vitamin E) to 25 h (with 20% vitamin E).

2.2. Functional Monomers

Another method to improve the affinity between soft contact lenses and drugs consists of incorporating functional monomers able to specifically interact with drugs (Figure 1b) [64]. This can be accomplished by the two different strategies explained below.

The first strategy is the addition of ionic compounds during polymerization to create strong binding points between the contact lenses and drugs. Generally, the ionicity of hydrogels is modified by adding acrylic/vinyl derivatives to HEMA [92]. Cationic monomers, such as methacryloylamino propyl-trimethylammonium chloride (MAPTAC), increase the loading of anionic drugs and delay their release [93]. On the other hand, anionic monomers, such as 2-methacryloxyethyl phosphate (MOEP) or methyl methacrylate (MMA), are used for cationic drugs [94,95]. Additionally, the combination of functional monomers is an alternative to modify the physical properties of hydrogels [96]. Through this ionic method, several *in vitro* studies loaded different ophthalmic drugs, obtaining a drug release lasting between a few hours to two months [97–103]. Under physiological conditions, the interaction between hydrogels and drugs has more complexity since ionic compounds of tears also interact with both elements.

The second strategy is the functionalization of hydrogels with cyclodextrins, which are used for hydrophobic drugs exclusively. Cyclodextrins are a family of cyclic oligosaccharides with a hydrophobic cavity to insert small drugs which are released over time [104]. The functionalized cyclodextrin can be bound to HEMA by copolymerization assisted by acrylic/vinyl derivatives, glycidyl methacrylate (GMA), or cross-linking. *In vitro*, some studies found a drug release lasting between a few hours to two weeks [64,97,105,106]. Besides, Li et al. [107] showed that the diclofenac sodium release was higher in rabbits compared to *in vitro* conditions for the first hour (73% and 42% respectively), but it lasted longer (three days and two days respectively).

2.3. Molecular Imprinting

Molecular imprinting creates a high-affinity binding between contact lenses and drugs by using a drug template during the polymerization reaction. Polymers show imprinted cavities with the most appropriate size and chemical group, where drugs can be reloaded by soaking (Figure 1c). This method also uses functional monomers, mainly acrylic/vinyl derivatives, whose arrangement depends on the molecular conformation of drugs [108]. The addition of high-affinity monomers can make drugs bind easily to contact lenses, but there is a risk that their release might be uncontrolled. For this reason, it is necessary to control the affinity ratio between functional monomers and drugs to obtain a constant and controlled release over time [109].

In 2002, two studies of Alvarez-Lorenzo and Hiratani imprinted soft contact lenses for the first time by using methacrylic acid (MAA) and MMA as functional monomers to load timolol into hydrogels of diethylacrylamide (DEA) and HEMA [110,111]. Both studies found that the *in vitro* release of timolol lasted for more than 12 h [112] and 24 h [111]. Since then, many ophthalmic drugs have been evaluated by this method, such as antibiotics [113], antihistamines [114], nonsteroidal anti-inflammatories [115], corticosteroids [116], or humectants for dry eye treatment [57], showing an *in vitro* release for a maximum of 2 weeks [113]. Most of the studies found in the scientific literature are *in vitro*.

2.4. Colloidal Nanoparticles

The development of nanomaterials permitted the encapsulation of drugs inside colloidal nanoparticles, such as liposomes, micelles, microemulsions, and polymeric-based nanoparticles. Nanoparticles (between 10 and 100 nm) represent a barrier against metabolic degradation while drugs

are released onto the ocular surface [117]. In soft contact lenses, functionalized nanoparticles can be incorporated during the polymerization reaction, by soaking, or being immobilized to the contact lens surface through chemical bonds (Figure 1d) [64]. Of all these methods, the soaking one is probably the most limited because it depends on the size relationship between nanoparticles and the porosity of hydrogels. Concerning the efficacy of functionalized contact lenses with nanoparticles, their drug release is sustained over a longer period compared to nanoparticles in solution [64,117].

Over the last decade, a large number of studies used different nanoparticles to incorporate ophthalmic drugs, such as antibiotics [118], antihistamines [119], immunosuppressors [120], corticosteroids [76], or glaucoma medication [121], into contact lenses. As examples of animal experimentation, different studies showed drug release for seven days with voriconazole-loaded chitosan nanoparticles in mice [122], 10 days with ketotifen-loaded silica shell nanoparticles in rabbits [119], and 14 days with cyclosporine A-loaded polymeric nanoparticles in rabbits [120].

2.5. Drug-Polymer Film Embedded

The addition of a coated drug film by a polymer is another option to increase the retention time of soft contact lenses. Thus, inside the matrix of the hydrogel, two different phases are created (Figure 1e). Some coat polymers used to bind drugs to pHEMA are poly-lactic-co-glycolic acid (PLGA) [60], polyvinyl alcohol (PVA) combined with chitosan [123], or ethyl cellulose (CE) combined with Eudragit S-100[®] [124]. An important consideration is that the physical properties of drugs must be similar to the ones of hydrogels to maintain the transparency of soft contact lenses, which is essential in order to ensure the visual quality during their wear. For those drugs which do not have similar properties to hydrogels, there is a possibility of synthesizing the drug film in the periphery of the lens, where its optical zone would not be affected.

The efficacy of these systems in terms of drug release seems to be directly proportional to the drug film thickness [60,123,124]. In vivo studies showed different strategies to sustain drug release for 12 h with nonsteroidal anti-inflammatories [124], two days with antibiotics [125] and antihistamines [126], or seven days with corticosteroids [127].

2.6. Supercritical Fluid

Supercritical fluids are all the compounds that reach pressure and temperature conditions over their critical point. Thus, both hydrophilic and hydrophobic drugs can be easily dissolved in supercritical solvents to be diffused into the matrix of soft contact lenses (Figure 1f). Drug loading is done by soaking the lenses in a supercritical solvent-drug solution under controlled conditions [128] or assisted by molecular imprinting [129]. The advantage of the first method is that it is possible to use commercial soft contact lenses, while the protocol assisted by molecular imprinting requires a previous polymerization reaction. In any case, both methods are more effective than conventional soaking in terms of the amount of drug released [128,129].

Compared to previously mentioned methods of loading drugs onto soft contact lenses, the use of supercritical solvents offers less promising results since the studies in the literature showed a drug release of only a few hours [128–131]. However, this statement should be carefully nuanced because more studies directly comparing supercritical fluids with other methods would be necessary.

3. Contact Lens Drug Delivery in Glaucoma

As previously mentioned in the introduction, there are three main treatments for glaucoma focus on reducing IOP: pharmacology, laser, and surgery therapies. Pharmacology is often the first option due to its simplicity, being complemented with the others if treatment does not reach the desired IOP. It must be taken into account that this chronic pathology is suffered mainly by the elderly population who do not have the manual dexterity necessary for applying drops, and that it has a high dosing frequency, which will increase the probability of noncompliance or forgetfulness [132,133], leading to a therapeutic failure of treatments [134–136].

With the aim of overcoming such limitations, new approaches for increasing the drug's residence time in the cornea, extending drug release, or increasing its bioavailability are being investigated, which will result in less frequent administrations, irritation, and both ocular and systemic side-effects.

Practically, since the development of CLs, several studies have demonstrated that they can be suitable drug delivery systems for the treatment of several chronic disorders, and especially for glaucoma. See Table 3 [137–139].

Table 3. Drug used with CLs as drug delivery systems for glaucoma.

Drug	Method Used	Loading Conditions	Results	Ref.
Melatonin and analogues.	Soak and release. Balafilcon A	1 mM concentration overnight (8 h)	In vitro: Increased time-release till 30 min	Figure 2 (original data)
Dinucleotides (Ap ₄ A and Gp ₄ G)	Soak and release. Balafilcon A	1 mM concentration overnight (8 h)	In vitro: Increased time-release till 60 min, with 3 days of consecutive release	Figure 3 (original data)
Pilocarpine	Soak and release. Sauton 85 (NVP and MMA)	25 mL of 10 mg/mL pilocarpine for three days	25 glaucomatous patients: Achieved same IOP control with 2 h worn than drop treatment, with a reduction of therapeutic dose (1% vs. 4%)	Hillman et al. [140]
Timolol or brimonidine	Soak and release. Varsufilcon A, etafilcon A and vifilcon CL	0.65 mg/mL or 0.2 mg/mL for seven hours	3 glaucomatous patients: Equivalent control of IOP than with eye drops with only using 30 min CLs per day for 14 days	Schultz 2009 [141]
Timolol	Soak and release. Lotrafilcon A	2.67 mg/mL or 8 mg/mL solution for seven days	Glaucomatous dogs: Same efficacy with one-third drug loading for 4 days (5 mmHg). No IOP changes in untreated eye	Peng 2012 [142]
Timolol	Soak with vit-E. Narafilcon A	3.5 mL of 1.5 mg/mL solution for seven days for control and 21 for vit E	Glaucomatous dogs: Same efficacy with 20% of dose on CL and eye drops. Increased time of hypotensive effects (4 days)	Peng 2012 [143]
Timolol and dorzolamide	Soak with vit-E. Senofilcon A	3.5 mL of 12.75 mg/mL timolol and 20 mg/mL dorzolamide for four days	Glaucomatous dogs: Increased hypotensive effects for 8 days even after cessation of therapy. Less doses needed to obtain hypotensive effects (6-fold less)	Hsu 2015 [91]
Bimatoprost	Soak with vit-E. Senofilcon A and narafilcon A	3 mL of 0.125 mg/mL bimatoprost for 2 days	In vitro: Increased time-release (>10 days) but reduces light transmission	Sekar 2019 [88]
Acetazolamide	Poly-CD. pHEMA CL	5 mL acetazolamide 0.1 mg/mL for 4 days	In vitro: Increased time-release (24 days)	Dos Santos 2008 [144]
Ethoxzolamide	Poly-CD pHEMA CL	1 mg/mL ethoxzolamide for 48 h	In vitro: Facilitated drug loading reaching 1 mg per lens. Increased time-release (>10 days)	García-Fernández 2013 [145]
Timolol	Molecular imprinted pHEMA CL	10 mL of 1 μM for three days	Rabbits: Increased time-release up to 180 min, twice as long as conventional CLs and three times as long as eye drops	Hiratani 2005 [146]
Timolol	Drug-PGT nanoparticles in Senofilcon A	1 g timolol during CL polymerization	Glaucomatous dogs: Reduction of IOP during 2 days (4 mmHg)	Jung 2013 [147]
Timolol and latanoprost	mPEG-PLA micelles in Ocufilecon D	50 μL of 100 μg timolol and 1 μg latanoprost	Rabbits with microspheres: Reduction of IOP during 7 days (7 mm Hg). Sustained drug release for up to 120 h for timolol and 96 h for latanoprost in tear film	Xu 2019 [121]
Latanoprost	PLGA between two layers of methafilcon	80 μL of 50 mg/mL latanoprost	Rabbits: Higher IOP control, with higher concentration in aqueous humor compared to drops (1473 vs. 54 ng/mL)	Ciolino 2014 [60]
Latanoprost	PLGA between two layers of methafilcon	30 and 40 μL of 10 mg/mL latanoprost	Glaucomatous monkeys: Increased time-release (>8 days). Higher IOP control than drop treatment (5.4 vs. 7.4 (low dose) and 9.3 (high dose))	Ciolino 2015 [148]

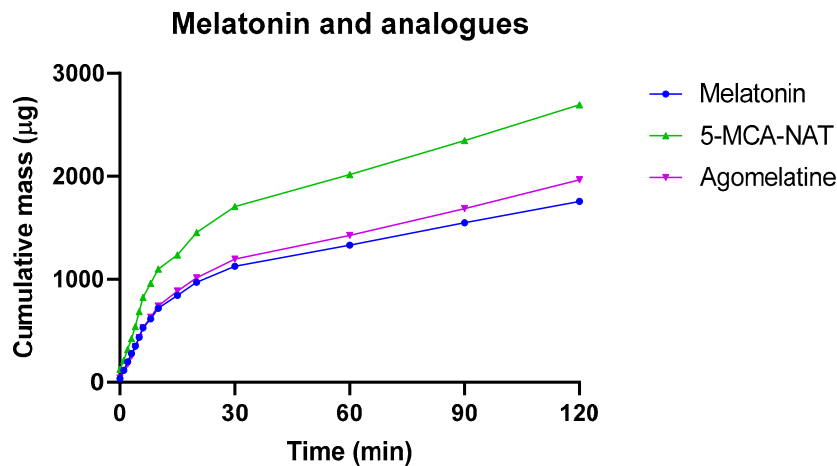


Figure 2. Soak and release method used with melatonin and analogues. There is a substantial release of drugs during the first 30 min and lasting for 2 h. (Balafilcon A. Silicon Hidrogel ionic).

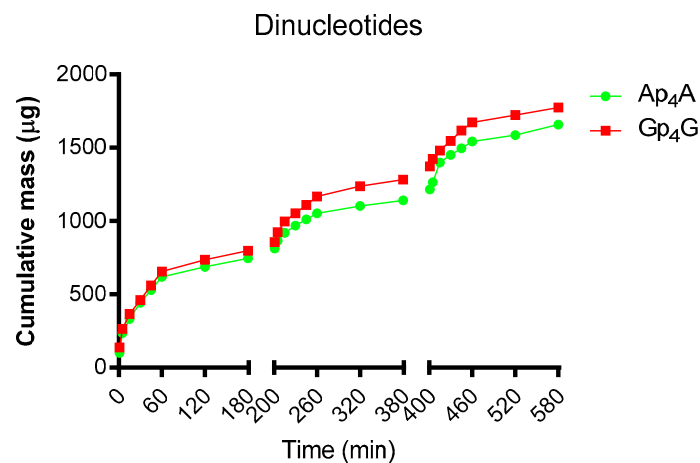


Figure 3. Soak and release method used with the dinucleotides Ap₄A and Gp₄G. There is a substantial release of drugs during the first 60 min, lasting 3 h that could be used for at least 3 consecutive days. This fact opens a new possibility for using multipurpose solutions such as protectors and carriers of drugs, recharging each night the CL with the selected drug. (Balafilcon A. Silicon Hidrogel ionic).

3.1. Soaking

The first approach was made with the soak and release method using pilocarpine [69]. After that, some modifications were made to achieve better results [71,72,140,149–151], reaching the same deduction with 2 h of contact lens loaded with 1% pilocarpine worn, than with 4% pilocarpine drop treatment [71]. The same strategy was also used with other drugs such as timolol and brimonidine, showing equivalent control of IOP using CLs only 30 min per day during 14 days [141]. Furthermore, the use of CLs decreases the possibility of an undesired systemic effect as showing no changes in IOP of untreated eyes [152].

This method has also been used with new potential treatments for glaucoma, such as melatonin and analogues (Figure 2) showing a prolonged release of the drugs during the first 30 min. In the case of dinucleotides such as Ap₄A and Gp₄G (Figure 3) there is a more sustained release of the compounds during the first 60 min and lasting for 3 h. Furthermore, it was proven that it could be used during 3 consecutive days with a similar release if CL were soaked overnight with the drug. This fact opens a new possibility for using multipurpose solutions as protectors and carriers of drugs, recharging each night CLs with the selected drug (non-published data).

It is worth noting that only using contact lenses for 30 min per day, has an equivalent control of IOP than with eye drops [141]. Nevertheless, no study showed a prolonged drug release exceeding 3 h, which implies the need to produce modified CLs with different characteristics to increase the efficacy.

The addition of vitamin E into the matrix of hydrogels creates a biocompatible diffusion barrier that extends the drug release over time [143]. In this sense, timolol loaded in vitamin E modified lenses showed good IOP control, requiring only 20% of the dose used in drop treatment and lasting four days [49].

Similar results were obtained by Hsu et al. [91] when using timolol, dorzolamide or a combination of both. The addition of vitamin E increases from 1 to 25 h the release for timolol and from 2.5 to 36 for dorzolamide. An equivalent control of IOP (5 mmHg) was found using six times less concentration than drop treatment and lasting for up to eight days after treatment cessation [91].

The same approach has also been used with bimatoprost, showing a controlled release at therapeutic doses beyond ten days [88].

However, this modification also has its limitations. Although silicone hydrogel compounds show benefits in the release of these drugs [49,91], pHEMA lenses have not shown any improvement in timolol or brimonidine, with the addition of vitamin E [153].

Even within silicone hydrogels, there are studies that do not find benefits in the use of vitamin E compared to lenses without this pre-treatment [151]. The uncertainty caused by the behaviour of the different materials, as well as the negative impact on oxygen diffusion and ion permeability, are the main drawbacks of this technique [143].

3.2. Functional Monomers

Cyclodextrins (CDs) were known since the 80 s as a promising drug delivery system due to the formation of an inclusion complex with a variety of drug molecules in solution and in the solid state [142]. The result of the application of these molecules to ophthalmology treatments is an increase in the capture and bioavailability of the drug, increasing the tolerability and reducing its cytotoxicity [154–158].

The chemical combination of dextrins with hydrogels of contact lenses can offer multiple alternatives for using them as a delivery device. This combination was first used as a vehicle of acetazolamide, showing a sustained release of the drug of up to 24 days. Furthermore, this release can be controlled by varying the beta-CD concentrations during copolymerization [157].

Similarly, different types of dextrins (alpha, beta, and gamma-dextrins), have been tried in order to improve those results. The use of poly-dextrins in contact lenses has been shown to facilitate the loading of high concentrations of ethoxzolamide (another carbonic anhydrase inhibitor), while ensuring a sustained release for several weeks [144].

These results are very promising, especially considering that, until now, both drugs have only been administered orally, which limits therapeutic action, and these results could lead to a drastic decrease in the therapeutic dose, and therefore a decrease in unwanted effects.

3.3. Molecular Imprinting

Molecular imprinting creates a high-affinity binding between contact lenses and drugs which will increase the time-release [109].

The study by Alvarez-Lorenzo with molecular imprinted CL for timolol showed an increase in absorption by 70% [110]. Following these results, Hiratani et al. trial of CLs on rabbits showed that the time-release was doubled compared to conventional lenses (180 vs. 90 min). Surprisingly, the drug release rate was similar to that of unmodified lenses, so this increase in time appears to be due to the improvement in drug loading of imprinted CL [145].

3.4. Colloidal Nanoparticles

In 2011, Jung and Chauhan [146] evaluated the use of nanoparticle-laden CL with PGT (propoxylated glyceril tryacilate) and EGDMA (ethylene glycol methacrylate) loaded with timolol,

showing controlled releases at therapeutic doses for two to four weeks at 25 °C. Furthermore, the released kinetics of the drug depend on the temperature, therefore, it would not be released during storage, and would be activated when inserted on the cornea.

The same authors carried out subsequent studies with lenses with PGT-timolol, verifying releases of up to one month, without the interference in the optical qualities, nor of permeability to oxygen or ions, with the concentration of nanoparticles used [147]. Likewise, they carried out a preliminary in-vivo study showing significant reductions in IOP for two days.

Recently, Xu et al. [121] also probed micelles-laden CL with mPEG-PLA (Methoxy poly(ethylene glycol)-poly(lactide) copolymer) loaded with timolol and latanoprost. When applied to hypertensive rabbits, IOP was reduced over seven days, thereby showing much better results than with eye drops [121].

3.5. Drug-Polymer Film Embedded

A further step in controlling drug loading and release through LC is the incorporation of a new material into the matrix that makes up CL. One of the first attempts was made by Ciolino et al. when incorporating a PLGA (polylactic glycolic acid) film loaded with latanoprost, between two layers of silicone-hydrogel [60]. In-vivo studies in rabbit showed therapeutic concentrations of latanoprost for four weeks, thus increasing by 30 times the concentration in vitreous humor compared to drop treatment. The same author carried out a study in glaucomatous monkeys, obtaining sustained therapeutic values for more than eight days. In addition, the therapeutic action was higher than that obtained by the administration of drug drops (9.3 mmHg vs. 5.4 mmHg) [158].

The use of a film, however, has the disadvantage of interfering with the optical properties of the lens and a hole in the optic zone must be made in the film in order to solve this problem [158].

4. Conclusions

Using contact lenses as a drug delivery mechanism is a promising system to treat some ocular pathologies like glaucoma [148]. There are some strong points to attest to that, but there are also some weak points to take into account for the future development of this type of drug delivery methods. Using contact lenses for antiglaucomatous, drug delivery increases the bioavailability due to it being able to maintain the drug for a longer time on the ocular surface, thereby enhancing the corneal epithelium passing and thus ensuring more drug concentration on the target point [50,51,83]. Moreover, the active agent penetration to the anterior chamber in topical instillation needs to raise the corneal epithelium permeability using various strategies, adding preservatives or other pharmacological compounds to the formula. The use of this compound increases the toxicity, and in the case of contact lenses, the symptoms would be higher due to the toxic compound remaining longer on the ocular surface. It has recently been reported that the effect of the diadenosina tetraphosphate (Ap_4A), present in the tear film [159], allows the entrance of antiglaucoma agents as a consequence of a decrease in the tight junction barrier function on stratified human corneal epithelial cells [160], as this compound is non-toxic and able to be released from contact lenses [84]. This release of kinetics could probably be the strongest feature of this system. It is important to keep the contact lens transparency when it is impregnated with drugs for treatment. The combination of contact lens with the treatment compound not only permits the treatment of the disease but it may also correct the patient's ametropias [100,161]. From a clinical point of view, drugs must present similar properties in terms of transparency and the index of refraction to commercial hydrogels or, otherwise, these contact lenses could show a certain degree of opacification affecting the visual quality of patients. This fact is also valid for other methods of loading drugs into contact lenses.

Regarding the weak points, contact lenses are a potential trigger of discomfort and dryness at the end of the day. This event has been called "contact lens discomfort" and could be the main reason for discontinuing the contact lens wear and leading to the change in treatment to another drug delivery system [162]. Another concern is the handling of the contact lenses. Glaucoma is more prevalent in the elderly [163] and the topical treatment, with high dosing frequency, could be a concern factor leading

to an increase in noncompliance and therefore, to the failure of the treatment. Contact lens drug delivery treatment would reduce this risk of dropout, however the contact lens manipulation could be more compromised than drug instillation, provoking discomfort during lens wearing, increasing the infection risk or finally, not wearing the contact lens, leading to a higher risk of treatment failure [80]. It seems evident that contact lens drug delivery is not the indicated option for all patients, especially for patients who only need to instill one drop a day. Consequently, a previous selection should be made. Finally, another concern is the contact lens regulation as a medical device [78]. There are some doubts about whether it should be regulated as a medical device, a drug, or a combination of both. The research in this field is more advanced than regulation, demonstrating a big gap in the regulations with regards to clarifying this emerging technology. Nowadays, only the soaking method, an off-label use of contact lens and drug combination is allowed. However, the drug release with this system only lasts for a short time, which is a limitation. Other methods, such as molecular imprinting, are able to maintain the supply of the drug for many days and so would be better for patients in terms of efficacy.

In summary, glaucoma patients could benefit from the emerging contact lenses drug delivery systems as treatment. Although it is still necessary to investigate new materials and the kinetic behaviour of such materials, it is important to note that an important field has been opened. Contact lens knowledge will be combined with other sciences such as pharmacology to potentiate the drug release from contact lenses with features that will make the patient's life safer and more comfortable.

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