

New Era of Ocular Drug Delivery Systems Based on Contact Lenses

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SUMMARY

Ocular drug delivery belongs to the most useful topical administration routes. Ocular drugs are applied on the eye mostly as ocular drops. However, eye drops present many limitations such as poor eye retention time and rapid drug removal from tear drainage. Currently, contact lenses as ophthalmic drug carriers have become very popular since they can extend the drug release time and therapeutic efficacy. It seems that contact lenses which are applied to the anterior chamber present extremely increased bioavailability above 50% which compared to low bioavailability of eye drops is highly beneficial. Moreover, via the topical delivery of ocular drug contact lenses side effects are diminished whereas patient compliance is improved. Despite their advantages, contact lenses as ophthalmic carriers have not been marketed yet. Nonetheless, the last decade, the research interest focused on developing novel contact lenses which can deliver controllable the drugs to the eye. In this review, we summarize the found on literature ocular drug delivery systems based on contact lenses according to their compounds, their designing methods as other characteristics. It can be said that in the foreseeable future more and more topical eye drug delivery systems will be appeared and contact lenses seem to provide the most desirable characteristics. Thus, the drug loaded contact lenses will bring a new evolution on the current marketed ocular formulations. To conclude, this review could be helpful for medical professionals, ophthalmologists and scientists of every subject who want to develop novel ocular contact lenses.

Key Words: Ocular, Drug delivery, Contact lenses, Hydrogels, Polymers, Drug design

Kontakt Lenslere Dayalı Oküler İlaç Taşıyıcı Sistemlerde Yeni Dönem

ÖZ

Oküler ilaç taşınması en kullanışlı topikal ilaç uygulama yollarındandır. Oküler ilaçlar, çoğunlukla göz damlaları olarak göze uygulanır. Ancak göz damlaları gözde kalış süresinin kısalığı ve gözyaşı drenajı ile hızlıca ortamdan uzaklaştırılma gibi çeşitli sınırlamalar gösterir. Son dönemde, kontakt lensler ilaç salım süresini ve terapötik etkinliğini artırarak oftalmik ilaç taşıyıcı sistemler olarak popüler olmaya başlamıştır. Gözün ön odacığına uygulanan ve düşük biyoyararlanıma sahip göz damlalarına kıyasla biyoyararlanımı %50'nin üzerinde artıran kontakt lenslerin son derece faydalı olduğu görülmüştür. Ayrıca, oküler ilaç içeren kontakt lenslerin topikal uygulanmasıyla yan etkiler azaltılırken hasta uyuncu da artırılmıştır. Avantajlarına rağmen oftalmik taşıyıcılar olarak kontakt lensler henüz piyasada satışa sunulmamıştır. Bununla birlikte, son on yılda yapılan araştırmalar kontrollü salım sağlayabilen yeni geliştirilen kontakt lenslere odaklanmıştır. Bu derlemede, literatürde bulunan bileşimlerine, tasarımlarına ve diğer karakteristiklerine göre kontakt lenslere dayalı oküler ilaç taşıyıcı sistemleri özetledik. Öngörülen gelecekte daha fazla topikal ilaç taşıyıcı sistemlerinin ortaya çıkacağı ve kontakt lenslerin istenen özellikleri sağlayacağı söylenebilir. Bu yüzden ilaç yüklü kontakt lensler güncel oküler formülasyonlara yeni gelişmeler getirecektir. Sonuç olarak, bu derleme sağlık profesyonelleri, oftalmolojistler ve yeni oküler kontakt lens geliştirmek isteyen her konudan araştırmacılar için yararlı olacaktır.

Anahtar kelimeler: Oküler, İlaç taşınması, Kontakt lensler, Hidrojeller, Polimerler, İlaç tasarımı

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INTRODUCTION

Ophthalmic diseases can be categorized as acute (R. Gupta, 2003) and chronic (N. Gupta & Kocur, 2014). In most cases, ocular diseases are not life-threatening, however, if they left untreated can lead to blindness or blurred vision. Eye is very complex organ and thus ocular drug delivery belongs to the most challenging field of drug administration routes (Siafaka et al., 2015; Üstündağ-Okur et al., 2014; Üstündağ-Okur, Yoltas, & Yozgatli, 2016; Üstündağ-Okur et al., 2015). Currently, topical application of ocular drugs is preferred since the systemic administration cannot reach eye efficiently (Başaran & Yazan, 2012). As topical eye formulations and most marketed products are used the conventional eye drops or suspensions. However, such formulations demonstrate very low ocular bioavailability and thus should be frequently dosing. Their low bioavailability resulted from various factors, such as rapid removal of drug due to nasolacrimal drainage, tearing and blinking as well as low permeability of the corneal membrane (Maulvi, Soni, & Shah, 2016; Siafaka et al., 2015; Üstündağ Okur, Yozgatli, Okur, Yoltaş, & Siafaka, 2019). Due to the above, novel formulations are designed aiming to overcome such drawbacks. Colloidal suspensions (Siafaka et al., 2015), matrix systems, liposomes (Taha, El-Anazi, El-Bagory, & Bayomi, 2014), microemulsions (Kesavan, Kant, Nath Singh, & Kumar Pandit, 2013), dendrimers (Chaniotakis, Thermos, & Kalomiraki, 2016), in-situ gels (Üstündağ-Okur et al., 2016;

Üstündağ Okur et al., 2019) and ocular inserts such as contact lenses (Alvarez-Lorenzo, Anguiano-Igea, Varela-García, Vivero-Lopez, & Concheiro, 2019) and films (Kapoor & Chauhan, 2008; Üstündağ-Okur et al., 2014; Üstündağ-Okur et al., 2015) are applied as possible sustained release drug carriers. The contact lenses seem to provide various promising characteristics and thus should be further evaluated in clinical trials and in vivo studying.

Contact lenses (CLs) are ocular prosthetic devices placed on the eye surface. They are widely used for correcting vision, aesthetics and therapeutic applications (Farandos, Yetisen, Monteiro, Lowe, & Yun, 2015). The first corneal lenses were developed, in 1949 whereas on 1960 the first corneal lenses based on poly (methyl methacrylate)-PMMA were used. In present, CLs are manufactured by PMMA, poly (hydroxyethyl methacrylate)- PHEMA (Achilias & Siafaka, 2017; Achilias, Siafaka, & Nikolaidis, 2012) and other materials such as silicone and poly (vinyl alcohol)-PVA, (Musgrave & Fang, 2019) (Figure 1). PMMA was first applied as CL compound however due to its limited oxygen permeability, it was replaced by PHEMA. The manufacture of optimal CLs associated strictly with the macromolecule and its polymerization conditions such as temperature, initiator type, polymerization mechanism (Musgrave & Fang, 2019) etc.

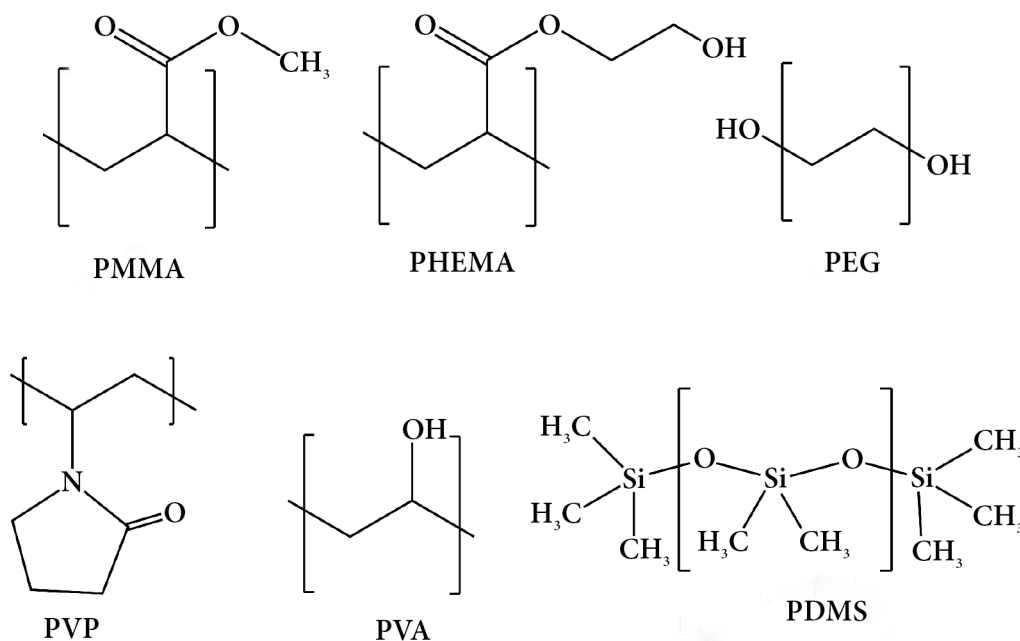


Figure 1. The chemical structures of common polymers develop CLs

Contact lenses (CLs) as drug delivery systems were first introduced in 1965 by Sedlacek (Kumar & Jha, 2011). It has been reported that as drug eluting CLs, the silicone hydrogels and other hydrogels are of the most optimal candidates (Jiawen Xu et al., 2018). Mostly, CLs are used as therapeutic tools for ocular surface and anterior chamber disorders. Besides, CLs have been reported to be applied as posterior segment diseases management (Guzman-Aranguez, Colligris, & Pintor, 2013). From pharmacological aspect, antimicrobials, corticoids, anti-inflammatory, immunosuppressants, lowering of ocular pressure agents are loaded in contact lenses so as to treat various diseases (Holgado, Anguiano-Domínguez, & Martín-Banderas, 2020). In further, CLs intended to be used as drug carriers should possess comfort, cytocompatibility and prolonged release (Ciolino et al., 2009). In fact, CLs present unique features such as increased bioavailability, extended wear time and improved retention time. Considering that the contact lenses are solid formulation can extent retention time from 1 to

3 minutes of eye drops to more than 30 minutes. Thus, the ocular bioavailability is also improved whereas dose frequency is eliminated and the drug is absorbed and reaches target ocular tissues. In addition, the drug systemic absorption is avoided and the related side effects are also diminished (Kumar & Jha, 2011; Maulvi et al., 2016).

The preparation methods for the development of CLs loaded drugs (Figure 2) are: a) soaking method, b) molecular imprinting and c) encapsulation of colloidal nanoparticles into CLs. In case of soaking method, CLs are soaked in drug suspension, followed by drug uptake and release in pre- and post-lens tear film. This method which is the easiest handled technique presents various disadvantages such as burst effect and rigorous release. On the other hand, the retention time compared to the conventional formulations is improved (Bengani, Hsu, Gause, & Chauhan, 2013; Hehl, Beck, Luthard, Guthoff, & Drewelow, 1999; Peterson, Wolffsohn, Nick, Winterton, & Lally, 2006).

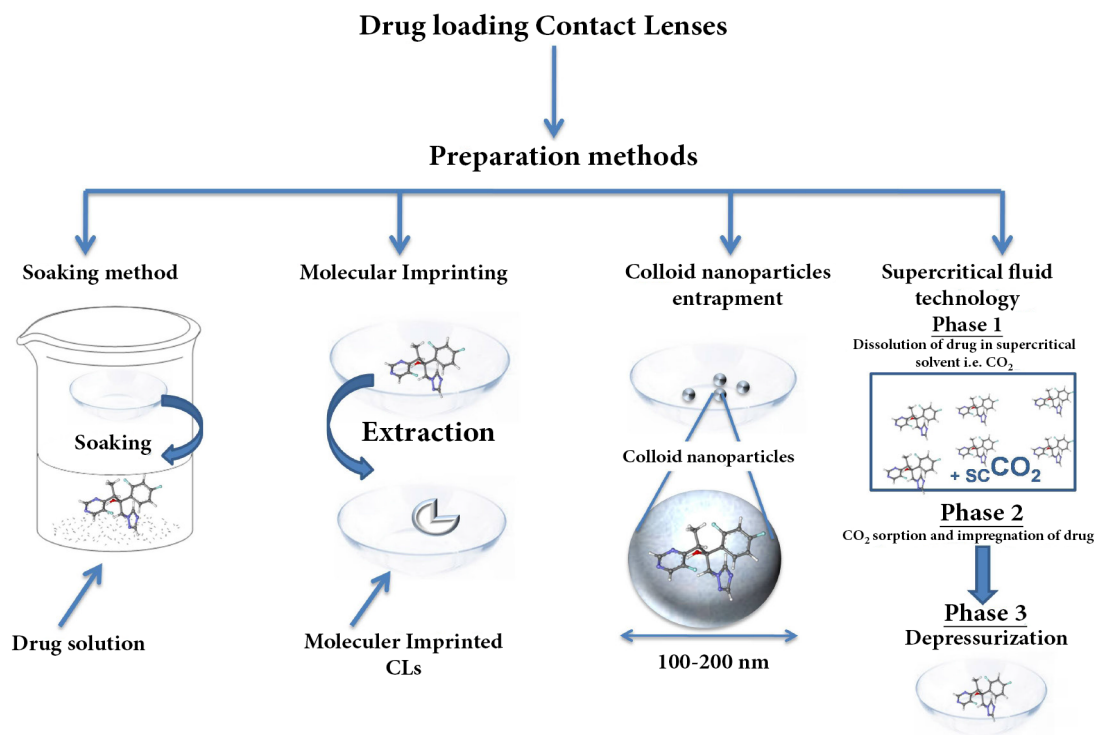


Figure 2. A schematic illustration of preparation methods of drug loaded CLs

The second technique molecular imprinting shows various advantages such as great retention time and controlled drug release. At this case, high drug loading is also achieved. During this method, the target drug is blended with the chosen monomers and

polymerized. Afterwards, drug is extracted from contact lenses leaving macromolecular memory sited and resulting in printing of 3D structure of drug into the polymeric network. Thus, an increased drug loading capacity is provided (Alvarez-Lorenzo et al., 2002; Hi-

ratani, Mizutani, & Alvarez-Lorenzo, 2005; White & Byrne, 2010). In the third technique, colloid nanoparticles i.e. polymeric nanoparticles, liposomes, niosomes, microemulsion, micelles impregnated drug and further loaded in CLs. During this method, drug is released in a prolonged way and also ameliorate the possibility of drug degradation (C. Gupta & Chauhan, 2010; K. H. Hsu, Gause, & Chauhan, 2014; Jung, Abou-Jaoude, Carbia, Plummer, & Chauhan, 2013). Another interesting technique is the supercritical fluid technology which is widely applied as method to

load drugs into contact lenses. During this technique, the drug is dissolved in supercritical solvent like CO₂ (at subcritical or supercritical conditions), followed by interaction with hydrogel contact lenses (Costa et al., 2010). In addition, the drug loading can be controlled by altering several parameters such as pressure, temperature, processing time and depressurization rate (Costa et al., 2010). The possible structures of the developed CLs due to the different preparation methods are seen in Figure 3.

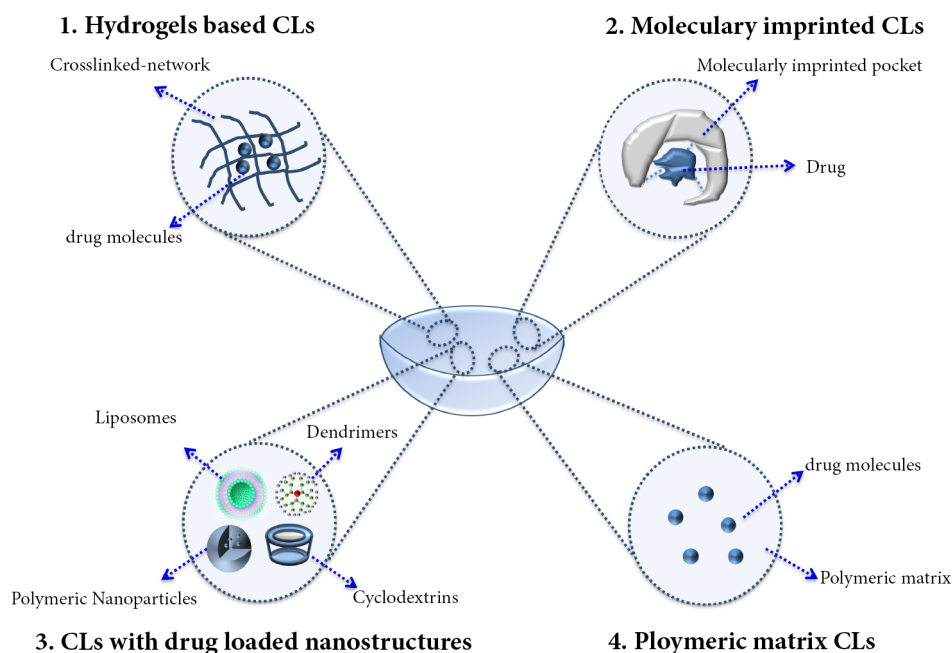


Figure 3. The possible structures of drug loaded CLs

Aim of this study, was to summarize the current drug delivery systems based on CLs due to their possible therapeutic efficacy and disease target. Thus, the contact lenses were categorized according to their drug incorporation to systems for glaucoma, inflammatory, allergic and infection ocular disorders.

ADVANTAGES OF CONTACT LENSES AS OCULAR DRUG DELIVERY SYSTEMS

The CLs compared to other topical eye drug delivery systems provide greater characteristics. As it was mentioned, the ocular delivery presents various limitations due to various eye barriers (Üstündağ Okur et al., 2019). In fact, the continuous tear dilution, the drug drainage due to blinking and tear flow, the non-specific absorption, and the irregular drug penetration which the conventional eye drops induce

(Sharma, Verma, Prajapati, & Pandey, 2013), can be overcome with the utilization of drug loaded CLs. At first, the position of CLs onto the cornea can separate the tear film from the external environment limiting the tear mixing and exchange (Muntz, Subbaraman, Sorbara, & Jones, 2015). Consequently, the drug can be eluting from the CLs in a sustained manner since the molecule residence time is prolonged (Kakisu, Matsunaga, Kobayakawa, Sato, & Tochikubo, 2013). In further, many active molecules can be entrapped in the CLs, generalizing and prolonging their therapeutic action. The prolonged release minimizes the frequent dosing improving the patient compliance. As topical system, the drug loaded CLs eliminate the drug of being absorbed from systemic circulation limiting its possible systemic side effects (Güngör, Erdal, & Aksu, 2013).

OCULAR DRUG DELIVERY BASED ON CONTACT LENSES-THERAPEUTIC APPLICATIONS

In this part, CLs as drug delivery systems are categorized according their possible therapy (Figure 4). As it was already mentioned, CLs can load drugs for both acute and chronic diseases. Topical delivery of

various drugs into the eye can be achieved by using ocular CLs which are capable of loading both hydrophilic and hydrophobic drugs. Biodegradable or non-biodegradable and biocompatible polymers are formulated on CLs aiming to produce contact lenses with minimize side effects.

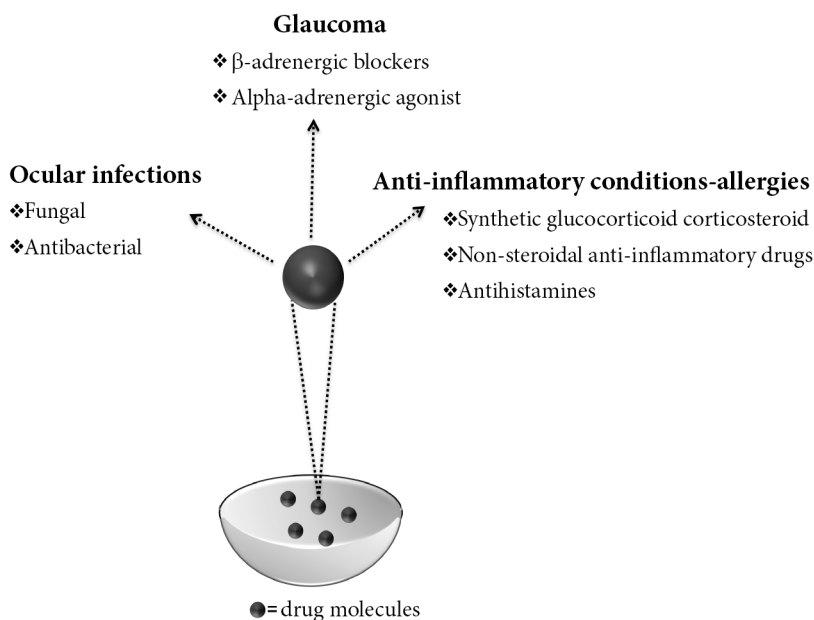


Figure 4. Ocular drug delivery based on contact lenses

Glaucoma

Glaucoma is the second notable cause of optic nerve eventual damage and vision loss worldwide (Jung et al., 2013). Various drugs are applied for glaucoma management but topical drops of β -adrenergic blockers, such as timolol maleate (TIM) (Siafaka et al., 2015), or miotics such as pilocarpine (Karasulu, Ince, Ates, Yavasoglu, & Levent, 2015) are extensively applied. Many researchers have focused on polymeric nanoparticles using biodegradable and non-biodegradable polymers, to develop therapeutic contact lenses to treat ocular diseases. Therapeutic silicone hydrogel contact lenses were developed by incorporating propoxylated glyceryl triacrylate nanoparticles-NPs loaded with TIM. The preparation of nanoparticle-laden silicone hydrogels was accomplished by adding particles to the polymerization mixture followed by free radical polymerization. In vivo studies on beagle dogs revealed that decrease on intraocular pressure whereas *in vitro* release confirmed prolonged release for 30 days. Nonetheless, the use of NPs reduce ion and oxygen permeability and the con-

tact lenses present negative effects (Jung et al., 2013). Similarly, crosslinked NPS based on propoxylated glyceryl triacrylate and ethylene glycol dimethacrylate encapsulated TIM and loaded into contact lenses. The drug loaded particles were dispersed in hydroxy methyl methacrylate (HEMA) gels, the common material for CLs. Herein, the drug was also released in a prolonged manner for 4 weeks. It was resulted that the mechanical strength was improved whereas the water uptake was decreased demonstrating promising characteristics (Jung & Chauhan, 2012). In another study, PHEMA CLs entrapped ethyl cellulose microparticles of TIM as therapeutic system for glaucoma. The microparticles were prepared by spray drying and dispersed in CLs. It was demonstrated that TIM was released for 48 hours due to its formulation on microparticles (Maulvi, Soni, & Shah, 2015). Microemulsions (MEs) based contact lenses have been designed from various researchers. For example, timolol loaded CLs lenses were loaded with o/w MEs of ethyl butyrate and Pluronic F127. The free radical solution polymerization with UV initiation was applied

for the microemulsion-loaded p-HEMA hydrogels. A controlled release of TIM was also depicted which is essential for glaucoma therapy (Li, Abrahamson, Kapoor, & Chauhan, 2007). In another study, TIM was incorporated in MEs stabilized by silica shell using octadecyltrimethoxysilane and were further dispersed in hydrogels. The CLs were synthesized by free radical solution polymerization of the monomer with chemical initiation. A prolonged release over 8 days was achieved (Gulsen & Chauhan, 2005). CLs soaked in TIM and brimonidine tartrate solution were obtained by Schultz et al. As it was expected, a burst phenomenon was provoked followed by sustained release. Clinical studies which were accomplished with reduced dose frequency, justified decrement on intraocular pressure (Schultz, Poling, & Mint, 2009). Another study evaluated molecular imprinted CLs comprised from hydroxyethyl methacrylate, methacrylic acid and methyl methacrylate. The drug loading rate of TIM was efficiently increased (Alvarez-Lorenzo et al., 2002). However, the study lacks of *in vivo* results. Anirudhan et al. prepared molecular imprinted CLs based on TIM imprinted copolymer of carboxymethyl chitosan-g-hydroxy ethyl methacrylate-g-polyacrylamide impregnated into PHEMA. A sustained release was depicted for TIM loaded CLs which according to authors' opinion can achieve the therapeutic efficacy needed in glaucomatous patients (Anirudhan, Nair, & Parvathy, 2016). TIM and Acetazolamide were significantly entrapped in Balafilcon A-silicon hydrogel CLs using a discontinuous supercritical solvent method. It was revealed that drugs were released in moderate pattern (Costa et al., 2010). Numerous works involved the use of lipophilic vitamins such as Vitamine A (VitA) and E (VitE) as agent enhancer agents. TIM released in greater extent when VitE was also incorporated in CLs (Peng, Kim, & Chauhan, 2010). Similarly, drug-eluting CLs sustained the release of TIM and Dorzolamide when VitE was also loaded (Kuan Hui Hsu, Carbia, Plummer, & Chauhan, 2015). A recent study, involve the use of VitE and VitA into hydrogel CLs based on PHEMA. It was revealed that TIM and brimonidine were loaded in great extent although their hydrophilic nature. However, *in vitro* release did not change (Lee, Cho, Park, & Kwon, 2016). A very interesting idea involved the use of light-mediated drug eluting CLs. The prepared CLs released TIM due to natural daylight exposure at more therapeutically optimal doses compared to conventional formulations. The cost effective CLs could really act as promising and alternative drug delivery system against Glaucoma as well as other ocular disorders (Mu, Shi, Liu, Chen, & Marriott, 2018). In further, another promising system composed by TIM and hyaluronic acid

(comfort agent)-loaded semi-circular ring-implanted CLs were developed by Desai et al. The active molecules were entrapped using the soaking method. *In vitro* release studies revealed prolonged release for 4 days while *in vivo* studies in rabbit model exhibited the TIM presence till 3 days after administration. Similarly, *in vivo* pharmacodynamics studies exhibited decrement on intraocular pressure with lower dosing than conventional eye drops (Desai et al., 2018). Guidi et al studied hyaluronic acid ability to alter TIM release from 2-hydroxyethyl methacrylate with 3-methacryloxypropyltris (trimethylsiloxy) silane (TRIS) or N,N-dimethylacrylamide (DMA) with TRIS molecular imprinted hydrogel CLs. It can be said that TIM was released for 2 days (Guidi, Korogiannaki, & Sheardown, 2014). Korogiannaki et al. developed CLs from a hydrophilic monomer, either 2-hydroxyethyl methacrylate or N,N-dimethylacrylamide and a hydrophobic silicone monomer of methacryloxypropyltris (trimethylsiloxy) silane and loaded with TIM using as wetting agents hyaluronic acid or PVP. The loading was achieved during the synthesis of the silicone hydrogels via the direct entrapment method. TIM was sustainable released from 4 to 14 days depending on wetting agents ratio (Korogiannaki, Guidi, Jones, & Sheardown, 2015). Both studies should be further evaluated for their *in vivo* performance.

Besides TIM, also other drugs as latanoprost, travoprost and bimatoprost are applied for Glaucoma management. Horne et al. developed silicone hydrogel lenses soaked in latanoprost solution. A controlled release was achieved for 96 hours (Horne, Judd, & Pitt, 2017). The same group, recently, revealed that more latanoprost could be loaded into silicone hydrogel lenses than PHEMA CLs (Horne, Rich, Bradley, & Pitt, 2020). In both cases, a sustained release was depicted which is desirable for glaucoma therapy. Latanoprost-eluting low-dose CLs and high-dose CLs were produced by encapsulating a thin latanoprost-polymer film within the periphery of a methafilcon hydrogel. *In vivo* studies in glaucomatous monkeys demonstrated sustained release of drug and great intraocular pressure reduction (Ciolino et al., 2016). Previously, Ciolino et al. produced Latanoprost-eluting contact lenses encapsulating latanoprost-PLGA films in methafilcon by ultraviolet light polymerization. *In vitro* and *in vivo* studies showed an early burst of drug release followed by sustained release for one month (Ciolino et al., 2014). Conventional PHEMA based CLs and silicone hydrogel soft CLs were soaked in Latanoprost solution and studied for their efficacy. *In vitro* results showed their possible efficacy as anti-glaucoma agents (Mohammadi, Jones, & Gorbet, 2014).

Anti-inflammatory ocular conditions

Inflammatory ocular diseases are disorders of high prevalence and seem to concern high part of population. Dry eye disorder and allergic conjunctivitis (Jeng, 2018) as well as uveitis which is the inflammation of the uvea are of the most known. Various active ingredients loaded eye drops have been used as anti-inflammatory agents, which lack of bioavailability. Ocular allergies are also quite common health problem. It is believed that the use of CLs as anti-allergic carriers can act as a physical barrier against airborne antigens and as drug carriers which can improve the treatment of ocular allergies (González-Chomón, Silva, Concheiro, & Alvarez-Lorenzo, 2016). The dry eye syndrome is a multifactorial disorder, which is related with patient discomfort, inflammation, visual disturbance, and tear film instability, which can lead to ocular surface damage. In most cases rewetting candidates are utilized as topical installations (McCann, Tomlinson, Pearce, & Papa, 2012; Vogel, Crockett, Oden, Laliberte, & Molina, 2010)

Endophthalmitis is a serious intraocular infection that occurs as post- surgery complications causing visual impairment or blindness. The utilization of topical applied nonsteroidal anti-inflammatory either prophylactically or as treatment for ocular post-cataract surgery inflammation is recommended (Taban, 2005). Thus, meloxicam aggregates of nanocrystals coated by bovine serum albumin were dispersed in PHEMA CLs showing sustained release. However, the study should be reinforced with *in vivo* results (Zhang et al., 2014). Another corticosteroid used for reduction of intraocular inflammation is triamcinolone acetonide. This drug was loaded in soft hydrogel contact lenses and the drug release was preferably sustained (García-Millán, Koprivnik, & Otero-Espinar, 2015). Diclofenac is an anti-inflammatory drug used to treat pain and inflammation after ocular surgeries. The drug was loaded in β -cyclodextrin which further grafted in hydrogels based copolymers glycidyl methacrylate. The obtained data demonstrated great drug loading and sustained delivery of diclofenac for 15 days (Rosa dos Santos et al., 2009). Molecular imprinted poly (HEMA-diethylaminoethyl methacrylate-co-polyethylene glycol (200) dimethacrylate) soft CLs were developed as diclofenac carriers. A zero-order release was achieved exhibiting desirable potential (Tieppo, Pate, & Byrne, 2012).

Dexamethasone (DXM) is widely applied for ocular inflammation. For example, Bengani et al. produced ACUVUE CLs surface coated with ionic DXM 21-disodium phosphate leading to improved wettabil-

ity and sustained release of drug to 2 days (Bengani & Chauhan, 2013). Another study, involved the use of hydrogel CLs based on methoxy (polyethylene glycol)-block-polycaprolactone micelles for the encapsulation of DXM acetate. More specifically, the drug was entrapped on the micelles and then incorporated in the lenses. The obtained data showed prolonged release for more than 30 days (Lu, Yoganathan, Koci-olek, & Allen, 2013). DXM was entrapped in CLs with 30% VitE so as its release to be extended. The drug was loaded in the CLs via two ways; by direct addition of the drug in the VitE-ethanol solution before soaking the pure lens in the solution or by soaking the VitE loaded lenses in a drug-PBS solution. In fact, DXM was released for 9 days revealing that VitE can act as dissolution enhancer agent (Kim, Peng, & Chauhan, 2010). A more promising study included the use of Chitosan NPs which firstly loaded with DXM and afterwards added in PHEMA CLs. *In vitro* release profile depicted a sustained rate for 10 days up to 22 days. This fact induced great ocular bioavailability (Behl, Iqbal, O'Reilly, McLoughlin, & Fitzhenry, 2016). Kim et al. produced extended wear silicone contact lenses for the delivering of TIM and DXM. The drug was loaded by soaking the gel in drug-PBS solutions. The CLs revealed extended release as it is required for ocular inflammatory disorders (Kim, Conway, & Chauhan, 2008). Flurbiprofen is also a common applied non-steroidal anti-inflammatory molecule applied as ocular therapeutic. A study involved its loading into endow CLs known as Hilafilcon B via supercritical fluid (SCF)-assisted molecular imprinting technique. The promising results revealed great drug loading and prolonged release (Yañez et al., 2011). Another used drug to reduce ocular inflammation is prednisolone. CLs loaded with prednisolone nanoparticles were prepared by soaking method. The developed CLs were transparent and permeable whereas drug was sustainable release (ElShaer et al., 2016). A similar study involved the use of prednisolone nanocapsules into CLs demonstrating also prolonged drug release (Katzner, Chaves, Pohlmann, Guterres, & Beck, 2017). Pirfenidone known for its use in chemical burns was entrapped in CLs with VitE demonstrating improved ocular bioavailability which is highly desirable for ocular drug release (Dixon et al., 2018).

Antihistamines are active molecules used in allergies. CLs loaded with sodium cromoglycate and ketotifen via soaking method and demonstrated great drug release which is desirable for allergies management (Phan, Weber, Mueller, Yee, & Jones, 2018). Ketotifen also entrapped in silicon hydrogel CLs via submerging them in drug solution. The developed

CLs exhibited improved drug loading and extended release profile. In vivo data showed that drug can be found in tear fluid 24 hours after administration (Jinku Xu, Li, & Sun, 2011). Olatapadine, utilized in allergic conjunctivitis, was also entrapped in molecular imprinted CLs exhibiting prolonged release and elimination of eye irritation (Kuan Hui Hsu et al., 2015).

Hyaluronic acid is widely used as wetting agent for dry eye syndrome. In the past, molecular imprinted CLs released hyaluronic acid for 1 day improving dry eye symptoms (Ali & Byrne, 2009). Moreover, these CLs can also act as treatment option in corneal wound healing and epithelial cell migration since hyaluronic acid is known for its healing properties (Gomes, Amankwah, Powell-Richards, & Dua, 2004). A more recent work evaluated in vivo the use of hyaluronic acid CLs. Rabbit animal models showed sustained release of hyaluronic acid for 2 weeks whereas a faster and complete healing was also observed (Maulvi et al., 2017).

Cyclosporine A is also a common applied drug for dry eye syndrome. The formulation based on an ocular emulsion due to its insolubility (Ames & Gallor, 2015). A study involved the use of Cyclosporine A loaded in silicone hydrogel CLs with VitE via soaking method. It was demonstrated that the drug retention time and bioavailability was significantly improved in comparison with the conventional eye drops. Moreover, drug release was extended for 30 days (Peng & Chauhan, 2011).

Ocular fungal and antimicrobial infections

Eye infections are a common health problem (Watson, Cabrera-Aguas, & Khoo, 2018). Various microorganisms have been identified as possible infective agents of an eye. Virus, fungi and bacteria are the most pathogenic microorganisms. Ocular infections should be immediately treated and require frequent dosing since various side effects can be caused. Blindness is among the possible outcomes if an eye infection left untreated. Topical eye drops are started as soon as possible after setting the diagnosis. However, due to the eye tear drainage, the most of the drug amount is diluting and the therapeutic outcome is delayed.

Bacterial keratitis and conjunctivitis are treated by antibacterial drugs. Moxifloxacin (MOX), a quinolone is widely applied as topical eye formulation but requires multiple dosing. Phan et al used various marketed contact lenses and soaked them in moxifloxacin solution of phosphate tamponade and artificial tears. This solution led to MOX release for 24 hours (Phan et al., 2016). MOX also loaded in CLs with Hyaluronic acid using the modified cast mould-

ing technology and the release was extended for 48 h (Maulvi et al., 2018). Similarly, MOX also loaded by soaking in acrylic intraocular lenses and the drug release was controlled and sustained for 2 weeks. The rabbit models data showed that the system can provide maximum therapeutic levels for endophthalmitis prophylaxis after cataract surgery (Filipe et al., 2019). Bajgrowicz et al. incorporated MOX and Ciprofloxacin to conventional hydrogel and silicone hydrogel CLs via soaking method. It was revealed that drug loading was optimal whereas release was differentiated by the sued CLs (Bajgrowicz, Phan, Subbaraman, & Jones, 2015). According to the study of Paradiso et al. the VitE incorporation in commercial silicone CLs prolonged the release of Levofloxacin and Chlorhexidine, which are used in bacterial keratitis and other eye infections. Hence, their frequent use can be minimized (Paradiso, Serro, Saramago, Colaco, & Chauhan, 2016). Ciprofloxacin was loaded in unilamellar liposomes and multilamellar liposomes and further incorporated in CLs. Multilamellar liposomes exhibited sustained release as it is required for CLs formulations (Jain & Shastri, 2011). Corneal targeted NPs of natamycin were also loaded in CLs in order to reduce dose and dosing frequency of the antibiotic drug. Gladly, *in vitro* release profile exhibited prolonged release for 8 hours and great antibacterial potential (Chandasana et al., 2014). The antimicrobial peptide melamine was covalently attached to CLs and studied for its ability to decrease bacterial keratitis in rabbit model wearing CLs. It was exhibited that *P. aeruginosa* induced bacterial keratitis was ameliorated (Dutta, Vijay, Kumar, & Willcox, 2016).

Fungal keratitis, a severe ocular disease, is one of the leading causes of blindness worldwide (Üstündağ Okur et al., 2019). Voriconazole, is an antifungal drug with various uses (Siafaka et al., 2016; Üstündağ Okur et al., 2018) and is also applied against fungal keratitis in the form of eye drops. Voriconazole loaded hybrid hydrogel CLs which were cross-linked through electrostatic interactions between quaternized chitosan, silver nanoparticles, and graphene oxide revealed very promising characteristics such as sustained release, good antimicrobial functions and great antifungal efficacy (Huang et al., 2016).

CONCLUSION

Drug loaded contact lenses provide a great potential on ocular drug administration, since they can deliver drug efficiently, show improved retention time and great patient compliance. It can be said that numerous contact lenses capable of eluting drugs have been developed; nonetheless, their marketing was not

obtained. This fact is highly related with economic, processing and other physicochemical parameters issues. Thus, a huge advancement must be done on addressing such drawbacks. For example, more efficient contact lenses which can be release drug in efficient time, with high oxygen permeability and the ability to be used from all age's patients as well as night and day are of the most critical drawbacks which should be overcome. Nevertheless, contact lenses can play the major role on the ocular drug delivery field since they possess high bioavailability and other characteristics, which are beneficial on ophthalmology field. To sum up, designing contact lenses for both chronic and acute eye disorder are of high need and scientists should focus on such direction.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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