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Contact lenses as drug controlled release systems: a narrative review

As lentes de contacto como sistema de libertação controlada de fármacos: uma revisão narrativa

Helena Prior Filipe[1,4], José Henriques[2], Pedro Reis[3,4], Pedro Cruz Silva[4], Maria João Quadrado[5], Ana Paula Serro[6]

ABSTRACT

Topically applied therapy is the most common way to treat ocular diseases, however given the anatomical and physiological constraints of the eye, frequent dosing is required with possible repercussions in terms of patient compliance. Beyond refractive error correction, contact lenses (CLs) have, in the last few decades emerged as a potential ophthalmic drug controlled release system (DCRS). Extensive research is underway to understand how to best modify CLs to increase residence time and bioavailability of drugs within therapeutic levels on the ocular surface. These devices may simultaneously correct ametropia and have a role in managing ophthalmic disorders that can hinder CL wear such as dry eye, glaucoma, ocular allergy and cornea infection and injury. In this narrative review the authors explain how the ocular surface structures determine drug diffusion in the eye and summarize the strategies to enhance drug residence time and bioavailability. They synthesize findings and clinical applications of drug soaked CLs as DCRS combined with delivery diffusion barriers, incorporation of functional monomers, ion related controlled release, molecular imprinting, nanoparticles and layering. The authors draw conclusions about the impact of these novel ophthalmic agents delivery systems in improving drug transport in the target tissue and patient compliance, in reducing systemic absorption and undesired side effects, and discuss future perspectives.

Keywords: *Contact lenses; Dry eye syndrome; Glaucoma; Allergy; Keratitis; Bioavailability; Residence time; Molecular imprinting; Nanoparticles*

RESUMO

A forma mais frequente de aplicação terapêutica em oftalmologia consiste na instilação de gotas oculares, mas dadas as limitações anatómicas e fisiológicas do olho, é necessária dosagem frequente com possível repercussão na adesão do paciente à terapêutica. Nas últimas décadas, as lentes de contacto (CLs) têm surgido como um potencial sistema de libertação controlada de fármacos na superfície ocular (DCRS) para correção do erro refrativo. Está em curso uma extensa investigação para entender a melhor forma de modificar as CLs, de modo a aumentar o tempo de residência e a biodisponibilidade do medicamento na superfície ocular dentro de níveis terapêuticos. Ao corrigirem a ametropia, estes dispositivos poderão simultaneamente desempenhar um papel na gestão de perturbações oftalmológicas, tais como a síndrome do olho seco, glaucoma, alergia ocular e infecção corneana, que podem comprometer o porte seguro e confortável das CLs. Nesta revisão narrativa, os autores explicam como as estruturas da superfície ocular determinam a difusão de fármacos no olho e sintetizam as estratégias para aumentar a permanência e biodisponibilidade dos mesmos. Em seguida, apresentam os resultados e as aplicações clínicas das CLs embebidas em fármacos, como DCRS, através da incorporação de barreiras de difusão, de monómeros funcionais, da liberação controlada por iões, da impressão molecular, de nanopartículas e pelo processo camada sobre camada. Os autores concluem avaliando o impacto destes novos sistemas de entrega de agentes farmacológicos ao melhorar o seu transporte no tecido alvo, reduzindo a sua absorção sistémica e os seus efeitos colaterais indesejáveis, e discutem perspectivas futuras.

Descritores: Lentes de contacto; Síndrome de olho seco; Glaucoma; Alergia; Queratite; Biodisponibilidade; Tempo de permanência; Impressão molecular; Nanopartículas

[1] Departament of Ophthalmology, Hospital of the Armed Forces - Lisbon, Azinhaga dos Ulmeiros, Paço do Lumiar, Lisbon, Portugal
[2] Department of Retina and Vitreo, Institute of Ophthalmology Dr. Gama Pinto, Lisbon, Portugal; IRL – Institute of Retina of Lisbon, Lisbon, Portugal.
[3] Departament of Ophthalmology, Hospital of the Armed Forces, Lisbon, Portugal; Department of Ophthalmology, Hospital of SAMS, Lisbon, Portugal.
[4] Department of Ophthalmology, Hospital of SAMS, Lisbon, Portugal.
[5] Department of Ophthalmology, Hospitals of the University of Coimbra, Faculty of Medicine of the University of Coimbra, Coimbra, Portugal.
[6] Center of Structural Chemistry, Complex I, Instituto Superior Técnico, University of Lisbon, Lisbon, Portugal; Center of Interdisciplinar Investigation Egas Moniz, Instituto Superior de Ciências da Saúde Egas Moniz, Caparica, Portugal.

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Introduction

Poly (methyl methacrylate) (PMMA) was the first successful polymeric contact lense (CL) material introduced in the market in the 1960s. These CLs are rigid, time consuming to fit and not very comfortable to wear. Research into new types of polymers led to the development of hydrogels, the first biomaterials designed for clinical use. They consist of a cross-linked polymeric network with a high capacity of water absorption and have been extensively used in numerous biomedical applications since the early 1960s. In 1965 Wichterle at al. pioneered the suggestion of their potential use in ophthalmic drug delivery as bandage soft CLs (SCL). Although the new materials were quite hydrophilic, which kept the lens soft and flexible, their gas-permeability was still low. The introduction of highly permeable silicone hydrogel (SH) in the late 1990s overcame SCLs' insufficient oxygen transmission to the cornea. SHCLs represented a significant leap for further research on CLs as ophthalmic drug controlled release systems (DCRS). [1-4]

Several factors emphasize their singular importance in the field of ocular therapeutics: the approximately 125 million worldwide CL wearers; well-studied CL biocompatibility and transparency; the familiarity of their use with minimal effect on ocular functions and a large residence time in the eye. Eye physiological and anatomical constraints compromise the correct drug concentration and optimal absorption of pharmacological agents at the specific action site requiring multiple dosage of eye drops eventually associated with noncompliance, overdosing and unwanted systemic side effects. The latter are especially important in chronic ocular diseases such as glaucoma, allergy and dry eye as in those requiring a timely and effective control, as infectious keratitis and corneal wound healing. [5-8]

Drug Routes, Ocular Surface and Effectiveness Constraints

The three main routes of administration of ocular medication are systemic, intraocular and topical. Effective systemic delivery requires a high drug concentration to achieve a therapeutically effective dose within the eye. Intraocular drug administration is effective but as with any invasive procedure it carries a not insignificant risk, especially if repeated treatments are required. Topically applied medication represents approximately 90% of aqueous ophthalmic formulations. They are simple to formulate, have minimal storage limitations and can be self-administered. However, significant drug losses occur with this administration form, which limit its therapeutic efficiency. Understanding the structure of the ocular surface, tear drainage physiology and drug diffusion mechanisms can shed an understanding on ocular drug pharmacokinetic and the reasons for such inefficiency. [9,10]

If the human tear film is approximately 7 ìl, a 30 ìl eye drop is rapidly squeezed out of the eye, the remainder being mixed in the tear volume with an estimated residence time of approximately 2 - 3 minutes. The conjunctiva presents a higher permeability than the cornea due to its vascularized nature and an area that is approximately 16 - 18 times larger. Thus, most of the solutes are absorbed by the conjunctiva, drained by the lacrimal system into the nose and enter the systemic circulation with potential unwanted systemic side effects. In this context, only 1-7% of the medication within an eye drop reaches the target tissue with effective therapeutic effect thus justifying multiple dosing over extended periods with potential association with low compliance or drug overdosing. [3, 10, 11]

The precorneal tear film allows corneal hydration and provides an epithelium-tear interface able to create a high refractive index. It presents an inner mucous layer anchored by microvilli to the epithelium, a middle aqueous layer with mucin and free lipid and an external thin lipid layer. It is divided into three compartments: precorneal, conjunctiva and tear menisci and is bounded by the corneal and the conjunctiva epithelia**.** CLs divide the tear film into a pre-lens tear film (PLTF) and a 4 micra thick post-lens tear film or pre-ocular tear film (POLTF), through which CL drug diffusion occurs. Eye opening leads to a limited drug release towards the PLTF and the CL motion promotes drug diffusion from the POLTF into the cornea or radially outwards from the CL into the tear lake. [10,]

The cornea is a multilayer structure with epithelium, stroma, and endothelium separated by the Bowman and Descemet's membranes. The cornea has both lipophilic and hydrophilic properties, which explains a transport resistance to hydrophilic drugs of approximately 90% and about 10% to hydrophobic preparations. Corneal diffusion is the main route for topically applied drug absorption leaving a lesser role for the conjunctival/scleral route to play in. Corneal epithelium is a stratified layer presenting Ca2+-dependent membrane adherent regions (zonula occludens, zonula adherens and desmosomes) creating tight junctions, highly resistant to drug diffusion. Bowman's membrane is a transitional and acellular structure approximately 8–14 ìm thick. Corneal stroma is a gel-like layer with 80% of water, collagen, mucopolysaccharides and proteins, and represents approximately 90% of the total thickness (around 500 ìm) of the cornea. Due to solubility and partition coefficient limitation it shows significant diffusion resistance for lipophilic drugs and minimal for hydrophilic drugs. Descemet's membrane is an approximately 6 ìm thick membrane deposited by the endothelial cells. These loose epithelia-like cells regulate stromal hydration and maintain the cornea transparent. They form a monolayer of cells of about 13 ìm of thickness, the endothelium that provides little resistance to paracellular drug transportation. [10, 12, 13]

The conjunctiva comprises several layers of epithelial and goblet cells that line the palpebral, culs de sac and the bulbar ocular surface to the corneal limbus. Most of the apical epithelial cells express mucin on their surface to create a protective glycocalyx. Goblet cells secrete gel-forming mucins that are relevant for eye lubrication and protection. The lacrimal gland produces smaller mucins. Diffusion through conjunctival epithelial cells follows a para-cellular path, ion channels, water channels, co-transporters, and transport pumps for ion, glucose, and water located in the cell membrane. [10, 13]

Drainage of the tear film from the eye is an active process that depends on blinking.[3, 10]

New delivery systems and devices to improve drug bioavailability

Morrison and Khutoryanskiy categorize the strategies to promote drug residence time and diffusion into the eye into three groups: Drug Solubility and Penetration Enhancement, Ocular Implants and Drug Retention from which we will emphasize CLs[14] (Table 1).

Hydrotropic compounds improve aqueous **drug solubility** of poorly water-soluble compounds. Hydrotropes, such as caffeine, urea and nicotinamide enhance the solubility of riboflavin, while cyclodextrins form drug complexes with steroids, carbonic anhydrase inhibitors, pilocarpine and cyclosporine A (CyA), which are too large to partition to the cornea. Formulating for higher drug concentration also increases bioavailability. The

Table 1

Strategies to promote drug bioavailability. Adapted from Morrison and Khutoryanskiy [14]

STRATEGIES TO PROMOTE DRUG BIOAVAILABILITY
Solubility and Penetration Enhancement
Hydrotropic compounds and higher drug concentration formulations.
Penetration enhancer formulations.
Ocular Implants
Implantable devices able to reside within the eye.
Retention Strategies
Viscosity-enhancing polymers, *in situ* gels and bio-adhesive formulations.
Ocular inserts to place and retain the agent in immediate contact with target tissue.

incorporation of compounds able to modify the corneal epithelia improves **drug penetration** and tissue drug partitioning. Benzalconium cloride (BAC), commonly used as a preservative in ocular drug formulations, cetylpyridinium chloride (CPC), ethylenediaminetetraacetic acid (EDTA), polyoxyethylene strearyl ether (PSE) and polyethoxylated castor oil (PCO) are examples of such compounds with well-known ocular surface toxic effects. [15,16]

Intraocular lenses such as **ocular implants** can be modified to provide a controlled release of pharmacological agents and prevent intraocular inflammation, infection and lens posterior capsule opacification**.** There are already available in the market injectable intraocular implants to treat several chronic eye diseases ensuring a drug sustained release for 2.5-3 years: Iluvien™ (Alimera Sciences Inc.) for diabetic macular edema, RetisertÒ (Baush &Lomb) and OzurdexÒ (Allergan) for chronic non-infectious posterior uveitis and Durasert™ (Pfizer Inc.) for glaucoma. [14, 17- 18]

Several **drug retention strategies** have been pursued to minimize the need for repeated treatments, especially in chronic diseases. They comprise **viscosity-enhancing polymers**, **"in situ" gels** undergoing phase transition from liquid to gel under physiological conditions, **mucoadhesives** and mucus-covered mucosal epithelial membranes, and **nanoparticles** drug-delivery systems as submicron structures in which drugs can be attached or encapsulated**.** Submicron-sized liposomes (ssLips) formulated as eye drops were effective in delivering coumarin-6 to the retina. **Ocular inserts** are drug-loaded devices designed to deliver a sustained drug release in direct contact with the conjunctiva or with the cornea and finally dissolve, erode or biodegrade. Ocusert® (Alza Corporation, Palo Alto) could deliver pilocarpine at either 20 ìg/h or 40 ìg/h. Ocufit SR® (Escalon® Medical Corp) is a silicone elastomer rod-shaped device to be placed in the lower conjunctival fornix. Minidisc Ocular Therapeutic System (OTS, Bausch & Lomb, UK) is a drug-loaded polymer disc (4–5 mm) to be placed on the upper or lower fornix and deliver gentamicin or sulfisoxazole over a period of 3 to 14 days. The human amniotic membrane can be used as a drug-loaded ocular device to deliver ofloxacin for up to 7 hours in vitro. CLs are hard or soft ocular insert devices designed to fit directly onto the cornea, up to now, mainly to correct ametropia. SCLs are produced from hydrophilic or hydrophobic hydrogel polymers. They can soak a large volume of aqueous solution relative to their anhydrous form with sufficient pharmaceutically active content able to diffuse from the polymer matrix into the tear film, bathe the eye and interact with the ocular tissue. Antibiotic and anti-inflammatory medication can be combined with a bandage CL to effectively manage ocular trauma, post-surgery conditions and promote epithelization. Several commercially available CLs were FDA approved to serve this purpose: Pure Vision (balafilcon A, Bausch+Lomb), Acuvue 2 (etafilcon A, Vistakon Inc.), Acuvue Oasys (senofilcon A, Vistakon Inc.), and Air Optix Night & Day (lotrafilcon A, Alcon). [13-15, 19]

Generating Contact Lense based Drug Controlled Release Systems and Clinical Applications

The three main objectives underlying the development of DCRS based on CLs to enhance effective drug delivery are:

1. To improve and extend CL wear tolerance by incorporating anti dry eye and allergy agents' formulations.
2. To enhance patient compliance and reduce unwanted systemic side effects especially in chronic diseases such as glaucoma and dry eye whilst correcting ametropia.
3. To manage corneal wound healing such as "bandage lenses" by incorporating antimicrobial or anti-inflamatory agents. [13]

Offering a higher drug bioavailability to the cornea than conventional forms of treatment, CLs look the ideal carrier for ocular medication. Several strategies have been attempted to extend drug residence time and improve bioavailability including: soaking, incorporation of diffusion barriers, functional monomers, ligands, colloidal nanoparticles, molecular imprinting, and surface multi layering. [15] (Figure 1).

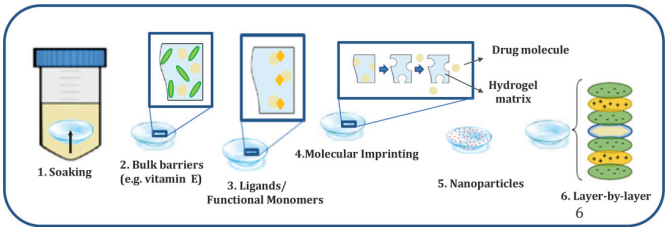

Figure 1: Schematic diagram of strategies commonly used to improve drug release behavior from drug loaded CLs: 1- Soaking, 2- Incorporation of diffusion barriers such as vitamin E, 3- Incorporation of ligands/functional monomers in the polymeric matrix, 4- Molecular imprinting 5- Incorporation of drug-loaded nanoparticles or other colloidal nanostructured systems and 6- Surface coating by multi-layering colloidal nanoparticles and ligands.

CLs **drug soaking** is the earliest and simplest procedure to prepare drug lense combinations. The hydrophilic matrix of SCLs, ranging from 30 to 80 percent water, can absorb the drug from a soaking solution till equilibrium and then release it by simple diffusion when inserted in the eye. Intraocular pressure decreased from 55.6 to 30.0 mm Hg after two hours' use of a 1% pilocarpine loaded CL following this process, to treat acute angle closure glaucoma. Assays with SCL hydrogels of poly (2-hydroxyethyl methacrylate) (pHEMA) loaded in drug solutions containing, pilocarpine, levofloxacin, chlorhexidine, timolol and dexamethasone have demonstrated dynamic drug diffusion. More recently epidermal growth factor-soaked CLs have shown a positive therapeutic effect in a rabbit model wound healing and improved the healing time in non-significantly inflamed

corneas of patients with delayed corneal re-epithelization when compared to saline-soaked CLs. [21-28]

SCL drug absorption and release is drug specific. Drug uptake depends on factors such as CL thickness and water content, the drug's molecular weight and gel matrix solubility. Similar CLs could absorb 7 to 8 mg of cromolyn sodium whereas only 0.07 mg of dexamethasone sodium phosphate. For most tested compounds such as prednisolone, pilocarpine, and ciprofloxacin, release by hydrophilic CLs was complete within 1 to 3 h, whereas ketotifen fumarate eluted from SHCLs over approximately 4-5 hours. [8,29]

In vitro release studies are commonly carried out in conditions that are far from simulating the physiological delivery conditions. In order to more reliably predict the drug's release kinetics in the eye, it is crucial to develop microfluidic models that mimic, as closely as possible, the hydrodynamic conditions of the eye such as volume of liquid in contact with the ocular surface and tear flow rate**.** [30]

Although simple, the drug loading method by soaking is limited by the rapid drug release and will be more appropriate to produce daily disposable therapeutic CLs. Research is now focused on novel approaches to control drug release. Several processes have been attempted to create additional barriers to CL drug release and generate ocular surface drug delivery over time at the correct dosage. [31]

Vitamin E aggregates incorporated within SHCLs block UV radiation and create a hydrophobic diffusion barrier to rapid drug diffusion without compromising proper oxygen permeability, ion permeability, and light refractive properties. Vitamin E loading proved to be very effective in increasing release duration of lidocaine, CyA, timolol, levofloxacin, chlorhexidine, dorzolamine, dexpantenol, betaine, dexamethasone and betamethasone, from hours to several days. [32-37]

Research on dry eye management has been increasingly focusing on the inflammatory aspect and CyA was FDA approved to treat moderate-to-severe dry eye disease. SHCLs were able to keep CyA delivery rates within therapeutic levels for 14 days. Vitamin E loaded CLs provided a CyA extended release up to one month. *In vivo* transport and toxicity studies are needed to assure the benefits of extended wear CLs for this purpose. CLs loaded with 30% of vitamin E showed a dexamethasone release time extended to 7-9 days for ACUVUE(®) OASYS™, NIGHT&DAY™ and O(2)OPTIX™, which is a 9 to 16 fold increase compared to drug release duration by CLs without vitamin E loading [11, 38, 39]

Serro et al. also showed that vitamin E loaded commercial CLs presented a significant increase of clorhexidine and levofloxacin release duration while retaining critical properties for *in vivo* use. [35]

Weak interactions between drugs and **polymer ligands** include hydrogen bonds, electrostatic interactions and host-guest interactions. They can induce drug loading and controlled release by ions in solution. Based on ion-exchange reaction these ligands store anionic or cationic drugs depending on the charge of their functional groups. Hydrogels containing cationic functional groups suit the delivery of anionic drugs whereas those containing anionic functional groups the release of cationic drugs. However, sustained release of these ions ligand-containing hydrogels last only several hours, making them unsuitable for extended drug delivery. Cyclodextrins (CDs) have hydrophobic internal cavities that can include "guest" drug molecules. Poly(2-hydroxyethyl methacrylate) hydrogels containing â-cyclodextrin (pHEMA/â-CD) have been investigated as a platform for sustained release of ophthalmic drugs. Incorporation of hyaluronic acid into hydrogels allowed timolol and ciprofloxacin release for a prolonged period. [39- 42]

The incorporation of **functional monomers** able to interact with the drug in the hydrogels may prolong release duration. Increased interaction of the drug with these monomers delays its diffusion from the hydrogel. For example, the combination of the hydrophobic monomer 3-(trimethoxy-silyl) propyl methacrylate and the ionic monomer N,N-dimethylaminoethyl methacrylate improved insulin and protamine loading and allowed their extended release from pHEMA SCLs. Andrade-Vivero et al. reported that the incorporation of 4-vinyl-pyridine (VP) and N-(3-aminopropyl) methacrylamide (APMA) monomers increased the amount of loaded ibuprofen up to 10-fold and diclofenac up to 20-fold without compromising lens properties. The sustained drug release process from pHEMA-VP lasted for at least 24 hours for ibuprofen and almost 1 week for diclofenac. Kim et al. designed a SH comprising a hydrophilic monomer N,N-dimethylacrylamide (DMA) and a silicone monomer methacryloxypropyltris (trimethylsiloxy)silane (TRIS), with a new macromer bis- alpha, omega-(methacryloxypropyl) polydimethylsiloxane (MW 7152). This extended wear SHCL enabled an extended release of timolol, dexamethasone, and dexamethasone 21-acetate (hydrophobic and hydrophilic drugs) from 2 weeks to 3 months depending on the composition of the hydrophobic and hydrophilic components. Corneal abscess and opacity were almost healed after wearing a gatifloxacin loaded P(HEMA-co-MAA) hydrogel CL for 48 hours. [8, 11, 43-45]

Colloidal nanoparticles are submicron-sized particles either encapsulating or mixed with the agent molecules. Two common forms are lipid spheres (liposomes) and colloidal polymeric nanoparticles. Due to their excellent biocompatibility, liposomes are promising candidates for dispersion or surface immobilization on CLs Nanoparticles are specifically designed to present high affinity for the drug of interest, being either dispersed in the matrix or coating the surface of the CL. Once inserted in the eye the agent diffuses out of the CL matrix away from the nanoparticle towards the tear film. Nanosphere - encapsulated ciprofloxacin incorporated into HEMA-based CL (Acuvue; Johnson & Johnson Vision Care, Inc., Jacksonville, FL) provided a sustained and effective bactericidal activity. Timolol-loaded nanoparticle incorporated in HEMA-based CLs maintained drug stability under refrigerated conditions and the temperature change promoted the drug release upon CL insertion. Nanoparticle loaded gels released timolol in phosphate buffered saline (PBS) for 2-4 weeks within therapeutic levels, looking promising for extended drug release applications. Sustained and effective bactericidal activity was provided by conventional hydrogel CLs incorporating nanosphere-encapsulated ciprofloxacin. [8, 11, 46-54]

Molecular imprinting consists of creating a template based on a macromolecular memory within a flexible network with a higher affinity towards a drug molecule. Functional monomers thus generated, should favorably interact with a specific drug and this change in formulation improves drug uptake and prolongs delivery. Commonly used monomers for CLs include acrylic acid (AA), acrylamide (AM), methacrylic acid (MAA), methyl methacrylate (MMA) and N-vinyl 2-pyrrolidone (NVP). Increased partitioning due to imprinting depends on the fraction of the functional monomers in CLs, temperature, pressure, drug-functional monomer ratio, initiator concentration and degree of

crosslinking. Imprinted hydrogels composed of HEMA and small amounts of MAA presented higher timolol uptake (12mg timolol/g dry hydrogel) than non-imprinted gels and a drug release during 8–10h. Ketotifen fumarate loading was 6-fold greater in the highest functionalized imprinted hydrogels and their diffusion coefficients were 10 times lower than in less functionalized hydrogels. [55-59]

Timolol is the most commonly used drug in imprinting studies but hyaluronic acid, diclofenac, ibuprofen, norfloxacin, ketotifen fumarate, acetazolamide, ciprofloxacin and prednisolone have also been studied.[7,11, 60-62]

Despite being different from typical functional monomers used in molecular imprinting, hyaluronic acid proved to be useful in modifying the drug release curve from model SH lenses having shown a controlled release over 24 hours. As a wetting agent, hyaluronic acid enhances comfort and additionally promotes corneal wound healing and epithelial cell migration,.[63]

Layer-by-layer platforms have been applied for drug delivery due to its simple and mild aqueous manufacturing conditions at room temperature. By sandwiching a poly[lactic-co-glycolic acid] layer (PLGA) in a 100 micron thick gel extended release of timolol and dexamethasone was achieved from 2 weeks to 3 months . Hydrogel containing a layer of ciprofloxacin loaded PLGA film sandwiched between layers of pHEMA was able to release medication for an extended period and prevent bacterial growth. Chitosan/alginate layers were tested to control the release of different ophthalmic drugs from a silicone-based hydrogel. A double layer of this coating led to a controlled release of diclofenac for one week. [64- 66]

Perspectives and Summary

Research in CL based DCRS shows promising results in a wide variety of situations such as a potential application to treat posterior segment diseases and a platform to culture and transfer limbal cells to treat limbal stem cell deficiency. In vitro experimental results and mathematical modeling suggested that a single CL worn for about 2 hours achieved the same therapeutic effects as hourly instillation of eye drops in controlling corneal cysteine crystals deposition in cystinosis. CL based DCRS can work as a responsive drug delivery platform to environmental triggers such as temperature, pH, ionic interactions or light stimulation. They can assist in the management of corneal persistent epithelial defects by using bandage CLs soaked in vibronectine, a protein that expedites corneal epithelial wound healing and in treating fungal keratitis with CLs as drug reservoir releasing agents for up to 21 days. [67-74]

Nevertheless, several challenges remain to extend this treatment option to the general population due to CLs' increased risk of infection, to processing, storage, safety, cost-benefit and regulatory issues. To our knowledge, a ketotifen-CL combination (Vistakon/Johnson&Johnson) for patients with allergic conjunctivitis (NCT 00432757) and a plant polysaccharide lubricant alginic acid–CL combination for dry eye CL wearers (NCT 01918410) represent an effort in the clinical application of these systems. [50, 75-77]

In summary CLs as DCRS are emerging as an effective treatment option for several ocular disorders, including those that can compromise a comfortable and safe CL wear such as glaucoma, allergy and dry eye. By improving bioavailability and effective localized drug delivery these systems can enhance patient compliance, reduce overdosing and avoid unwanted side effects, whilst correcting ametropia. They promote the safe and comfortable wearing of CLs by the incorporation of wetting agents, provide a timely and efficient medication release in corneal epithelial defect, treat infection and promote healing.

Drug incorporation in CLs can be achieved with several techniques from which soaking is the earliest. There is exciting, ongoing research on techniques to increase drug retention on ocular surface and obtain a sustained release within therapeutic levels. The incorporation of vitamin E, ligands, functional monomers, drug-loaded nanoparticles, molecular imprinting, and layering are under study. An ideal CL drug delivery system should involve high drug loading and controllable drug release without compromising the biomaterial properties of CLs.

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Corresponding Author:
Helena Prior Filipe
Departament of Ophthalmology, Hospital of the Armed Forces - Lisbon, Azinhaga dos Ulmeiros, Paço do Lumiar, 1690-020 Lisbon, Portugal - Department of Ophthalmology, Hospital of SAMS, Rua Fialho de Almeida, 1070-128 - Lisbon, Portugal
Phone: +351967061457
E-mail: hpriorfilipe@gmail.com