Improvements in Topical Ocular Drug Delivery Systems: Hydrogels and Contact Lenses

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ABSTRACT - Purpose. Conventional ophthalmic systems present very low corneal systemic bioavailability due to the nasolacrimal drainage and the difficulty to deliver the drug in the posterior segment of ocular tissue. For these reasons, recent advances have focused on the development of new ophthalmic drug delivery systems. This review provides an insight into the various constraints associated with ocular drug delivery, summarizes recent findings in soft contact lenses (SCL) and the applications of novel pharmaceutical systems for ocular drug delivery. Among the new therapeutic approaches in ophthalmology, SCL are novel continuous-delivery systems, providing high and sustained levels of drugs to the cornea. The tendency of research in ophthalmic drug delivery systems development are directed towards a combination of several technologies (bio-inspired and molecular imprinting techniques) and materials (cyclodextrins, surfactants, specific monomers). There is a tendency to develop systems which not only prolong the contact time of the vehicle at the ocular surface, but also at the same time slow down the clearance of the drug. Different materials can be applied during the development of contact lenses and can be combined with natural inspired strategies of drug immobilization and release, providing successful tools for ocular drug delivery systems.
ABBREVIATIONS: CDs (cyclodextrins), SCL (soft contact lenses), HEA (2-hydroxyethyl acrylate), PHEA (2-hydroxyethyl acrylate), MβCD (methacrylated βCD), MHP-βCD (methacrylated HPβCD), PMMA (polymethylmethacrylate), (pHEMA) 2-hydroxyethyl methacrylate, MMA (methyl methacrylate), (MAA) methacrylic acid, TRIS (trimethyl siloxy silane), NVP (N-vinylpyrrolidone), (DMA) N,N-dimethylacrylamide, GMA (glyceryl methacrylate), PC (phosphorylcholine), Cyc (cyclosporine), BSA (bovine serum albumin), MX (meloxicam), TA (triamcinolone acetonide), MA (methacrylic acid).

INTRODUCTION

Ocular drug delivery is one of the most interesting and challenging endeavors faced by the pharmaceutical scientist, due to the critical and pharmacokinetic specific environment of the eye (1). The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The eye structures, which come in contact with drug delivery systems topically administered, are the ocular globe and the nasolacrimal drainage system. The exposed part of the eye is covered by a thin fluid layer designated by the precorneal tear film. The film thickness is approximately 3-10 µl and the resident ocular volume is about 10 µl (2) and, in normal conditions, the eye can accommodate only a very small volume of administered drugs without overflowing (3, 4).

The cornea is a clear, transparent and avascular tissue to which nutrients and oxygen are supplied by the lacrimal fluid and aqueous humor. The cornea and anterior sclera are protected against incidental injury and particulate abrasion by the eyelids and the lacrimal system (5). The conjunctiva is a thin transparent membrane, which lines the inner surface of the eyelids and is reflected onto the globe. At the corneal margin, it is structurally continuous with the corneal epithelium. The membrane of the conjunctiva is vascular and moistened by the tear film (6).

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The nasolacrimal drainage system consists of a secretory, distributive and collection parts. The secretory portion is composed by the lacrimal gland proper, which reflects tears induced by peripheral stimuli, e.g. chemical or mechanical irritation, temperature due cold, and light. Reflex stimulation may increase lachrymation a 100 - fold, even up to 300 µl/min resulting in a wash out of the foreign body, including drugs (7). The absorption of lipophilic drugs can occur through the nasal mucosa during drainage, or can cause, adverse side effects and even toxic reactions (8).

Various precorneal factors (9) described in Figure 1 can limit the ocular absorption of drugs by shortening corneal contact time of applied formulations. As a result, only a few percentage of the applied dose will be delivered into the intraocular tissues. The rest will be washed away and absorbed through the nasolacrimal duct and the mucosal membranes of the nasal, oropharyngeal and gastrointestinal tract. In consequence, the major part (50-100 %) of the administered dose will be absorbed into the systemic drug circulation which can cause several side effects (9).

The continuous secretion of tear fluid limiting the contact time of topically applied drugs with the eye surface, again reduces their ocular bioavailability, especially after application of low viscosity aqueous eye drop solutions (10). Consequently, less than 5% of the applied drug is absorbed through the cornea into the eye (9, 11).

In order to overcome these drawbacks novel ocular drug delivery systems such as dendrimers, cyclodextrins, nanoparticles, liposomes, implants, polymer coating devices viral and non-viral vector based delivery system, polymeric micelles, smart hydrogels and SCL have been designed to enhance drug bioavailability after ocular administration. This article provides an introduction about hydrogel for ocular application with specific focus of hydrogel as contact lenses for topical ocular drug delivery.

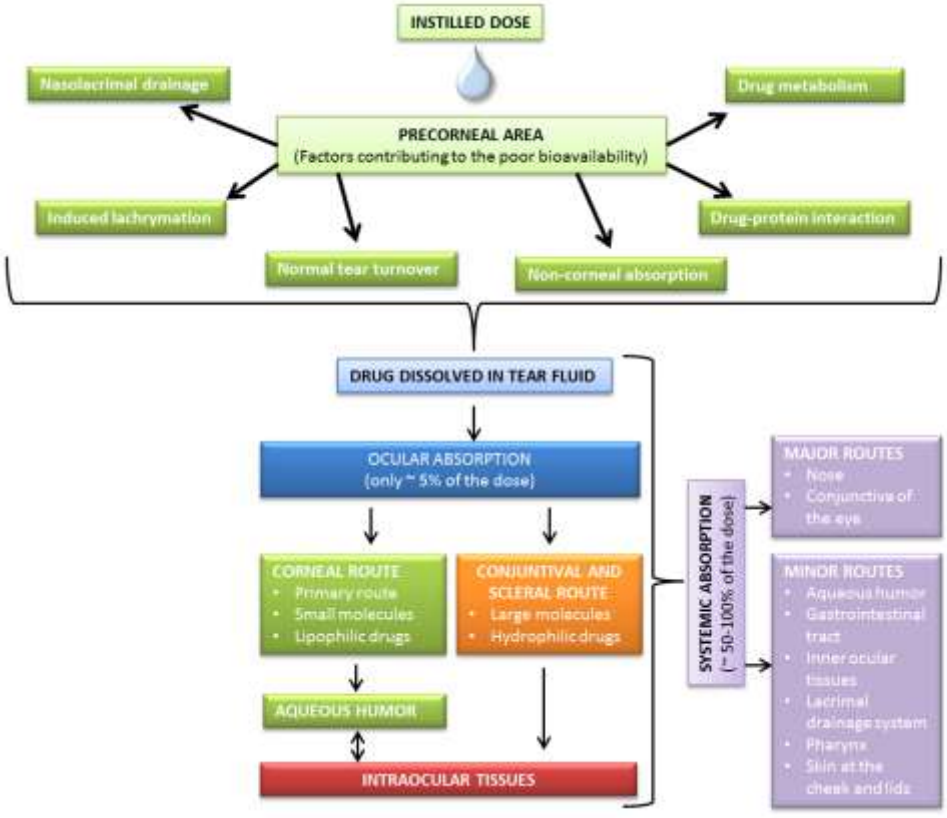

Figure 1. Precorneal factors that influence bioavailability of ocular drops: main absorption routes of topically applied ophthalmic drugs (Adapted from (9)).

HYDROGELS

Hydrogels are three-dimensional hydrophilic networks and can be defined as polymers chains that present the ability to swell in water or aqueous systems, without dissolving (12). Due to the hydrophilic properties of hydrogels polymer chains, they are able to retain a large amount of water or biological fluids within their structures. The high biocompatibility of hydrogels results from their high water content and soft-surface properties (13). Hydrogels are versatile materials because they can be tailored-made to possess various properties by manipulating the synthetic or processing methods. Hydrogels can be made to respond to environmental stimuli, such as temperature, pH, light and specific molecules (13, 14).

Hydrogels are being exploited for a variety of biomedical applications, including the area of tissue engineering, e.g. the artificial cornea (15), and to produce controlled drug delivery systems (12, 16, 17). Their highly porous structure can easily be tuned by controlling the density of cross-links in the gel matrix, the affinity of the hydrogels for the aqueous environment in which they are swollen, and also allows drug loading into the gel matrix for subsequent drug release at a rate dependent on the diffusion coefficient of the drug through the gel network (13). Hydrogels can be prepared from both natural and synthetic polymer materials. Natural polymers are cross-linked by either physical or chemical bonds, whereas synthetic hydrogels can be easily prepared by cross-linking polymerization of synthetic monomers (18). Table 1 shows several criteria for hydrogels classification, depending on their preparation method, physicochemical properties and advantages of hydrogel for clinical use.

Hydrogels are then classified based on the nature of the cross-linking, which can be chemical or physical. When the polymer chains of a hydrogel are connected by covalent cross-linking, they are described as chemical gels.

Once the polymer chains are covalently linked to each other, hydrogels cannot be reshaped once set, being also called thermoset hydrogels. Physical gels are defined as continuous, disordered and three-dimensional networks formed by non-covalent cross-links (19), which include hydrogen bonding, hydrophobic interaction, stereo complex formation, ionic complexation and crystals formation (18).

Other classification comprises hydrogels with interconnected pores, which provide unique properties of fast-swelling kinetics and high swelling ratios. A variety of methods can be used to prepare porous hydrogels, such as the porosigen technique, phase separation technique, cross-linking of individual hydrogel particles and gas-blowing (or foaming) technique (20, 21). In general, two different methods are used to prepare chemical hydrogels, which results from the polymerization of water-soluble monomers, such as acrylic acid, acrylamide, hydroxyethyl methacrylate, hydroxypropyl acrylate and vinylpyrrolidone in the presence of multifunctional cross-linking agents. These hydrogels can also be prepared by cross-linking water-soluble polymers using chemical reactions that involve functional groups of the polymers such as vinyl, hydroxyl, amine, and carboxyl groups (19, 22). Physical hydrogels are prepared by cross-linking without chemical reactions by non-covalent bonds that can be formed through electrostatic interactions, hydrogen bonding, antigen-antibody interactions, and supramolecular chemistry associations (23-25).

The swelling ratio of hydrogels in aqueous media is also an important property for their applications. It describes the amount of water that is contained within the hydrogel at equilibrium as a function of the network structure, hydrophilicity, crosslinking ratio and ionization of the functional groups (14). The cross-linking density of a hydrogel is also closely related to other important properties such as mechanical strength and permeability.

When hydrogels are used as drug delivery systems, several methods for controlled release can be used, such as diffusion, dissolution, osmosis and ion exchange. The incorporation of additives into hydrogels can change the viscosity of the microenvironment and/or its polarity, changing the distribution of drugs and modulating their release. These effects are more remarkable when the additive interacts with the drug or the polymer chains, altering the drug-hydrogel interactions (26, 27). As a result, hydrogels are commonly used in clinical practice and experimental medicine for wide range applications, including diagnostics, coating, molecular immobilization, tissue engineering, cells separation, scaffolds, design and production of devices as contact lenses. The main advantage offered by hydrogels for drug delivery

Table 1. Classifications of hydrogels and advantages of their use in clinical practice and experimental medicine (Adapted from (18)).

CRITERIA	CLASSIFICATION	Hydrogels in clinical practice and experimental medicine	ADVANTAGES
Origen	Natural (proteins, polysaccharides and nucleic acids) Synthetic (PGE-PLA-PGE, poly(vinyl alcohol) Combination of Natural and Synthetic (collagen-acrylate)		▪ Protect different actives and cells ▪ Good transport properties ▪ Easy to modify ▪ Can be injected ▪ Swelling activation ▪ Drug delivery ▪ Good Cell adhesion ▪ Biocompatible ▪ Sterilizibility ▪ Water content ▪ High mechanical strength ▪ Porosity ▪ 3D orientation ▪ Reproducible ▪ Mimetic ▪ High loading ▪ Release variable ▪ Inexpensive ▪ No cytotoxicity
Water content or degree of swelling	Low swelling Medium swelling High swelling		
Porosity	Nonporous Microporous (10 to 100nm range) Macroporous (100 nm to 10 μm range) Superporous (10 to 1000 μm range)		
Cross-linking	Chemical (or covalent) Physical (or noncovalent)		
Ionic charge	Neutral Cationic Anionic Amphophlytic		
Physical structure	Amorphous Semi-crystalline Hydrogen bonded Supermolecular Hydrocolloidal		
Biodegradability	Biodegradable Nondegradable		
Methods of preparation	Homo-polymer Copolymer Multi-polymer Interpenetrating polymeric		
Responsiveness to stimuli	pH Temperature Ionic strength		

applications includes the possibility for sustained release, which results in a high local concentration of the active pharmaceutical ingredient over a long period of time (13).

The Use of Cyclodextrins as a Strategy to Improve the Design of Hydrogels Characteristics for Topical Ocular Delivery

Despite many advantageous properties, hydrogels also present few limitations. One problem is related to the drug delivery from hydrogels, where the quantity and homogeneity of the ocular drug loading into hydrogels may be limited especially for hydrophobic drugs. Due to the high water content and large pore sizes of most hydrogels, a relative rapid drug release over a few hours to a few days may occur (13). Several well-known chemically cross-linked hydrogels may be obtained using homopolymers or copolymers, and grafted, branched or linear polymers (28). Cyclodextrins

(cyclic oligosaccharides, CDs) have been proposed as a new attractive biomaterial (29-31) to obtain hydrogels, combining both, the favorable property of CDs to form inclusion complexes and the swelling behavior of hydrogels. The CDs hydrophilic exterior, maintains the bulk hydrophilicity and the swelling state of the hydrogel. On the other hand, their hydrophobic interior, facilitates the entrapment and controls the release of hydrophobic drugs (32). Because of these reasons, CDs are presented as a useful material to use in hydrogels preparation for ocular applications (13).

CD-containing hydrogels can be prepared loading drug complexes into hydrogels after gel cross-linking for a proper drug delivery system. Kanjickal *et al*. observed a favorable release kinetic when a CD-cyclosporine inclusion complex for drug loading in a poly (ethylene glycol) hydrogel was used (33). In the development and formulation of hydrogels, CDs play multiple roles such as crosslinking agents, conveying peculiar structural and physicochemical properties to the matrix, and interacting by means of inclusion complexes with lipophilic drugs. Salmaso *et al.* reported that CD-based hydrogel can be a properly controlled and sustained drug delivery system. High cross linked polymer networks made with acrylic or vinyl monomers of CDs are particularly promising materials for controlled delivery systems for the administration of lipophilic drugs (28).

Copolymerization of CDs with acrylic monomers, yielding acrylamidomethyl-γCD, was also reported to improve the loading and release capacity of lipophilic drugs such as triamcinolone (34). Furthermore, CDs have been combined or chemically conjugated with various hydrophilic polymers such as polyacrylates. An example is poly(hydroxyethyl methacrylate-co-methacrylated-βCD), a chemical conjugated that can modulate the degree of swelling, mechanical properties, the drug loading and release rate from hydrogels without compromising their cytocompatibility (35). Liu and Fan synthesized hydrogels by the copolymerization of a monovinyl CD monomer with 2-hydroxyethyl acrylate (HEA), loading the inclusion complex of *β*CD with a drug molecule in the poly (2-hydroxyethyl acrylate) (PHEA) hydrogel. The *N*-acety-5-methoxytryptamine (melatonin) was used as a model drug. The formation of melatonin/*β*CD complex retarded the diffusion rate of melatonin, and a sustained release of melatonin from the PHEA hydrogel with high content of *β*CD was obtained by comparison to the hydrogel without *β*CD (29). In another study, Xu *et al*. incorporated mono-methacrylate βCD into hydrogels by photopolymerization, observing an increase in the equilibrium between the swelling ratio and the tensile strength. The molecule model used to loading studies was the antioxidant puerarin and the release of the drug showed dependent of the βCD content in the hydrogel (36).

Grafting the CD to the hydrogel provides improved control over drug release kinetics. Ribeiro *et al.* explain the role of CDs, βCD and γCD, in the loading and the release rate of acetazolamide and ethoxzolamide from N,N-dimethylacrylamide-co-N-vinylpyrrolidone (DMA-co-NVP) hydrogels. The results showed that the role played by the CDs is strongly dependent on the drug physicochemical properties and their ability to form inclusion complexes; being particularly relevant for slightly soluble drugs, that have high affinity for CDs cavity (37). Recently, contact lens materials were functionalized with methacrylated βCD (MβCD) and methacrylated HPβCD (MHP-βCD), and their ability to deliver antifungal agent natamycin *in vitro* were evaluated. The authors observed that the functionalization with MβCD and MHP-βCD improved the total amount of drugs released but only up to a threshold loading concentration. The addition of more methacrylate CDs decreased the amount of drug released (38).

Successful incorporation of active molecules and their sustained release can be achieved using CDs combined with hydrogels. Several antibiotic and anti-inflammatory compounds were used as guest molecules and were delivered from CD complexes. The hydrophilic networks with conjugated βCD provided the controlled release of an antimicrobial 5,6-dimethoxy-1-indanone N4-allyl thiosemicarbazone, which was able to inhibit bacterial growth and can be used as an optimal therapeutic for the antimicrobial ocular treatment (39).

Another approach use are bio-inspired system, intelligent control system and molecular imprinting technology that provides the opportunity to fulfill the increase of hydrogel loading capacity, optimizing the drug residence time on the ocular surface and the biocompatibility with the eye tissue.

CONTACT LENSES

The contact lens is an optical device that is positioned over the cornea of the eye in such a mode that the lens remains on the surface of the eye throughout blinking. Beyond the purpose of wearing a contact lens to correct vision deficiencies, it has been developed as therapeutic devices for the treatment of ocular diseases (40).

Current contact lens technology covers an extensive area of therapeutic applications, including drug delivery devices for the treatment of ocular diseases. Contact lenses are classified as either hard or soft contact lenses (SCL) according to their modulus of elasticity (41). SCL are composed of polymers, which absorb large quantities of water to form hydrogels. The aqueous phase of the hydrogel is oxygen permeable (40).

Although more durable, hard lenses tend to be less well tolerated and require longer adaptation periods. Hard and soft hydrophobic lenses require a relatively thick tear film between their posterior surface and the cornea of the eye. However, hydrogel contact lenses for therapeutic applications can alter corneal physiology in three broad areas due to induced variable degrees of hypoxia, to produce low-grade and chronic mechanical trauma to the corneal epithelium, and to alter tear film distribution and functions over the corneal surface (42). Hydrogel contact lenses are normally more comfortable than other types and are easier to fit (43).

SCL adhere closely to the cornea with a tear film of capillary thickness between the lens and the corneal surface. With all kinds of contact lenses, the cornea surface must be wet and oxygenated at all times to remain transparent and healthy (40). Thus, with any type of contact lens, interference of the oxygen supply to the cornea surface must be minimized either by oxygen-rich tear exchange under the lens, by oxygen permeation through the lens or by both (40).

Important parameters in the contact lens design are polymer type, lens thickness, central posterior curve, lens diameter and water content. Considering the polymer, the oxygen permeability is a very important factor, where oxygen permeability of a contact lens polymer can be determined under laboratory conditions and are reported as the Dk value (41). The higher the Dk value the greater the oxygen permeability. Polse *et al*. suggested that Dk values greater than 20 under open eye conditions or greater than 75 during periods of prolonged eyelid closure are sufficient to prevent the corneal hypoxia or edema (44).

In addition, contact lenses have been found to alter tear physiology as well as the tear pH. The trilaminar tear structure is disorganized, then spreading and mixture are changed and the precorneal-contact lens tear film is stagnated, increasing the tear evaporation rate (45).

Beside intrinsic polymer characteristics, another significant factor is water content. Since water molecules are the medium of oxygen flux in a hydrogel lens, the greater the water content, the greater the oxygen permeability. Water content of a hydrogel lens depends on both, the particular monomer subunits and the number of crosslinks. As crosslinks increase in number, water is excluded from the gel matrix and oxygen flux decreases. Ideally, a rigid lens should float on the tear film, moving with an eyelid blink to allow tears to flow under the lens. Essential determinants of contact lenses movement are base curve and lens diameter. A steeper base curve or a larger diameter will reduce the movement of the contact lens, thus reducing tear exchange and ultimately oxygen delivery to the cornea. Other parameters include edge design and peripheral curvatures (41), having a refractive index similar to that of the cornea (~1.37), being optically transparent and biocompatible in the ocular environment (46).

Polymethylmethacrylate (PMMA) was primarily used to produce contact lenses due to facilitated manufacturing, light weight, and excellent optical properties. PMMA lenses are lathe cut from rods or buttons of PMMA obtained by bulk free-radical polymerization of methyl methacrylate. One disadvantage is related with the lower oxygen permeability of this material, which limits the long-term wear of these lenses. To reduce problems associated with corneal anoxia, PMMA lenses tend to be small in diameter and float on the precorneal tear film, thereby allowing oxygenation of the cornea via tear film exchange during blinking and movement of the lens (5). The newest hard plastic contact lenses are designed to improve corneal anoxia.

One of the new oxygen-permeable hard contact lens materials is cellulose acetate butyrate, which is softer and undergoes distortion more than PMMA. Others oxygen-permeable hard contact

lenses are made from copolymerizing methyl methacrylate (MMA) with methacrylate-functionalized siloxanes such as methacryloxypropyltris (trimethyl siloxy silane) (TRIS). The oxygen permeability, modulus of elasticity, hardness and wettability of these materials are modulated by the MMA/TRIS crosslinker ratio (5).

The first SCL material, poly 2 hydroxyethyl methacrylate (pHEMA), was developed by Otto Wichterle and Lim, and was considered as the prototype (47). The original pHEMA contained approximately 38-40% water in the fully hydrated state, had excellent wettability and offered the benefit over rigid lenses, increasing patient comfort and reducing their adaptation time (5).

Posteriorly, other monomers composed by a variety of hydrophilic or hydrophobic subunits have been introduced in SCL manufacturing. An example is the hydrophilic monomer N-vinylpyrrolidone (NVP) (48), which have an amide group, giving it polarity, excellent biocompatibility with living tissues and extremely low cytotoxicity (49, 50). Glyceryl methacrylate (GMA), which is more hydrophilic than HEMA due to the fact that the monomer contains two hydroxyl groups (46, 51, 52), is used to produce contact lenses for daily applications. The other hydrophilic monomer used is the methacrylic acid (MAA), which can produce soft lenses with ionized groups (negatively charged) within the polymer matrix, allowing the lenses to absorb more water. Unfortunately, this also has its disadvantages, due the sensitive to changes in tonicity and pH (46).

Silicone hydrogel materials have been specifically developed to produce contact lenses (48). These materials can dramatically improve corneal oxygen supply (six times greater) when compared to other hydrogel materials (53) resulting in fewer hypoxia. Silicone-containing polymer has several characteristics for an ideal material for contact lenses production, including excellent optical properties and is soft and easily molded. However, it presents serious deficiencies which limit its clinical use. These include intense hydrophobicity, lipid adsorption, protein deposition and dimensional changes with aging (41, 54). Phosphorylcholine (PC) is a material usually used as a coating that is incorporated to produce contact lenses with superior biocompatibility, to reduce bacterial adhesion and encrustation and it can reduce infection when used in the clinical situation (55-57). In European Patent EP 2 365 360 A2, Pinsley *et al*. proposed a method for reducing protein deposition on contact lenses by adding butylated hydroxytoluene or hydroxyamines in the reaction mixture (58).

In addition to the applications of SCL in the correction of vision, they have substantial challenges to be used for ocular drug delivery. The residence time of drug on the eye surface and ocular bioavailability increases. The release of the drug is extended by SCL when comparing to conventional eye drops (Figure 2).

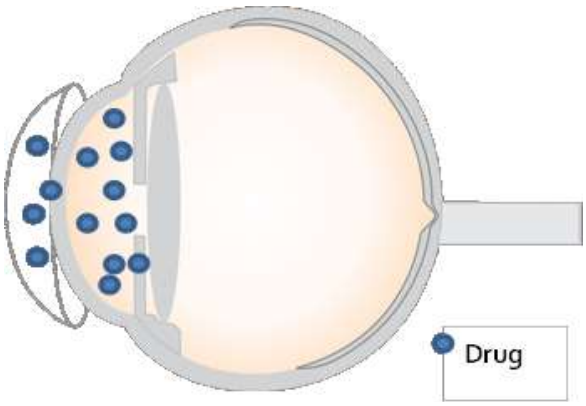

Figure 2. Scheme of ocular drug delivery by soft contact lenses.

Soft Contact Lenses for Ocular Drug Delivery and Strategies to Improve Bioavailability

Contact lenses have been investigated in terms of devices for controlled ophthalmic drug delivery, being comfortable, biocompatible and presenting significant increase drug residence at the ocular mucosa (59). Many methods have been developed to modify the conventional contact lenses to improve their drug loading and release (16, 52, 60-65). The use of a device from which a drug may diffuse can improve the contact time of the drug with its target tissue. Contact lenses have been utilized as such delivery devices (41, 42, 66). There are several methods for drug loading from contact lenses such as drug-soaked lenses (67), inclusion complexes (25), supercritical solvent-soaked lenses (68) and molecular imprinting (60). The application of the molecular imprinting technology during SCL

manufacture enables the creation in the lens structure of imprinted pockets that memorize the spatial features and bonding preferences of the drug and provide the lens with a high affinity for a given drug (60).

Many efforts have been made by researchers to develop a proper ocular drug delivery system via drug-soaked lenses and molecular imprinting technology (Table 2) (63). Some studies were performed on commercially available, contact lenses (e.g. Balafilcon, Lotrafilcon, Etafilcon, Omafilcon and Acuvue) or contact lenses synthesized by combinations of various monomers. In general, the results *in vitro, ex vivo* or *in vivo* tests were promising and indicated biocompatibility, high drug loading and sustained and controlled release times from both synthesized hydrogel and traditional commercial contact lenses (Table 2).

Several methods have been proposed to achieve an extended and controlled release of ocular therapeutics via contact lenses such as carrier-mediated release and surfactant mediated release (16, 61). Garcia-Fernandez *et al*. used with success poly(cyclo)dextrins as carriers able to solubilize the carbonic anhydrase inhibitor ethoxzolamide in poly(2-hydroxyethyl methacrylate)-based contact lenses (78). Cyclosporine (Cyc) is an immunosuppressant drug that has been used for treatment of various ocular diseases. Kapoor and Chauhan showed that pHEMA hydrogels loaded with Brij 98, a surfactant, and Cyc, exhibited an extended release of the drug, and they conclude that contact lenses made with this material could be used for ocular delivery of Cyc (16, 61). More recently, molecular imprinting design approaches have been applied to maximize the affinity of a network for some ocular drugs. The formation of pocket memory cavity in hydrogels during polymerization by biomimetic technique increases the binding affinity of polymer to drug and controls the release in different media (63).

Table 2. Examples of studies of ocular drug delivery in contact lenses and results.

Ocular drug	Classification	Condition	Results	References
Acetazolamide	Anti-glaucoma	*In vitro*	Drug release in 48h	(62)
Ciprofloxacin	Antibiotic	*In vitro*	Drug release in 7 days	(69)
Dexamethasone	Steroid	*In vitro*	Inhibited by *Staphylococcus epidermidis* biofilms	(70)
Dorzolamide	Anti-glaucoma	*In vitro*	Sustained release	(71)
Ethoxzolamide	Anti-glaucoma	*Ex vivo*	No cytotoxicity	(72)
Timolol	Anti-glaucoma	*In vivo*	Ocular bioavailability in tear film ↑	(73)
Ketotifen fumarate	Anti-histamine	*In vivo*	Ocular bioavailability in tear film ↑	(67)
Gentamicin	Antibiotic	*In vivo*	Ocular bioavailability in tear film ↑	(74)
Hyaluronic acid	Corneal healing aid	*In vitro*	Sustained release	(75)
Levofloxacin	Antimicrobial	*In vitro*	Sustained release	(76)
Nanosilver	Antimicrobial	*In vitro*	Antimicrobial activity	(77)
Puerarin	Antioxidant	*In vivo*	Ocular bioavailability in tear film ↑	(36)

↑ Increase

The contact lens have to present controllable zero-order release profiles with no burst drug release, and the drug concentration have to be sustained at a maximum safe concentration and at a minimum effective concentration in tear fluid. The shape is also important considering that the contact lens can retain the transparency, stability during release of drug and can maintain an acceptable oxygen and carbon dioxide permeability regarding to the contact lens thickness (79). Therapeutic contact lenses are useful in a variety of ocular surface diseases and can deliver several ophthalmic drugs on the ocular surface.

Lin *et al*. synthesized a silicone hydrogel composed by poly(dimethyl siloxane-urethane)/Pluronic F127. After ophthalmic characterization and *in vitro* cytotoxicity studies, they concluded that it was a better material and could be potentially used to ophthalmic devices including contact lenses (80). Guido *et al.* synthesized silicone hydrogels with variable composition and dexamethasone-loaded. They showed a positive correlation between loading mass and equilibrium water content and Higuchi model rate constants showed strong correlation between the equilibrium water content, and release controlled by the aqueous phase diffusion (81).

Santos *et al*. developed contact lens able to load diclofenac drug at 1300% and they were able to prevent drug leakage in common conservation liquid to SCL (82). Kim *et al.* developed silicone hydrogels using NVP and N,N-DMA and demonstrated that the composition can be tuned to obtain an extended β-adrenergic antagonists timolol drug release in a period varying from 10 days to a few months (48). Molecular imprinted hydrogels was prepared by Hiratani and Alvarez-Lorenzo to improve the timolol-loading capacity of the hydrogels to ocular application (83). Loaded imprinted contact lenses were able to prolong drug release, in 0.9% NaCl aqueous solution, for more than 24 h. Venkatesh *et al*., showed the potential of biomimetic hydrogels as carrier to load relevant amounts of the ketotifen drug. They also showed sustained release therapeutic dosages of antihistamine *in vitro* for a period of 5 days (84).

One way to take advantage of the emerging field of biomimetics is to select ideas and inventive principles from nature and apply them to engineering products (85). Carbonic anhydrase inhibitors are used for treatment of glaucoma and other ocular disorders. Ribeiro *et al.*, recently synthetized biomimetic hydrogels suitable as high water-content SCL using N-vinyl-2-pyrrolidone and N,N-Dimethylacrylamide (NVP-DMA) for loading and the delivery of ocular medication acetazolamide and ethoxzolamide (72). Additionally, NVP-DMA hydrogels had a beneficial effect of blocking UV radiation, which will reduce the corneal damage due to UV light (72). The SCL made with HEMA or NVP presented good oxygen permeability, ensuring more comfort for wearers (86). In parallel, Ribeiro *et al.* applied molecular imprinting method to synthesized biomimetic pHEMA hydrogels with high affinity for carbonic anhydrase inhibitor drugs. The active site of the physiological metallo-enzyme receptor of CAI was mimetizeded by combining zinc methacrylate, 1- or 4 vinyl imidazole (1VI or 4 VI), and N-hydroxyethyl acrylamide (HEAA) to reproduce in the hydrogels the cone-shaped cavity of the Ca^{+2} (which contains a Zn^{+2} ion coordinated to three histidine residues). This strategy demonstrated that biomimetic networks can load more drug and control better drug release than conventionally synthesized pHEMA hydrogels, being useful for the development of advanced controlled release systems (62).

In other different strategy, Zhang *et al*. (64) dispersed bovine serum albumin (BSA) coated meloxicam (MX) nanocrystals encapsulating nanoaggregates (BSA–MX–NA) in contact lenses to reduce drug ocular irritancy and increase drug release time. This study showed that this system could be very useful for extended delivery in ocular treatment as postcataract endophthalmitis. Garcia-Millan *et al*. showed improve triamcinolone acetonide (TA) loading capacity and release properties of HEMA-SCL based on microstructural modifications using water during the polymerization process. NVP or methacrylic acid (MA) as comonomers were used, however, *in vitro* TA release kinetics shows that NVP hydrogels released the drug significantly faster than MA-hydrogels (87).

Additionally, ideal contact lenses for ocular drug delivery systems else than be biocompatible, must provide a precise dose, the drug release should follow zero-order release kinetics, maximize ocular drug delivery by controlling dose, cause minimal inflammation and irritation, minimal loss in the storage process, easy handling and have the least interference with the patient's vision.

CONCLUSIONS

Important advances have been made to improve the properties of hydrogels used as drug delivery devices. A brief look through the literature cited in this review reveals a significant increase in successful instances of SCL applied for mediated ocular drug delivery, specifically during the past 10 years. Hypoxia related problems can be solved using more hydrophilic monomers, increasing the solubility and bioavailability of insoluble drugs and increasing the sustained drug delivery. Significant contributions to ophthalmic therapeutics will be obtained using bioinspired materials and technology to produce devices for controlled drug delivery. In this review different advanced systems were well characterized and they showed potentialities to open a new direction to improve therapeutic activity of drugs for ophthalmic applications.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

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