WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 9, 207-216. Review Article ISSN 2277– 7105

CONTACT LENSES: A DEVELOPMENT TOWARDS OCULAR DRUG DELIVERY SYSTEM

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Article Received on
23 June 2017,

Revised on 13 July 2017,
Accepted on 03 August 2017

DOI: 10.20959/wjpr20179-9234

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ABSTRACT

Contact lenses are upcoming as an alternative ophthalmic drug delivery system to resolve the drawbacks of the conventional topical application methods. In the ocular pharmacology market, there is a noteworthy unmet demand for more efficacious delivery of ocular therapeutics. Contact lenses drug delivery systems have been developed to provide an increased residence time of the drug at the surface of the eye leading to enhanced bioavailability and more convenient and efficacious therapy. Several research groups have already explored the feasibility and potential of contact lenses loading conventional drugs used to treat anterior eye disorders. Drug incorporation to the lens body is achieved with techniques, like simple soaking, inclusion of drug-loaded colloidal nanoparticles, or molecular imprinting. Regardless of the technique used, key properties of the contact lens, such as transparency and oxygen permeability, should be preserved. In this article, we reviewed the different techniques used for drug delivery through contact lenses, analyzing their advantages and disadvantages, and focused on articles describing contact lens-based ophthalmic drug delivery systems with significant potential to use in ocular therapeutics.

KEYWORDS: contact lens, Bioavailability , Inclusions, Ocular Therapeutics.

INTRODUCTION

The eye is characterized by its complex structure and high resistance to foreign substances, including drugs that makes ocular drug delivery a major challenge to pharmacologists and drug delivery scientists. Currently, more than 90% of ophthalmic drugs are delivered in the form of solutions or suspensions. These conventional ophthalmic formulations generally show low ocular bioavailability due to various factors, such as reflex tearing and blinking,

nonproductive absorption, nasolacrimal drainage, metabolic degradation, and the relative impermeability of the corneal epithelial membrane. As a consequence of these physiological and anatomical constraints, only a small fraction of an administered dose (1%–7%) is productively absorbed.[1] To overcome the low ocular bioavailability, frequent application of doses of drugs at high concentrations is used to achieve the desired therapeutic effects. This discontinuous dosing not only results in extreme fluctuations in ocular drug levels but, also, a significant portion of the applied solution can be absorbed in the conjunctiva or collect in the nasolacrimal system, which drains into the nasal cavity and leads to absorption in the bloodstream. The presence of certain drugs in the bloodstream can induce undesirable systemic side effects. For example, fluoroquinolones can produce not only corneal, but also systemic toxicity (e.g., hepatotoxicity, nephrotoxicity, and neurotoxicity).[2–4] Glaucoma treatments, in particular, b-adrenergic receptor blockers, such as timolol, can also generate deleterious effect in the heart. Additionally, the real dose effectively administered can vary by the application technique, the type of eye drop carrier, and the compliance of the patient. Thus, a significant variation in the concentration of drug present in the eye can occur during eye drop treatment.

The problems associated with topical ocular administration of drugs by eye drops have prompted the research of alternative approaches for ophthalmic drug delivery, such as mucoadhesives and viscous polymer vehicles, nanoparticles, in situ gel-forming systems, iontophoresis, or punctal plug. An ideal ocular drug delivery system should be able to increase the residence time of the drug in the eye, and to avoid large fluctuations in the ocular drug concentration as well as possible systemic side effects. In this context, soft contact lenses (SCLs) are gaining an increasing attention as new vehicle for ophthalmic drug delivery. In the eye, contact lenses are separated of the cornea by a thin fluid layer called postlens tear film. The fluid in the postlens tear film is not well-mixed with the remaining tear fluid. The mixing time of the fluid in the postlens tear film with the outer tear fluid is about 30 min. Thus, ophthalmic drugs released from the SCLs will have a residence time in front of the cornea for at least 30 min compared to 2 min for eye drops. The enhanced residence time may lead to an increase in drug bioavailability to possibly as large as 50% compared to 1%–5% by eye drops.[5] This increased corneal bioavailability also implies the decrease of the amount of drug that enters in the systemic circulation, thus potentially reducing side effects. Accordingly, SCLs are an attractive system for ophthalmic drug delivery and several approaches are being currently investigated to enhance drug loading

capability and to control the release rate of drugs from the contact lens. In this review, we describe different strategies used in the design F1 c and development of contact lens for drug delivery (Fig. 1) and the therapeutic applicability of these devices in the treatment of various ocular disorders.

Methods of incorporation of drug in contact lens based drug delivery system soaking of lenses in drug solution

The simplest way to incorporate a drug into SCLs is to soak preformed lenses in the drug solution. The delivery of very diverse drugs, such as pilocarpine, antibiotics, timolol, dexamethasone from SCLs made from poly (2- hydroxyethyl methacrylate) (pHEMA) hydrogels (with a high water content that facilitates the diffusion of solutes) has been investigated mainly in in vitro assays. In these experiments, after soaking SCLs in drug solutions, the dynamic drug release was monitored. SCLs based on commercially available silicon-containing hydrogels or polyvinyl alcohol hydrogel have also been examined for delivery of ophthalmic drugs.[6]

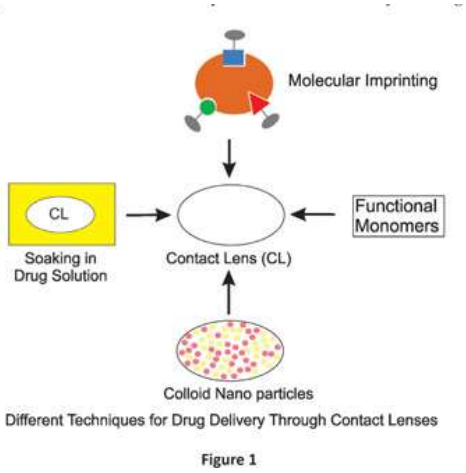

Fig. 1: Schematic representation of different techniques used for drug delivery through contact lenses: soaking of lenses in drug solution, copolymerization of the contact lenses hydrogels with functionalized monomers, incorporation of drug-loaded colloidal nanoparticles, and molecular imprinting.

First, the drug uptake in SCLs depends on several factors (the water content and thickness of the lens, the molecular weight of the drug, the solubility of the drugs in the gel matrix.) that can limit the loading capacity in some cases, resulting in low drug loading. This compounded lens has more drug loading capacity; however, oxygen and carbon dioxide permeabilities of the compounded lens are smaller compared with regular SCLs, due to the presence of 2

separates sheets of lens material, which may induce corneal edema. A second limitation of the soaking method is that the release of the drug from soaked contact lenses tends to occur very quickly with the entire drug diffusing in a few hours. For example, the corticosteroid prednisolone, the glaucoma drug pilocarpine, and the antibiotic ciprofloxacin were released from hydrophilic contact lenses within 1 to 3 h. Thus, slow and extended drug release is not properly accomplished for soaked contact lenses.

An alternative approach has been developed to extend the release duration from silicone hydrogel contact lenses.[7] In this approach, vitamin E aggregates are incorporated within contact lenses to create barriers to drug diffusion, resulting in increased releases times from drugs that are loaded into the lenses from hours to several days. These vitamin E-loaded lenses maintain proper oxygen permeability, ion permeability, and light refractive properties to be used as extended wear contact lenses.

Copolymerization of the contact lens hydrogels with functional monomers

Another method to make ophthalmic drugs deliverable by SCLs involves the incorporation of monomers able to interact with the target drug into the hydrogels. The monomers act as drug binding points for protonizable or hydrophobic molecules, and communicate functionality to the hydrogels. Cationic monomers, such as methacrylamide propyltrimethylammonium chloride have been used to enhance the loading capacity and to extend the release of anionic drugs based on an ion-exchange reaction. In physiological conditions, the tear fluid ions compete with the drug for the ionic groups of the hydrogel and the drug is released. Acrylic acid has also been shown as an useful monomer to increase hydrogel affinity for insulin, oxprenolol, or timolol.33 On the other hand, the simultaneous use of several monomers has also been reported. Thus, the combination of the hydrophobic monomer 3-(trimethoxy-silyl)propyl methacrylate and the ionic monomer N,N¢-dimethylaminoethyl methacrylate, improved the loading of insulin and protamine and their extended release from pHEMA SCLs.[8] Dried loaded pHEMA–APMA and pHEMA–VP hydrogels quickly swelled in water; but ionic/hydrophobic interactions limited the drugs released to be below 10%. Once the water-swollen hydrogels were transferred to pH 5.8 or 8.0 phosphate buffers or NaCl solutions, the release was prompted by competition with ions in the media. Under these conditions, extended release was achieved due to remaining of hydrophobic interactions and the high polymeric density of the pHEMA hydrogels (sustained release process happened for 24 h for ibuprofen and almost 1 week for diclofenac).

Dispersion or immobilization on the contact lens surface of drug-loaded colloidal nanoparticles

This method is based on incorporation of drug-loaded colloidal particles (nanoparticles, liposomes, microemulsions, etc.) into the matrix of contact lenses. Drug-loaded colloidal particles entrap a large amount of drug, and then are dispersed in the lens material during polymerization. The drug must first diffuse through the nanoparticles and penetrate the particle surface to reach the hydrogel matrix. Thus, it is expected that colloidal particle loaded contact lenses can deliver drugs at a slow rate for a long period of time. Following this technique, lidocaine loaded dimyristoyl phosphatidylcholine liposomes were dispersed in pHEMA contact lenses.[9] Lidocaine was released for 7 days with 2 separate time scales; there was an initial burst that released about 15%–30% of the drug in the first few hours, and then there was a much slower release over a time scale of days. The presence of the dispersed liposomes reduced the transparency of the contact lenses (80% of transmittance as compared to 90% for the pure pHEMA contact lenses). In contact lenses bearing 2 layers of liposomes, levofloxacin release was completed in 30 h, while liposomes of 5 or 10 layers maintained a sustained delivery of levofloxacin until 120 h.45 However, this multilayer scheme of liposomes may be inconvenient, since oxygen and carbon dioxide permeabilities were decreased.

Molecular imprinting

Molecular imprinting allows the creation of macromolecular memory for a template molecule embedded within a flexible macromolecular network.46 In this technique, the components of the hydrogel network are organized in such a way that high-affinity binding sites for the drug are created. Drug is added before polymerization, and the monomers should arrange as a function of their ability to interact with the drug molecules. After polymerization, the drug molecules that have acted as templates are removed, and the polymer network may exhibit tailoredactive sites or imprinted pockets with the size and the most appropriate chemical groups to interact again with the drug. Improvement in drug loading and extended release can be also reached when multiple functional monomers are included instead of single monomers. Thus, 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.[10]

Physical Properties of Contact Lens Drug Delivery Systems

Transparency of the lens

Optical clarity of the contact lens should be maintained after incorporation of drugs. Novel approaches have enabled to generate contact lens drug delivery systems with acceptable transparency, although it could be improved in some cases. For instance, pHEMA gels loaded with liposomes showed a transmittance of 80% compared with 90% for the pure pHEMA gels.38 In contrast, surfactant laden SCLs were transparent and clear and 100-mm-thick hydrated gels had transmittance values larger than 98.5% at a wavelength of 600 nm, and so are suitable for contact lens application.

Oxygen permeability

Drug eluting contact lens should allow transfer of oxygen to the eyes since low oxygen permeability can cause severe side effects, such as corneal edema. To avoid hypoxia, a minimum value of oxygen transmissibility (Dk/t) around 125 has been suggested. Oxygen permeability comprised in contact lens is generated using some approaches, like contact lenses characterized by a hollow cavity binding 2 lenses24 or contact lenses containing multilayer scheme of liposomes. The silicone hydrogel contact lenses show excellent oxygen permeability. imprinted silicone hydrogel contact lenses for drug delivery have been generated; however, data about oxygen permeability of the lenses were not provided.

Glass transition temperature

Thermomechanical characteristics are important commercial contact lens properties, since they will control some of 4 their functional features as ophthalmic devices, including comfort. Glass transition temperature has been measured in drug eluting contact lenses manufactured by various approaches. Analysis by differential scanning calorimetry did not show significant differences in glass transition temperature when monomers were incorporated in pHEMA SCLs as compared to pure pHEMA SCLs.

Wettability

Wettability of contact lenses is a critical variable that affects their physiological compatibility and the stability of the prelens lacrimal fluid. It can be determined by contact angle measurements. Wettability of pHEMA contact lenses was slightly increased when copolymerized with high proportions of glycidyl methacrylate, but slightly decreased when cyclodextrins were attached. Likewise, contact angle values of surfactant-laden pHEMA SCLs were lower than those for control pHEMA SCLs.40 On the other hand, the supercritical

solvent impregnation method did not affect greatly the contact angle measurements when compared to control SCLs.[11]

Water content

Water content of contact lenses is crucial as it likely impacts comfort and an increase in the water content enhances the oxygen permeability of pHEMA contact lenses. For pHEMA hydrogels, SCLs containing comonomers (4-VP and APMA) less than 20% of the aqueous phase of the hydrogel consisted of free water, in good agreement with data reported for pure pHEMA hydrogels.35 Similarly, water content was not altered in molecularly imprinted pHEMA hydrogels contact lenses designed for norfloxacin and ketotifen fumarate release.49,52 In contrast, an increase in water content was detected in surfactant-laden pHEMA SCLs, presumably due to the formation of small pores (less than 40 nm), which are filled with water.

Treatment by Contact Lens-Based Drug Delivery Systems

Antibiotics for ocular infection

Infection of the eye leads to conjunctivitis, keratitis, endophthalmitis, and other diseases, which are responsible for increased incidence of morbidity and blindness worldwide. Ciprofloxacin has a broad spectrum of antibacterial activity against both Gram-positive and -negative bacteria and it is commonly prescribed for treating microbial keratitis, conjunctivitis, or endophthalmitis. To reach a sustained release, a contact lens integrating a thin ciprofloxacin–PLGA film into a pHEMA hydrogel was designed.56 This drug-eluting system showed zero-order release kinetics at a therapeutically relevant ciprofloxacin concentration for 1 month. The larger thickness of this contact lens could complicate patient acceptance and decrease oxygen and carbon dioxide permeabilities. Nevertheless, this disadvantage has been subsequently overcome due to the new design of a thinner curved contact lens integrating the drug–polymer film. Recently, conventional hydrogel contact lenses that incorporate nanosphere-encapsulated ciprofloxacin have been synthesized.[12]

Corneal injury

Corneal defects with delayed re-epithelization can result from a variety of causes, including corneal dystrophies, recurrent corneal erosions, ocular trauma, corneal surgery, and decreased corneal innervation. A contact lens can act as a bandage to shield the leading edge of the healing epithelium from damage because of blinking, allowing newly reproduced epithelial cells a greater opportunity to recover the corneal surface. EGF-treated contact lenses

achieved a significantly higher overall healing rate of corneal epithelial defects as compared to saline-soaked contact lenses. Consistent with this finding, a pilot clinical assay with patients revealed that the use of EGF-soaked contact lenses improved the healing time in noninflamed corneas of patients with delayed corneal re-epithelization.[13]

Allergic conjunctivitis

Antihistamines, such as ketotifen fumarate, are used to alleviate the sign and symptoms of allergic conjunctivitis through multiple pharmacological actions. In in vitro assays, all the contact lenses released an amount of ketotifen fumarate higher than the dosage provided by eye drops) with the majority of the drug released within the first hour. Under these conditions of quick releasing, a lower amount of drug should be loaded into the lens to prevent an overdose.[14]

Glaucoma

Glaucoma is a group of progressive optic neuropathies, characterized by the damage caused to the optic nerve, fiber layer, and ganglion cells. If it is not treated, it results in visual field loss.92 Imprinted pHEMA hydrogels that mimic the active site of carbonic anhydrase were designed to generate contact lenses with high affinity for carbonic anhydrase inhibitors, such as acetazolamide or ethoxzolamide. Hydrogels sustained in vitro release of these antiglaucoma drugs for 2 weeks, after which the amount released was still < 50%.58 These hydrogels were cytocompatible and possessed adequate oxygen permeabilities to be used as medicated SCLs.

CONCLUSIONS

Considering the disadvantages associated with topical ocular administration of drugs by eye drops (i.e., low bioavailability, frequent instillation requirement, patience compliance, potential systemic side effects.) efforts have been focused in the development of new therapeutic devices for delivery of ophthalmic drugs. In this context, therapeutic contact lenses can be considered as an excellent alternative to release ocular medication. An ideal SCL-based ophthalmic drug delivery should exhibit a high drug loading and controllable drug release. While the first generation of drug soaked contact lenses released the drug very quickly, progress in the field has lead to produce therapeutic contact lenses by other techniques (i.e., molecular imprinting) with higher therapeutic loading and controlled, extended release. Most of the studies performed to evaluate contact lens drug delivery systems were in vitro assays. In vivo validation of therapeutic contact lenses has not been so

widely studied and this aspect deserves further research. On the other hand, efforts should be led to generate therapeutic contact lenses with physical and mechanical properties that mimic those of commercial lenses on the market. Thus, drug-loading contact lenses could be potentially used as combined devices for simultaneous therapeutic and correction of refractive deficiencies.

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