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Review

Contact lenses as drug-delivery systems: a promising therapeutic tool☆

M.A. Holgado, A. Anguiano-Domínguez, L. Martín-Banderas*

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, Sevilla, Spain

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ABSTRACT

The ocular administration of drugs using traditional pharmaceutical forms, including eye drops or ointments, results in low bioavailability, as well as requiring multiple administrations per day, with the consequent danger of therapeutic non-compliance. Although, through the use of pharmaceutical technology, attempts have been made to use various solutions in order to increase bioavailability in the most common pharmaceutical forms, it has not been entirely satisfactory. In this context, contact lenses are presented as drug delivery systems that largely remedy these two major problems and offer other additional advantages. Therefore, the use of contact lenses as drug carrying systems has been increasingly investigated in recent years, as they can increase the bioavailability of these drugs, leading to an increase in therapeutic efficacy and compliance.

The main techniques used to achieve this goal are included in this review, including immersion in drug solutions, use of vitamin E barriers, molecular printing, colloidal systems, etc. The most interesting results, depending on the different eye pathologies, are presented.

Although the use of contact lenses as a vehicle for the release of active ingredients is a relatively novel strategy, there are already many studies and trials that support it. In any case, further research needs to be carried out to finally reach an effective, safe, and stable product that can be marketed.

Lentes de contacto para vehiculizar principios activos: una prometedora herramienta terapéutica

Palabras clave:
Lente de contacto
Biodisponibilidad ocular

RESUMEN

La administración ocular de fármacos utilizando formas farmacéuticas tradicionales, como las gotas oftálmicas o pomadas entre otras, proporciona una baja biodisponibilidad de los fármacos así como múltiples administraciones al día con el consiguiente peligro de incumplimiento terapéutico. Aunque la Tecnología Farmacéutica ha intentado proponer

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* *Corresponding author.*
E-mail address: holgado@us.es (M.A. Holgado).

Liberación controlada
Patologías oculares

diversas soluciones para aumentar la biodisponibilidad en las formas farmacéuticas más comunes, no ha sido del todo satisfactorio. En este contexto, las lentes de contacto se presentan como sistemas de liberación de fármacos que subsanan en gran medida estos dos grandes problemas y ofrecen otras ventajas adicionales. Por ello, en los últimos años, se ha investigado con más empeño el uso de lentes de contacto como sistemas portadores de fármacos, ya que pueden aumentar la biodisponibilidad de los mismos, proporcionando un aumento de la eficacia y cumplimiento terapéuticos.

En la presente revisión se han referenciado las principales técnicas utilizadas para alcanzar dicho fin: inmersión en soluciones de fármaco, uso de barreras de vitamina E, impresión molecular, sistemas coloidales, etc. A continuación se recogen los resultados más interesantes encontrados en función de las distintas patologías oculares.

El uso de lentes de contacto para la vehiculización y liberación de principios activos es una estrategia relativamente novedosa aunque ya tiene muchos estudios y ensayos que lo sustentan. De todas formas se deben seguir investigando para alcanzar finalmente un producto eficaz, seguro y estable, y que pueda llegar a ser comercializado.

Introduction

Treating ocular disorders by instilling and drugs on the ocular surface has been an adequate strategy for a long time.[1] The most widely used pharmaceutical form in this administration route are ophthalmic drops, i.e. solutions or sterile suspensions, representing over 90% of all ophthalmic formulations, followed by ophthalmic ointments.[2] These medicaments are easy to use and do not require qualified health professionals for their application.

However, said pharmaceutical forms comprise a significant limitation due to the anatomy and physiology of the eye, which is equipped with a number of physiological barriers and elimination mechanisms for protective purposes that successfully restrict the passage of external substances including medicaments.[2] On the other hand, active principles have a very limited permanence on the ocular surface (between 2 and 3 min on the lacrimal film) due to physiological defense mechanisms designed to to eliminate them such as blinking, nasolacrimal drainage, on-site metabolic degradation, tear dilution capabilities and low corneal epithelium permeability.[3,4]

In addition, the conjunctiva easily absorbs substances in comparison to the cornea due to its greater permeability and surface area. This absorption is regarded as nonproductive because the drug would enter directly into systemic circulation.[5]

It is also known that approximately 50% of drops instilled in the eye are drained directly through the nasolacrimal duct, which means that the bioavailability of a drug does not exceed 1–5%.[3,4] This fact entails the need of formulating a drug in high concentrations if there are no limitations in the manufacture thereof, i.e., a medicament must be feasible from the viewpoint of preparation, stability and innocuity.

An additional consequence is the requirement of administering it repeatedly, facilitating noncompliance and poor therapeutic adherence to treatments (particularly in chronic diseases), in addition to giving rise to large fluctuations in pharmacological concentrations.[1] In addition, some groups of patients exhibit specific manipulation difficulties involving the risk of contamination in the administration of the drug (between 20 and 80% of patients) and the fact that some patients do not instill exactly one drop.[4,6]

Despite the above drawbacks, pharmaceutical technology endeavors to utilize formulation strategies and excipients that enhance the ocular bioavailability of drugs and minimize losses. Table 1 summarizes said strategies on the basis of currently utilized pharmaceutical forms, indicating critical excipients in their formulation as well as the most important limitations.

In this context, contact lenses become drug-releasing systems that largely overcome the above limitations in addition to offering additional advantages. Accordingly, in recent years the use of contact lenses as drug-carrier systems has been researched extensively due to the potential to increase bioavailability thereof, providing an increase in efficiency and therapeutic compliance.

Accordingly, the general objective of this article is to describe developments in the use of contact lense systems for releasing active principles for treating ocular pathologies. To this end, the following partial objectives are proposed: i) to determine the structural and technological requirements of contact lenses for adequately releasing active principles; ii) to study the different manufacturing strategies of said lenses, and iii) analyze therapeutic applications and types of drugs that can be utilized in said lenses.

Material and methods

The present bibliographic review has been carried out searching information in databases including Pubmed, ProQuest, Web of Science, Scopus or ScienceDirect. Said databases have been accessed through the electronic resources of the Seville University website, selecting databases on Pharmacy and Medicine.

Table 1 – Formulation strategies and limitations of pharmaceutical forms utilized at present.

Pharmaceutical form	Excipients	Limitations	References
Eyedrops	- Permeability enhancing its (sodium salt of ethylenediaminetetraacetic acid and benzalkonium chloride) - Viscosity enhancers (polyvinyl alcohol, hydroxymethyl cellulose and hydroxyethyl cellulose) - cyclodextrins	- Corneal bioavailability < 5%. - Conjunctival capillaries carry a significant fraction to systemic circulation, diminishing the therapeutic effect	7,8
Ointments	Fatty excipients (vaselin, lanolin and fatty alcohols)	Discomfort, irritation and blurred vision	5,9
Hydrogels	Preformed gels (mucoadhesive polymers: methylcellulose, hydroxypropyl methylcellulose, sodium hyaluronate and polyvinyl alcohol)	The preparation loses water	7
	On site gels (transition from liquids to generally due to changes in pH, temperature or ionic strength in the environment)	Low patient complicity	
Insertions	Ocusert® (insoluble alginate and polyethylene vinyl acetate insertion)	Withdrawn due to patient discomfort	10
	Lacrisert® (soluble hydroxypropylcellulose insertion)	Hypersensitivity to HPC	11–13
Intraocular injections and implants	- Ozurdex® (copolymer of lactic-glycolic acid) - Iluvien® (polyvinyl alcohol + polyimide)	Invasive method	7

The search strategy for bibliographic articles aimed at achieving the final objective of the review, i.e., to describe and analyze contact lenses that release active principles and the operation thereof. Said search was focused on drug-releasing contact lenses without defining a range of years on the above-mentioned databases utilizing the following descriptors in the English language: *contact lenses*, *drug delivery*, *ophthalmic administration* and *ocular bioavailability*. The inclusion criteria in the search for information comprised both reviews and experimental articles in English and Spanish on the topic. The search excluded editorials, abstracts of meetings and clinical trials.

Results and discussion

The administration of drugs through contact lenses has attracted a lot of attention in recent years due to the demand for noninvasive treatments with the potential to increase bioavailability while improving treatment compliance by patients.

In addition, said contact lenses have the advantage of providing a dual function at the same time, i.e., correcting refractive defects and administering drugs.[6,14] The technical and pharmacological challenge is to achieve adequate release of the active principle without sacrificing any critical property of the lens such as permeability to ions and oxygen, transparency and humectability among others. It is also important to ensure processing and storage conditions without the active principle losing any of its properties.[15]

After searching for references described in the Methodology section, 50 articles were identified. After a thorough analysis, 46 articles fulfilling the inclusion criteria were selected.

The following figure illustrates the distribution of scientific production per country (Fig. 1), the number of articles per year (Fig. 2) and the distribution per area of knowledge (Fig. 3).

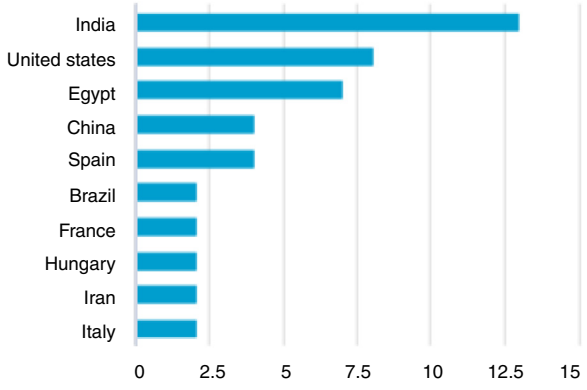

Fig. 1 – Distribution of scientific production per country.

The results on production per country (Fig. 1) indicate significant differences between the first 3 producing countries (India, United States and Egypt) and the rest. It should be noted that Spain is the first producing country in Europe and the 5th in the world. In what concerns the number of articles published per year (Fig. 2), evolution shows a clear increase in the interest on these systems as drug carriers. Lastly, Fig. 3 shows the scientific areas of the publications. As could be expected, the higher percentage involves the Pharmacological and Pharmaceutical Technology area with about 63% of publications.

Contact lenses as drug-releasing systems

Consulted references demonstrated that the corneal bioavailability of drugs carried by contact lenses is significantly higher than that of ophthalmic drops. Said bioavailability is estimated at 50% for the former and less than 5% for the latter.[16] When a contact lens is placed over the eye, it remains separated from the cornea by a thin layer of fluid that takes about 30 min to dilute. If a certain concentration of drug could be

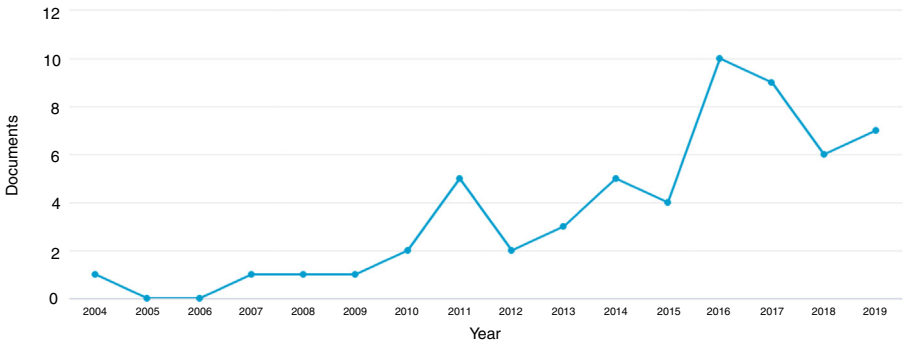

Fig. 2 – Number of articles published per year.

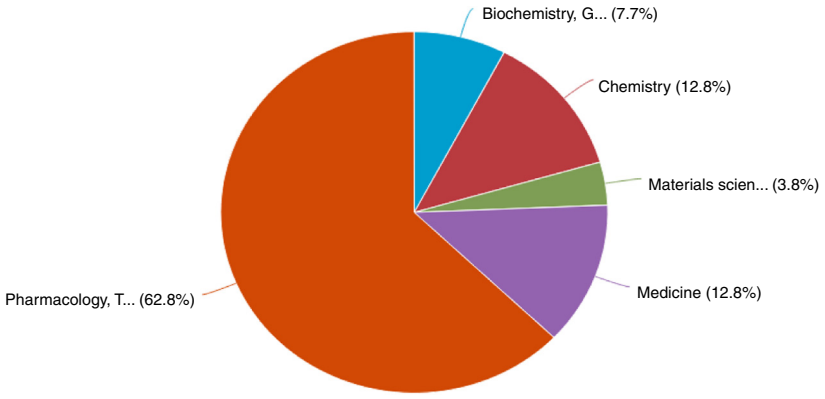

Fig. 3 – Percentage of articles published per area of knowledge.

included in said layer, the time of contact between the drug and the cornea would be increased and therefore bioavailability would increase to approximately 50% when compared to the application of ocular drops (between 1–5%). In addition, conjunctival absorption would diminish and therefore a smaller amount of active principle would enter the systemic circulation, entailing less adverse effects.[17]

Said bioavailability increase would also diminish the dosage, enabling high therapeutic compliance for patients and fulfilling a dual function, i.e., refractive correction and administration of a drug. At the same time, the use of disposable or daily contact lenses would diminish exposure to preservatives included in the formulation of the ophthalmic drops.[18]

In 1965, Otto Wichterle and Drahoslav Lim filed the first patent for administering drugs through contact lenses.[4,18,19] Said lenses were manufactured with poly-2-hydroxyethylmetacrilate (p-HEMA). Said authors also studied the diffusion of boric acid as anti-bacterian through this material for subsequent release.[13]

After said initial experiments, other studies assessed different variables such as type of drug, concentrations, preparation methods and lens shape among others, taking into account that all were based on the same methodology, i.e., to soak the lens in a solution of a drug. This new administration system demonstrated higher bioavailability than ophthalmic drops but also involved an important drawback, which was that the drug was massively released as soon as the lens was placed. This hindered the development of this type, leading to loss of market interest due to this drawback.[15,18]

In recent years, said systems have attracted attention due to a different manufacturing methodology. Lenses are being designed to include drugs in their structure instead of soaking them in drug solutions.[18] In addition, these lenses have a huge market potential considering that over 125 million individuals in the world use contact lenses.[11]

Contact lens characteristics

Contact lenses are optical devices designed to cover the cornea. When placing the lens over the cornea, the posterior surface of the lens is adhered closely to the ocular globe due to the surface tension of the lacrimal film.[20]

Contact lenses can be rigid or soft according to their elasticity module.[21] Rigid lenses are not adequate for prolonged administration of drugs because they are not very permeable to humidity and due to their rigidity are uncomfortable for users, to the point of requiring a period of adaptation. However, soft contact lenses are very easy to use and well tolerated, making them adequate as drug carriers.[14]

In what concerns soft contact lenses, Wichterle and Lim developed a prototype manufactured with p-HEMA containing approximately 40% of water (in the fully hydrated state) with excellent humectability and several advantages over rigid lenses, increasing patient comfort and diminishing adaptation time.[21]

Subsequently, monomer subunits were introduced as hydrophilics in the manufacture of soft contact lenses. For example, the N-vinylpirrolidone hydrophilic monomer which,

together with its amide group, provides polarity, excellent biocompatibility and very low cytotoxicity.

Glycerol methacrylate, comprising 2 hydroxyl groups and exhibiting higher hydrophilic properties than HEMA, is used for daily use contact lenses. An additional hydrophilic monomer is methacrylic acid (MAA) which, due to the negatively charged ionized groups contained within the matrix, allows the contact lens to absorb more water. But unfortunately this also comprises some drawbacks related to sensitivity, changes in tonicity and pH. Phosphorylcholine is used as a covering to increase biocompatibility, diminish bacterian adhesion and incrustation.[21]

The material that makes up soft contact lenses is based on polymers that absorb a large amount of water (30–80%) to form hydrogels having an aqueous phase permeable to oxygen. These can be hydrogel or silicone hydrogel.

The material of *hydrogel lenses*, that exhibit excellent humectability and initial comfort, is soft and flexible. Drawbacks include lens dehydration problems, dryness at the end of the day, possibility of allergies and low oxygen permeability coefficient.[21] The latter is extremely dangerous because extended use of said lens could produce serious adverse effects such as vascularization and corneal ulceration.[19] As the cornea is a nonvascular tissue, it depends on the supply of atmospheric oxygen to maintain its metabolic processes.

The *silicone hydrogel*, specifically developed for manufacturing contact lenses, allows an oxygen supply up to 6 times higher compared to other hydrogel materials. Silicone hydrogel exhibits excellent optical properties in addition to being soft and easy to shape. However, it also exhibits deficiencies that restrict its clinic use. It is more hydrophobic and absorbs lipids and in addition proteins frequently deposit on this type of lens and change their dimensions with the passage of time. In addition, the cost of silicone hydrogel lenses is much higher and they are slightly harder, which could produce some discomfort.[21]

As can be expected, the ocular surface must remain humid and oxygenated at all times, so any interference in the supply of oxygen should be minimized either through lacrimal exchange with the film created under the lens, through permeability of the lens to oxygen or both.

The parameter to measure oxygen permeability is the Dk coefficient of each material. Dk is defined as the amount of oxygen passing through a contact lens material during a specific period of time under specific conditions. Higher Dk of a lens signifies higher permeability to oxygen. Dk numbers over 20 during the day and above 75 during the night (prolonged closure) are regarded as adequate to prevent corneal hypoxia and edema.[21]

The tear has a triple layer structure (lipidic, aqueous and mucous) which becomes disorganized in the presence of contact lenses (Fig. 4). The pre-lens lacrimal film becomes stagnant and causes increased evaporation. In addition, it has been found that contact lenses could alter the physiology and the pH of tears.

Water molecules are the oxygen suppliers because oxygen can be dissolved in water and diffused towards the cornea. For this reason, the aqueous phase of a hydrogen is very important because greater water content equals greater permeability to oxygen.

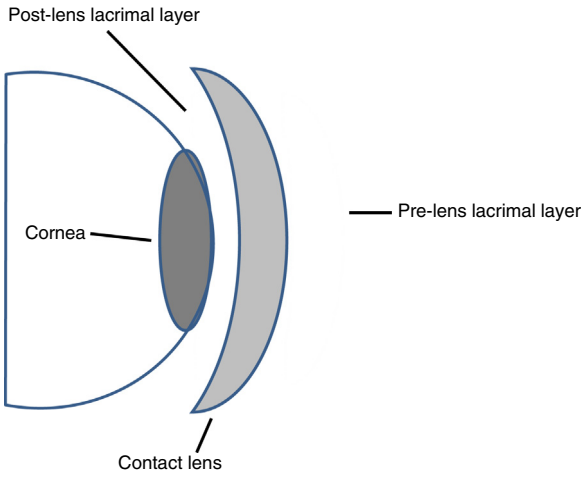

Fig. 4 – Tear disorganization in the presence of a contact lens (Author: M.A. Holgado, March 27, 2019).

Water content depends on the particular monomer subunits and the number of crossed links. With higher numbers of crossed links the amount of water diminishes together with the oxygen flow. A rigid lens should float over the lacrimal film, moving with blinking and facilitating the flow of tears under its surface. The base curve and diameter of the lens are what determines this movement. Larger diameters diminish lacrimal exchange and therefore impair the supply of oxygen to the cornea.[21]

Contact lenses should also have a refraction index similar to that of the cornea, in addition to being optical transparent and biocompatible.

Manufacturing strategies for drug-carrying contact lenses

Manufacturers have devised several strategies for manufacturing contact lenses which carry and release active principles. The most interesting strategies are summarized below.

a) immersion of the lens in a drug solution

The first attempt to obtain drug-releasing contact lenses was submerging a conventional lens in a drug solution between 2 and 8 h.[9,22] This was the easiest and cheapest method, which has been used with numerous medicaments.[1]

The use of commercial lenses of this type has the advantage of easy access in the market, ensuring a consistent and reproducible product. These lenses have demonstrated greater efficacy in the administration of drugs when compared to ophthalmic drops because the drug molecules remain longer in the post-lens lacrimal film, leading to increased flow thereof through the cornea and diminished drug drainage through the nasolacrimal duct.[20]

Contact lenses comprise inner channels and cavities which can house the molecules of the drug. This housing capacity will mainly depend on the content of water, lens thickness, molecular weight of the drug, period of immersion and concentration of the medicament in the immersion solution.[3] The main limitations of this strategy are poor carrying efficiency for some drugs[23] and the release kinetics tend to be fast and uncontrolled because the material of these lenses was not

designed for releasing active principles. In approximately one hour the entire contents are released, making these lenses inadequate for long-term administration of medicaments.[5,15] In addition, in some cases the transparency of the lens is compromised due to the precipitation of the drug on the lens.[23]

The main application of said strategy could involve conditions in which the dose of the administered medicament is more important than the rate at which it is released. One example is ocular allergy, where a single daily dose of a drug is prescribed. Accordingly, a disposable lens that releases said dose while correcting refractive errors could be feasible and very useful.[5]

b) vitamin E barriers

This strategy is applied for commercial market lenses in order to slow down the rate of release of a drug. Its consists in utilizing vitamin E which by nature is hydrophobic and exhibits low solubility in water to create a tortuous pathway and thus prolong the diffusion time of a drug through the lens. In addition, vitamin E is entirely biocompatible.[19]

Placing a layer of vitamin E over the surface of hydrogel or silicone hydrogel contact lenses makes the delivery pathway more tortuous and prolonged for hydrophilic drugs which must overcome said obstacle to reach the ocular surface, thus extending diffusion time. However, hydrophobic drugs tend to diffuse through the vitamin molecule reaching the ocular surface faster. This phenomenon increases significantly up to 400 times the diffusion period for hydrophilic drugs such as timolol and 16 times for dexamethasone.[19]

The inclusion of the vitamin E barrier is through immersion of contact lenses in a solution of vitamin E in ethanol. The composition of the solution may vary according to the desired amount to be administered.[5] Subsequently, the lens is introduced in water to remove ethanol, leaving the vitamin trapped within the lens. The presence of vitamin D in the lens does not obstruct its transparency.[24] However, its presence can affect to some extent the size of the lens, the diffusion of oxygen and ionic permeability, which depends on the thickness of the deposited barrier.[5] On the other hand, the antioxidant properties of vitamin E provide a certain degree of protection for the cornea against ultraviolet light and prevent the oxidation of some susceptible medicaments.[5,24]

c) Molecular imprinting

At present, molecular imprinting is one of the most researched methods. This technology was optimized by Álvarez-Lorenzo et al.[25] It consists in synthesizing the polymer that makes up the lens in the presence of the substance in question, i.e., the active principle. In this way, the drug would act as a mould during the polymerization processes. Initially, the drug is mixed with a solution of monomers that form the lens, which must have the capacity to generate reversal covalent links, ionic links or hydrogen bridges with the drug.[25]

Said system is subject to polymerization, subsequently removing the drug from the polymer meshwork. This gives rise to a number of pockets or cavities known as a macromolecular memory sites. These 3D sites imitate receptors of the active principles that interact with the molecules of the active principle if making contact with them again, thus increasing the charge of drug in the lens.[5,19,24]

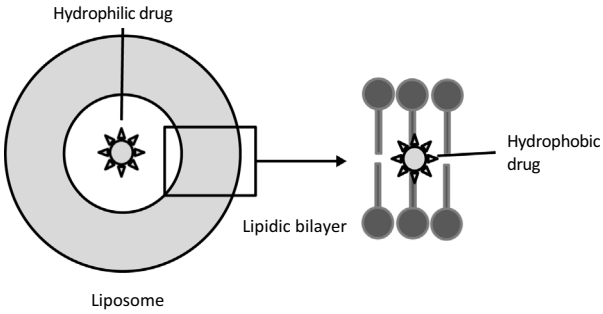

Fig. 5 – Diagram of a liposome showing the position of hydrophobic and hydrophilic active principles (Author: M.A. Holgado; March 27, 2019).

The medicament is loaded by immersing the lens in a solution allowing it to seek out the memory sites where it will interact with the previously created cavities.[24]

d) Colloidal systems

An additional strategy is the utilization of colloidal particles of diverse nature loaded with a medicament and dispersed within the lens or fixed on its surface by means of chemical links.[1,2]

Several types of systems have been studied. These are briefly described below.

Polymeric nanoparticles. These are most widely studies at present. Nanospheres are solid spheres constituted on the basis of a dense polymeric matrix in which the drug is dispersed. These nanocapsules are constituted by reservoirs surrounded by a polymeric membrane.[26]

One of the most widely studied medicaments in this type of systems is timolol.[27,28] In addition, research on the antimicrobial activity of nanoparticles of silver dispersed in contact lenses has achieved satisfactory results against Pseudomona aeruginosa and *Staphylococcus aureus*.[29]

Liposomes. These are small spherical vesicles between 100 and 400 nm, made up of lipidic bi-layers of phospholipids that surrounds an inner aqueous phase. Both the bi-layer and the aqueous phase can contain hydrophobic and hydrophilic medicaments respectively, making liposomes a highly versatile vehicle (Fig. 5).[30]

Phospholipids can be made up of phosphatidylcholine and cholesterol. The concentration of the latter influences the size of the liposomes as well as the efficacy of drug encapsulation and its subsequent release.[7]

The first studies on liposomes for ocular administration were carried out by Smolin in 1981. Said authors encapsulated idoxuridine and demonstrated increased corneal penetration of the active principle in herpetic keratitis compared to a solution of the drug in free form.[30]

Liposomes exhibit high biocompatibility as well as amphiphilic properties, i.e., compatibility with hydrophile and hydrophobic groups within the same structure and low toxicity. However, their stability is regarded to be lower than polymer systems because phospholipids can undergo oxidative degradation. In addition, the cost of natural phospholipids is very high for the limited volume they allow.[26]

Niosomes. These are chemically stable, biodegradable, and biocompatible chemical structures comprising 2 non-ionic

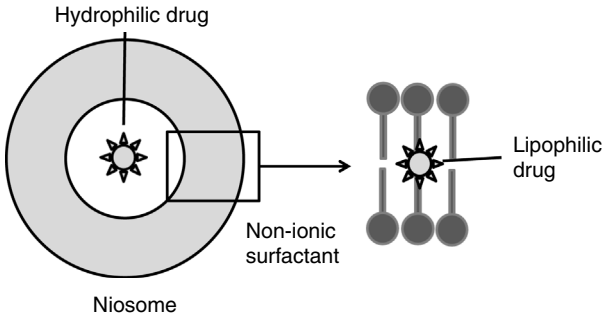

Fig. 6 – Diagram of a niosoma showing the position of the lipophilic and hydrophilic active principles (Author: M.A. Holgado; March 27, 2019).

surfactant layers and are able to carry lipophilic as well as hydrophilic molecules (Fig. 6). Their size ranges between 12 and 16 μm.[26]

Tests were made with Span® 40 and 60 surfactants with cholesterol in various molar ratios, the most effective being 7:423.

Dendrimers. Three-dimensional polymeric, ramified and spherical structures in tree shape and sizes between 3 and 20 nm. These structures are useful as drug carriers because of their drug-carrying capacity (Fig. 7). The amount of functional groups on their surface could lead to multivalent interactions that could lead to an increase of mucoadhesive properties, diminished lacrimal exchange and improved pre-corneal permanence. This is achieved due to strong electrostatic interactions between the mucine of tears and said dendritic structures.[30]

Nanoemulsions. These are inner phase droplet-size emulsions having a diameter of approximately 200 nm. The

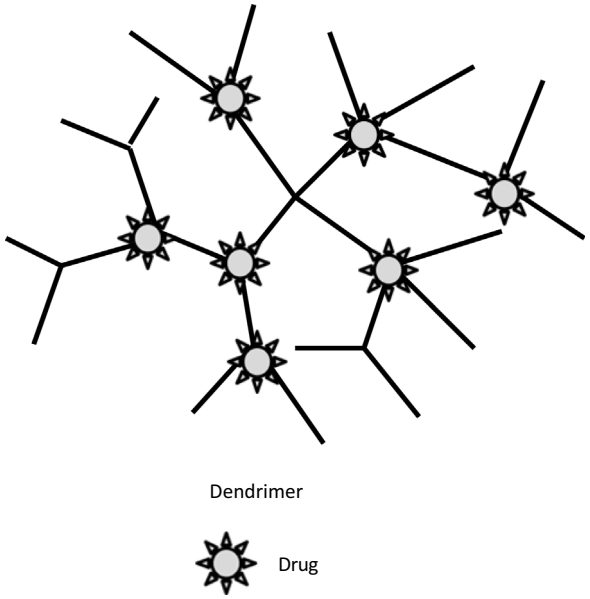

Fig. 7 – Diagram showing a dendrimer with drug molecules anchored to its structure (Author: M.A. Holgado; March 27, 2019).

inclusion of this system in contact lenses was researched for the polymerization stage, obtaining rapid initial release of the drug and subsequently remaining constant during a 10-day period. The only drawback was related to toxicity produced by some of the surfactants that were utilized.[4,18]

Nanomicelles, made up of amphiphilic molecules which can be polymeric or surfactant. Interest in nanomicelles is due to their high encapsulation capacity, ease of preparation and small size ranging between 10 and 100 nm.[30,31]

Lysozyme activated diamond nanogels. This alternative has been described recently and it consists in including a nanogel based on carbon and chitosan which, when making contact with lysozyme in tears releases the drug in a controlled manner. In order to avoid jeopardizing lens parameters (transmittance, permeability to oxygen and water content) said nanogel is dispersed in the p-HEMA metric that makes up the lens.[32]

Treatment of ocular pathologies with contact lenses containing medicaments

Pharmacological therapy with these devices has been utilized in ocular surface as well as anterior and posterior segment pathologies. A summary of the most widely studied pathologies and medicaments[33] follows.

• *Antibiotics*. The administration of this type of drug is of great importance because some infectious conditions require multiple daily doses.

A 24-hour release of moxifloxacin was obtained after immersing off-the-shelf contact lenses in a solution containing said medicament.[34] A number of parameters was studied in the trial and it was concluded that a fundamental factor was the composition of the drug solution, i.e. a phosphate tamponade and a solution of artificial tears. Release was slower in the latter form, probably due to higher viscosity.[34] The same medicament was utilized in contact lenses together with hyaluronic acid as a comfort agent, giving rise to a lens known as “dual action lens”. The release of moxifloxacin was extended to 48 h in addition to avoiding the “red eye syndrome” due to the utilization of hyaluronic acid.[35]

• *Corticoids*. This group of drugs is broadly utilized for the ocular pathway, one example being dexamethasone. This drug was added to lenses with vitamin E barrier to achieve release periods ranging between 7 and 9 days.[36]

Dexamethasone was also included in chitosan nanoparticles.[19] After manufacturing said particles, these were mixed with HEMA monomers, subsequently carrying out polymerization to obtain the lens. These lenses had a thickness of 50 μm and a transmittance between 95–98%. In vitro studies showed that the drug was released during 10 days, reaching constant levels up to 22 days. This provided increased bioavailability which reached 72% when compared to eyedrops during the first 10 days.[19]

An additional study with prednisolone obtained similar results.[37] Contact lenses were submerged in a suspension containing nanocapsules of said drug. SEM analysis reveals the adherence of nanocapsules to the surface of the lens without altering parameters such as transparency and permeability. The drug release profile evidenced delivery sustained in time.[37]

• *Anti-Inflammatories*. Using the molecular imprint method, sodium diclofenac was added to p-HEMA lenses reticulated with polyethylene glycol dimethacrylate. It was demonstrated that the drug interacted with the lens polymers through ionic joins, achieving a zero order released during 48 h.[5]

A further strategy carried out with the same drug involved its inclusion in lenses with a multilayer of alginate-chitosan-alginate deposited over the lens surface. This layer was dense, homogeneous and highly hydrophilic. I did not impair the refraction index and diminished transmittance only slightly, achieving diclofenac release during one week.[38]

• *Immunosuppressants*. Cyclosporine A is nearly insoluble in water and for ophthalmic use it is formulated only as an emulsion. This involves some drawbacks such as blurry vision, pain at the instillation site, irritation and tearing.[39] For these reasons it could be very useful and beneficial for the patient to have a more adequate and comfortable administration system. Cyclosporine was included in contact lenses comprising vitamin E barriers, achieving zero order release profiles for an approximate period of one month.[40]

Pirfenidone is utilized for alkaline chemical burns, an important cause of corneal blindness. This medicament was included in contact lenses with vitamin E barriers, obtaining results indicating 40% bioavailability increase compared to the same drug formulated as ophthalmic drops.[41]

• *Ocular allergy*. A dual approach is considered for this type of pathology, i.e., the ability of contact lenses to act as a physical barrier against airborne antigens and the utilization of the same lenses for releasing drugs. Said dual action could improve symptomatology of some ocular allergies.[42]

Therapeutic management of ocular allergy involves different types of drugs according to the severity of symptoms and response to treatment. A preventive approach involves mast cell stabilizers in order to diminish the release of histamine and/or an approach with antihistaminics to prevent the action of the previously released histamine. An example of the first group includes sodium cromoglycate and ketotifen for the second group. In both cases, drug release took place relatively fast, mainly during the first hours and never beyond 4 h.[43]

Soluri et al. utilized 14 different types of market contact lenses submerged during 24 h in ketotifen solution.[44] The results were very similar despite the large range of lens compositions, i.e., the majority of the drug was released in the first hours, leading to think that the immersion of the drug in the lens did not produce prolonged release profiles.[44]

Additional studies with olopatadine with the molecular imprint method demonstrated adequate levels of drug delivery sustained during a full day, minimizing ocular irritation and the release of histamine.[45]

• *Glaucoma*. This chronic disease characterized by increased intraocular pressure requires long-term administration of drugs. In general, the pharmaceutical administration pathway is through eyedrops. In the treatment of glaucoma it is essential to maintain constant therapeutic levels for an indefinite period of time. Accordingly, a zero order release would be perfect.

In vitro research using commercial lenses immersed in a drug solution has demonstrated the same results given by other drug types, i.e., rapid and uncontrolled release.[5]

Contact lenses with vitamin E barriers were also researched for glaucoma treatment. Experiments were carried out with timolol and dorzolamide.[5,45] These lenses increased the release time from 4 to 84 h in *in vivo* studies with glaucomatous dogs, in contrast to dogs treated with eyedrops or unmodified commercial lenses and submitted to an immersion processes in solution of said drugs.[5]

Molecular imprinting has also been tested with timolol. MAA was the chosen function monomer used in a p-HEMA lens. It was observed that the addition of MAA produced a significant increase in the carrying capacity and enabled the release of timolol during more than 24 h.[5]

Other trials have developed soft contact lenses utilizing N,N-diethylacrylamide and methacrylic acid monomers that released timolol during approximately 24 h, paving the way to enable the sustained release of hydrophilic drugs in utilizing hydrogels.[46]

The use of prostaglandin analogs such as latanoprost, travoprost and bimatoprost is highly extended in glaucoma treatment due to its dosage frequency of once a day and low amount of adverse effects.

Said group of drugs have been assayed with various methodologies including immersion and PLGA nanoparticles demonstrating promising results.[5,47]

Horne et al.[48] utilized silicone hydrogel lenses submerged in a solution of latanoprost in propanol. A release essay *in vitro* utilizing a medium of artificial tears evidenced a controlled delivery profile through diffusion sustained during 4 days.[48]

Conclusions

The utilization of contact lenses carrying active principles for treating ocular pathologies could give rise to novel therapeutic options. The composition of the lens as well as the drug interaction strategy determine the performance in the loading of the drug and its release profile. Both parameters are extremely important for the success of a pharmacological therapy. On the other hand, requirements of safety, efficacy and stability must also be taken into account to optimize the production of said systems if they are to become medicaments in their own right.

Conflict of interests

No conflict of interests was declared by the authors.

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