REVIEW ARTICLE

Am J Drug Deliv 2006; 4 (3): 131-151
1175-9038/06/0003-0131/$39.95/0

Contact Lenses for Drug Delivery

Achieving Sustained Release with Novel Systems

Carmen Alvarez-Lorenzo,[1] *Haruyuki Hiratani*[2] and *Angel Concheiro*[1]

1 Departament of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Santiago de Compostela, Santiago de Compostela, Spain
2 Menicon Corporation Ltd, Kasugai, Aichi, Japan

Contents

Abstract

Currently, approximately 100 million people are estimated to be wearing contact lenses, and the number is increasing exponentially. Although the main use of contact lenses is for correcting ametropia problems, they also hold interest as therapeutic devices for the relief of ocular pain, promotion of corneal healing, mechanical protection and support, maintenance of corneal epithelial hydration, and drug delivery. Ocular drug administration is particularly challenging and recent research has been directed towards the design of novel drug delivery systems capable of prolonging the permanence of the drug in the precorneal area and, thus, potentially increasing bioavailability and minimizing adverse effects.

Conventional hydrogel soft contact lenses have the ability to absorb some drugs and release them into the post-lens lacrimal fluid, minimizing clearance and sorption through the conjunctiva. Their ability to be a drug reservoir strongly depends on the water content and thickness of the lens, the molecular weight of the drug, the concentration of the drug loading solution and the time the lens remains in it. However, the ability of contact lenses to load drugs and to control their release is in general inadequate and the following approaches, based on

modifications of the polymer network, are currently under evaluation: (i) covalent binding of the drug to the lens network via labile bonds; (ii) inclusion of the drug in colloidal structures that are dispersed in the lens and are responsible for controlling drug release; (iii) functionalization of the network with chemical groups that work as ion-exchange resins; and (iv) 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 and selectivity for a given drug. In this review, the possibilities and the advantages/drawbacks of these new types of contact lenses as drug delivery systems are critically analyzed.

Contact lenses are mainly intended for the correction of ametropia problems, but can also be used for therapeutic purposes to meet different demands, such as relief from ocular pain, promotion of corneal healing, mechanical protection and support, maintenance of corneal epithelial hydration, and if medicated, drug delivery. The use of contact lenses as drug delivery systems is gaining increasing attention; this review outlines current methodologic approaches to the development of medicated contact lenses and discusses the advantages/limitations of each approach as a system for delivering drugs.

1. Drug Delivery onto the Eye

1.1 Advantages and Limitations of Topical Instillation

The eye can be affected by many pathologic conditions. In addition to the vision impairments associated with failure of the cornea and lens to focus the image on the retina, the eye structures can suffer lesions and diseases of varied origin that are mostly related to infection, allergic, vascular (glaucoma), and degenerative processes.[1,2] The ocular structures are almost never accessible from the general circulation and the success of systemic treatments is conditional on the serum-ocular tissue concentration gradient and the efficiency of the blood-ocular barriers (blood-aqueous humor, blood-retina, and blood-vitreous humor) against drug penetration.[3,4] Therefore, in order to attain therapeutic ocular effects, in most cases the body has to be exposed to high drug doses, which can lead to important adverse effects and toxicity. To avoid these unwanted effects, drugs can be directly administered through topical, periocular or intraocular (intracameral or intravitreal) routes. For safety reasons, the two latter invasive routes are reserved for the treatment of severe infections when other approaches are not viable or for the laboratory study of new delivery systems for hormones, peptides, or gene material.[1,5,6] In contrast, topical treatments combine sufficient levels of convenience, safety, and efficiency as to make them the preferred strategies for treating both surface and intraocular diseases. Antimicrobials, antivirals, β-adrenoceptor antagonists, miotics, mydriatics, local anesthetics, and anti-inflammatory and antiallergic-antihistaminic drugs are often topically administered.

After topical administration, the drug may pass through the cornea to the aqueous humor, or may be absorbed through the conjunctiva resulting in absorption that is mostly unproductive.[7,8] The amount of drug that penetrates into the cornea depends on the permeability of the epithelium, the permanence of the drug in the precorneal area, and the dynamics of the lacrimal fluid.[7,8] Useful models for a quantitative evaluation of the effects of these variables have been developed.[9] A typical ophthalmic dropper delivers 30μL, but when blinking occurs the eye can hold only approximately 10μL of tear fluid.[1] Additionally, the normal human tear turnover, 10–20% per minute, facilitates the removal of the remaining drug solution from the conjunctival cul-de-sac.[10] Therefore, most of the administered drug is rapidly lost through nasolacrimal drainage, which contributes to important systemic absorption. For example, when pilocarpine is administered as eyedrops, the precorneal disappearance/transcorneal penetration ratio is estimated as 100, i.e. the formulation is washed away from the precorneal area 100 times faster than the drug penetrates the cornea,[11] and, in general, the fraction of dose that penetrates into the ocular structures is limited to 1–10%.[12] To overcome these limitations, a small volume (ideally 5–10μL)[13] of extremely concentrated solution should be instilled twice at an interval of 5 minutes, and this sequence reproduced several times a day.[14] However, this pulsatile mode of administration has the drawback of giving rise to extreme fluctuations in the ocular level of the drug, which increases the risk of untoward adverse effects.

1.2 Approaches to Prolonging Drug Permanence in the Precorneal Area

To prolong the permanence of the drug in the precorneal area and, consequently, to enhance ocular bioavailability, different types of systems (such as polymeric viscous/mucoadhesive solutions and semisolid formulations, colloidal systems, and inserts) have received a great deal of attention.[5,15-19] While assessment of the performance of these ocular formulations is not easy because of the varied origin of the data and the different *in vitro* and *in vivo*

evaluation procedures used,[20] the available data suggest that they can significantly increase the efficiency of ocular therapy.

The viscosity of the tears when resting varies in the range of 1.05–5.97 centipoise (cPs).[21] It has been observed that the corneal contact time of ophthalmic solutions increases proportionally to the viscosity of the formulations up to 20 cPs; further increases result in reflex tearing and blinking in order to regain the original viscosity.[14] The bioavailability increase associated with this longer precorneal permanence allows the frequency of drug application to be reduced. Several synthetic polymers, which include polyvinylalcohol (PVA), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), polyacrylic acid (PAA), and many cellulose derivatives, are commonly employed as viscosity enhancers because of their physiologic compatibility and satisfactory physicochemical properties.[17,22] A more sophisticated approach consists of using polymers that provide the liquid formulation with semisolid consistency only when it is placed in the precorneal area. In this way, easy instillation of the solution is followed by prolonged permanence as a result of the viscoelastic properties of the formed gel. This *in situ* gelling phenomenon is caused by a change in the conformation of the polymer(s) that can be triggered by the temperature, pH, or ionic content.[16,23-25] Representative examples of *in situ* gelling systems are the once-daily formulations that combine gellan gum (Gelrite®)[1] and alginates to prolong the ocular delivery of timolol for glaucoma treatment (commercially available as Timoptic®)[26] or PAA and cellulose ethers to sustain the delivery of ofloxacin.[27] Additionally, some polymers can interact, via noncovalent bonds, with conjunctival mucin and maintain the formulations in contact with precorneal tissues until mucin turnover leads to their removal. The mucoadhesive properties of the polymers usually stem from their numerous hydrophilic functional groups, such as carboxyl, hydroxyl, amide, and sulfate, which are capable of establishing electrostatic interactions with glycoproteins. Extensive reviews on the potential of mucoadhesive materials in ocular drug delivery have been published recently.[19,28] Two of the main drawbacks of viscous and mucoadhesive formulations are blurring and an unpleasant sticky feeling in the eye. As a consequence, patients may find compliance with treatment schedules difficult.

Administration of the drug as a suspension can also be useful for prolonging its permanence in the precorneal area. After topical instillation, microparticles are expected to be retained in the culde-sac and the drug slowly dissolved or released from the polymeric structures by diffusion, polymer degradation, or ion exchange.[29] Solid particles must be smaller than 5–10μm to avoid ocular discomfort or irritation. Drug-loaded colloidal systems such as liposomes, nanoparticles, and nanocapsules have been also assayed for ophthalmic applications.[30,31] Liposomes enhance corneal drug absorption by entering into intimate contact with the cornea and conjunctiva.[5,32] Nanoparticles and nanocapsules could even penetrate into the corneal epithelium and facilitate drug release towards the aqueous humor.[33] Niosome- and nanoemulsion-based systems are also receiving growing attention because of their ease of preparation and greater stability.[16,34] Although very promising, commercial development of these colloidal systems remains limited because of the complexity of their manufacture, particularly in relation to stability problems during sterilization, which are not offset by substantial improvements in pharmacokinetic and pharmacologic performance.[17]

Ophthalmic inserts (i.e. solid or semisolid devices of appropriate size and shape designed to be placed in the lower and, less frequently, upper fornix or on the cornea) can be classified into three main categories: soluble, bioerodible, and insoluble.[17] These solid devices allow accurate dose delivery, avoid the use of preservatives, and can notably increase ocular bioavailability. Drug release from soluble inserts involves two steps: (i) fast release of a drug portion as the tear fluid penetrates into the system; and (ii) slow release as a gel layer is formed on the surface of the device. As the initial dissolution step is usually fast, the solubilized components can often cause blurred vision. Collagen shields made from porcine scleral collagen or bovine corium tissue,[35] and devices obtained by moulding, extrusion or compression (minitablets) of gelling polymers, belong to this category.[36] Bioerodible polymers (e.g. cross-linked gelatin derivatives and polyesters) can be used to prepare erodible inserts. These matrices act as simple reservoirs or interact with the drug molecules through labile bonds; the ease with which these bonds can be broken regulates release of the drug. As the erosion rate is largely dependent on the conditions of the physiologic environment, drug-release profiles usually show a high inter- and intraindividual variability. Finally, insoluble inserts can have a reservoir or matrix structure. Ocusert® was the first marketed reservoir system able to release a drug, pilocarpine, at a programmed rate for a long period of time (7 days). Despite the remarkable therapeutic advantages of these inserts, difficulties with handling, the sensation of a foreign body in the eye, and the high risk of accidental expulsion greatly limit their practical use.[22] However, most of these drawbacks could be overcome, without losing the control-release performance, through use of drug-loaded contact lenses.

As previously stated, this review discusses the characteristics and advantages/disadvantages of medicated contact lenses. While the release of hydrophilic polymers (e.g. PVA or PVP) from lenses

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Classification of contact lenses according to the US FDA. All contact lenses shown as examples of the hydrophilic contact lenses are available for therapeutic use or have been used in an off-label manner as therapeutic lenses[44-46]

Classification	Group	Description	Examples: material (polymer composition; brand name)
Hydrophilic	I	Non-ionic[a], low water content	Crofilcon A (MMA-GMA; CSI® 38), lotrafilcon A (DMAA-siloxane macromer; Focus® Night & Day™), polymacon (HEMA-NVP-CMA; Optima® FW and Plano T)
	II	Non-ionic[a], high water content	Afilcon A (HEMA-NVP-CMA; Soflens® 66), omalfilcon (HEMA-phosphorylcholine; Proclear Compatibles®)
	III	Ionic[b], low water content	Balafilcon A (siloxane macromer-NVP; PureVision®)
	IV	Ionic[b], high water content	Etafilcon A (HEMA-MAA; Acuvue® 2), methafilcon (HEMA-MAA; Kontour® 55), vifilcon A (HEMA-MAA-NVP; Focus® Monthly)
Hydrophobic	I	Without silicon and fluorine	Porofocon A (CAB; RX56), arfocon (t-butyl styrene; Airlens)
	II	With silicon but not fluorine	Pasifocon (silicone acrylate; Boston® II and Boston® IV)
	III	With silicon and fluorine	Itafluorocon A (FSC; Equalens®), tisilfocon A (FSC; Menicon Z™), paflucon (FSC; Fluoroperm®), flusifocon (FSC; Fluorex®), Enflucon B (FSC; Boston® EO)
	IV	With fluorine but not silicon	Fluorofocon A (PPFE; 3M Fluoropolymer)

a Having an ionic content of <1% mole fraction at pH 7.2.

b Having an ionic content of >1% mole fraction at pH 7.2.

CAB = cellulose acetate butyrate; **CMA** = cyclohexyl methacrylate; **DMAA** = N,N-dimethyl acrylamide; **FSC** = fluorosiloxane acrylate; **GMA** = glycerol methacrylate; **HEMA** = hydroxyethyl methacrylate; **MAA** = methacrylic acid; **MMA** = methyl methacrylate; **NVP** = N-vinylpyrrolidone; **PPFE** = polyperfluoroether.

to increase the comfort to wearers[37,38] is also generating interest (already commercialized as Focus® Dailies® with AquaRelease™, and 1-day Acuvue® Moist™ Contact Lenses), this is outside the scope of this review.

2. Contact Lenses as Therapeutic Devices

Since the development of the first device that can be considered a contact lens, made by Leonardo da Vinci in the 16th century, enormous efforts were made until well into the 20th century to adapt glasses to the eye for both surface protection and correction of ametropia.[39] Once it was realized that glass materials hinder the natural exchange of oxygen and nutrients and, therefore, cannot be withstood for more than a matter of minutes by some individuals, an active search for alternative materials was, and is still being, carried out. The major boost for the popularization of contact lenses for vision correction was the development of acrylic polymers, such as polymethyl methacrylate (PMMA) in 1936, and poly(2-hydroxyethyl methacrylate) [PHEMA] in 1954.[39-41] These materials, which combine the high optical clarity of glass with a lower density and better mechanical properties,[42,43] served as a starting point for designing new polymers able to improve the quality of the lenses. Since contact lenses for vision correction are categorized as medical devices, the materials used for making the lenses must have proven safety and performance characteristics. Oxygen permeability, mechanical strength, optical clarity, resistance to deposition of tear film components, comfort, and ease of manufacture, handling and insertion are critical aspects.

Daily wear contact lenses are currently classified into hydrophilic ('filcon') or hydrophobic ('focon') lenses according to their chemical composition and physical properties (table I).[44] The first hydrophobic hard contact lenses made with PMMA demonstrated excellent transparency, but their low water content (<10% w/w) still gave the wearer the sensation of a foreign body in the eye. Thus, the improvements offered by the more comfortable and oxygen-permeable hydrophilic soft contact lenses, originally based on PHEMA, explain why their use is widespread nowadays. These soft contact lenses are flexible, slightly cross-linked hydrogels that can absorb and retain large amounts of water (>35% w/w), in which oxygen can dissolve and diffuse towards the cornea. Their high degree of biocompatibility prompted their approval for extended wear (up to 6 nights and 7 days) in the late 1970s. The search for new materials to reduce the hypoxia induced while wearing the lenses during closed-eye periods led to the development in 1979 of gas-permeable hard lenses with greater oxygen permeability, and which therefore maintained optical clarity and the ease of handling characteristic of hard lenses.[41,43]

The rank order of oxygen solubility for the following materials is: carbon-based polymeric materials < water < silicone-containing materials. The high gas permeability of silicone-based lenses is explained by the bulkiness of the silicone group $(-Si(CH_3)_2-O-)$ and by the chain mobility that characterizes such materials.[43,47] However, silicon elastomer is too hydrophobic (if not treated on its surface) and its mechanical properties may not be optimal for contact lenses. Therefore, it must be combined with more hydro-

philic monomers such as hydroxyethyl methacrylate (HEMA), N-vinylpyrrolidone (NVP), or methacrylic acid (MAA); in such combinations, the silicone component is responsible for the oxygen permeability, and the hydrophilic component is responsible for the ions and water permeability, which are necessary for the on-eye movement of the contact lens.[43,48] Improvements in the composition of these lenses and the development of new materials, such as siloxane and fluorosiloxane hydrogels, led to the approval of soft contact lenses for continuous wear (up to 29 nights and 30 days) in 2001.[48,49]

The market is split between the various types of contact lenses and that market has been recently estimated at 82% soft lenses, 16% rigid gas permeable lenses, and 2% hard lenses.[41] The number of people who regularly wear contact lenses (currently *ca.* 100 million people) is exponentially increasing and within the next decade is expected to surpass the number of people who regularly wear traditional pairs of glasses.[50]

Although contact lenses are mainly intended for the correction of ametropia problems, they also have interesting potential in therapeutics. In fact, the US FDA classifies contact lenses according to their intended uses as (i) nontherapeutic contact lenses (e.g. for correction of refractive ametropia, aphakia, and presbyopia); (ii) specialized use contact lenses (e.g. for the treatment of keratoconus); and (iii) therapeutic contact lenses, which have proven to be an effective tool in the management of a wide variety of ophthalmic disorders refractory to other treatment modalities.[45] The reason for wearing therapeutic contact lenses are diverse but can be categorized as follows:[51]

1. relief of ocular pain;
2. promotion of corneal healing;
3. mechanical protection and support;
4. maintenance of corneal epithelial hydration;
5. drug delivery.

Lenses able to accomplish some of the first four aims have been extensively evaluated and comprehensive reviews can be found elsewhere.[41,45,52-55] By contrast, use of contact lenses as drug delivery devices is atypical, although this strategy has attracted the attention of many researchers and clinicians, particularly since the advent of the first extended-wear soft lenses, which may allow prolonged delivery of drugs on the cornea.[56,57] On the other hand, the risks of lesions and infections associated with common usage of conventional and therapeutic nonmedicated lenses[48,54,58,59] must also be considered.

2.1 Conventional Contact Lenses as Drug Delivery Systems

2.1.1 Therapeutic Interest

In 1886, Galezowski pioneered the use of contact lenses as ocular bandages by successfully applying gelatin discs loaded with different drugs (cocaine and sublimate) to prevent complications after cataract surgery.[54,60] However, the first real sign of the potential of contact lenses in drug delivery was not seen until the introduction of the first PHEMA contact lenses, as postulated by Sedlacek in 1965[61] and Gasset and Kaufman in 1970,[62] and subsequently taken up by numerous researchers.

The contact lens is thought to act as a reservoir that slowly releases the loaded drug. Immersion in aqueous solutions of concentrated drugs was the first approach used to load the lenses.[63-66] Another way consisted of placing the drug solution in the concavity of the lenses before placement on the eye, or instillation of eyedrops on their surface ('splash') after insertion.[67-70] As shown in recent studies, the drug administered in this way is released to the post-lens tear film, between the cornea and the lens, where it can remain for long periods (figure 1). Additionally, since during the time interval between blinking the external surface of the lens becomes dry, the amount of drug that diffuses towards the corneal epithelium is estimated to be 5-fold greater than the amount that is released to the lacrimal fluid bathing the external surface of the lens.[71] This explains why drug-presoaked or eyedrop-splashed contact lenses can provide remarkable improvements, compared with conventional administration of eyedrops, in both ocular

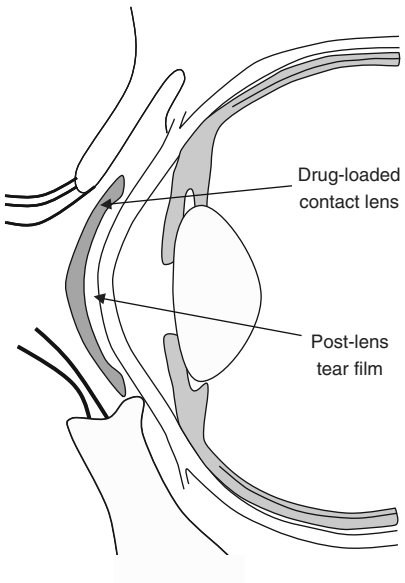

Fig. 1. Delivery from a drug-loaded soft contact lens. The drug travels through the lens matrix and enters the post-lens tear film, from where it can penetrate into the cornea.

bioavailability and pharmacologic response.[63,68,69,72] Therefore, contact lenses may be particularly convenient for clinical conditions requiring a high intraocular concentration of drug, such as anterior segment inflammation, angle closure glaucoma, or infections. In some cases, drug delivery through soft contact lenses can even lead to a decrease in the dose required to attain the desired therapeutic effect.[70]

2.1.2 Loading Conditions and Loading/Release Efficiency

Drugs penetrate hydrophilic lenses at a rate that depends on the mesh size of the polymer network (determined by the cross-linking density and the degree of swelling), the molecular size of the drug, and the concentration of the drug in the loading solution.[73] Earlier studies with pilocarpine showed that drug uptake by a contact lens increases over the time of immersion, approaching a maximum after soaking for 30–60 minutes, although 24 hours may be required to reach saturation (e.g. 400–500μg in a Sauflon lens).[64,74] Drug equilibration throughout the lens can markedly influence the performance of the lens as a delivery device; when the drug diffuses out from the surface layers, it can be replenished from the deeper part of the lens, which acts as a reservoir, making more sustained and reproducible release possible.[70,75] For example, instillation of pilocarpine 1% drops on a soft contact lens was significantly more effective in lowering intraocular pressure than direct instillation of pilocarpine 8% solution.[76] Similarly, instillation of diclofenac eyedrops on contact lenses provided significant pain relief for patients with corneal abrasions and shortened the healing time in most cases to 24 hours.[77] The application of antibacterial-presoaked soft contact lenses for half an hour provided a significantly higher ocular drug bioavailability than subconjunctival injections, while minimizing adverse effects.[70] Six hours after the beginning of an experiment, polymacon and alphafilcon A lenses saturated with ciprofloxacin (by immersion in a commercial eyedrop solution for 1 hour) resulted in markedly higher drug levels in both corneal tissue and aqueous humor than direct application of the eyedrops (cornea: polymacon 8.034μg, alphafilcon 6.432μg, eyedrops 0.451μg; aqueous humor: polymacon 0.361μg, alphafilcon 0.240μg, eyedrops 0.0071μg).[78,79] Etafilcon A (1-Day Acuvue®) lenses, when loaded by immersion in eyedrop solutions, can provide higher concentrations of antifungals, aminoglycosides, and fluoroquinolones in aqueous humor than when eyedrops are directly instilled.[80-82] In a study conducted in patients who required cataract extraction, all patients who wore ofloxacin-loaded lenses for 4–5 hours preoperatively and 92% of patients who wore ciprofloxacin-loaded lenses preoperatively had aqueous humor concentrations above the minimum inhibitory concentration at which 90% of *Staphylococcus epidermidis* isolates are inhibited at the beginning of surgery.[82] The proportion of patients who reached similar levels using the conventional protocol for eyedrops instillation was only 65% with ofloxacin and 41% with ciprofloxacin. Since no corneal erosions were observed during the wearing of the lenses, these findings could be attributed to the reservoir function of the lenses and to a slight hypoxic effect on the cornea that enhanced hydration and epithelial permeability.

The main drawback to the general use of soft contact lenses as drug delivery systems is their low affinity for most drugs.[83] For example, PHEMA lenses load amounts of chloramphenicol, epinephrine (adrenaline), and pilocarpine similar to those taken up by intact human crystalline lenses.[84,85] Thus, soft contact lenses generally achieve only one-tenth of the aqueous humor concentration of drug that can be achieved when eyedrops are used.[84-86] Furthermore, in the presoaking technique, loading is carried out by immersion in a concentrated drug solution, most of which will be not loaded and is therefore wasted. This high drug concentration may cause conformational changes and discoloration of the lenses, with resultant damage to their optical properties. In the few cases in which loading is sufficient for therapeutic purposes, the major limitation lies in the fact that release occurs far too quickly to maintain therapeutic levels in the ocular structures for sufficiently long periods of time.[41,46,56,86] Less commonly, it can lead to an excessive contact time between the drug and the cornea, exacerbating the topical adverse effects of the drug.[57]

2.1.3 Role of Lens Thickness

As a possible means of increasing the ability of the lenses to load drugs and control their release, the effects of lens thickness and water content were evaluated. In the 1970s the generation of therapeutic soft contact lenses with increased thickness (up to 0.7–1.3mm) enabled the release of, for example, fluorescein, tetracycline, or chloramphenicol for up to 24 hours.[87-89] Thick PHEMA lenses have also been shown to play a useful role in the delivery of diethylenetriamine and disodium ethylenediamine tetraacetate for the treatment of severe acid and lime burns, or of cysteine hydrochloride for the treatment of corneal burns and ulcers.[56] In comparison with classical ocular therapy, the use of these drug-loaded lenses halved the period of treatment. However, the practical possibilities of increasing the thickness of the lenses are limited not only for comfort reasons but also by the requirements of oxygen permeability. Unlike other tissues, the cornea has no blood supply and largely receives oxygen from the surrounding air to maintain its structure, transparency, and functionality.[90,91] The ability of a specific lens to deliver oxygen to the cornea is described by the coefficient of oxygen permeability referred to thickness unity, i.e. Dk/l, where D is the diffusion coefficient, k is the oxygen solubility coefficient and l is the thickness of the

lens.[43] *Dk* is usually expressed in Barrer units (1 Barrer = 10^{-10} $cm^2 \bullet s^{-1} \bullet cmHg^{-1}$ or, in SI units, 7.5005×10^{-18} $m^2 \bullet s^{-1} \bullet Pa^{-1}$), in honor of the leader in the research of diffusion of gases, namely Richard M. Barrer (1910–1996). To avoid ocular hypoxia during the night, a minimum of 87 Barrers is required.[92] Therefore, the possibility of increasing the thickness is limited by the need to maintain a permeability that is sufficient to preserve corneal homeostasis.

2.1.4 Role of Water Content

The water content of the hydrogel plays a major role in loading when no specific interactions of the drug with the network occur. The aqueous phase of the hydrogel is in equilibrium with the loading solution and, thus, the drug concentration in both is the same.[93] The amount of drug loaded is, therefore, expected to be proportional to the volume of water in the hydrogel (equation 1):[94]

$$\text{Drug in aqueous phase (w/w dry hydrogel)} = \left(\frac{V_s}{W_p}\right) \times C_0 \quad \text{(Eq. 1)}$$

where V_s is the volume of the aqueous phase in the hydrogel, W_p is the weight of dried hydrogel, and C_0 is the drug concentration in the loading solution.

This explains why, for example, high water content (71%) Permalens® lenses provide higher tobramycin concentrations in corneal tissue when the antibacterial is instilled on the lens, and for longer periods of time, than low water content (38.6%) Plano T therapeutic lenses.[69] At the same time, sustaining the release of the drug is in general more efficient from low water content lenses,[75] as explained in section 2.1.5.

The water content also conditions the oxygen permeability of hydrophilic contact lenses (equation 2):[95,96]

$$Dk = 2.00 \times 10^{-11} \exp(0.041 \times V_s) \quad \text{(Eq. 2)}$$

Thus, the greater the water content of this type of contact lenses, the greater its oxygen permeability and drug-loading capability. Soft contact lenses with water content up to 80% can be achieved using HEMA copolymerized with more hydrophilic monomers, such as NVP, N,N-dimethyl acrylamide (DMAA) or MAA. By contrast, hydrophobic silicone-based lenses usually have a low water content and, as the water content is increased, the oxygen permeability exponentially decreases,[96] limiting their potential as drug reservoirs.

2.1.5 Drug Release Kinetics

The approaches described above generally assume that the drug diffuses passively through the aqueous phase of the network without interacting with the polymeric structure. This places limitations on both the amount loaded and the control of its release, which is deficient in the absence of mechanisms of drug retention in the hydrogel. As well as uptake being generally rapid, a burst or dose-bumping release of the drug is generally observed. The rate of drug release from a hydrogel is not a random event but rather obeys the laws of diffusion, the main determinants of which are the thickness of the lens, its degree of hydration, and the drug concentration in the lens. The following equation can be used to predict, under sink conditions, the release of a drug by diffusion through hydrophilic lenses (equation 3):[93]

$$\frac{dM}{dt} = \frac{8DM_\infty}{l^2} \exp\left(\frac{-\pi^2 Dt}{l^2}\right) \quad \text{(Eq. 3)}$$

where M_∞ represents the total amount of drug released, l is the lens thickness, and D is the coefficient of drug diffusion, which is expected to remain constant if no changes in the degree of swelling of the lens occur during drug release.

For a given drug, the diffusion time decreases as the water content of the lens increases and for a given lens, the lower the molecular weight of the drug, the shorter the release time.[93] Bearing this in mind, the differences in the ability of silicon-containing (lotrafilcon and balafilcon) and PHEMA-containing (etafilcon, alphafilcon, polymacon, vifilcon, and omalfilcon) commercial contact lenses (see characteristics in table I) to absorb and release cromolyn sodium, ketorolac tromethamine, dexamethasone sodium, and ketotifen fumarate are very illustrative.[46] An *in vitro* rapid uptake and release (<1 hour) was observed for the first three drugs regardless of the lens material. This behavior can be explained by the low molecular size of the drugs and the relatively high water content of the lenses. Similar kinetics have been reported for cromolyn sodium, ciprofloxacin, idoxuridine, pilocarpine, and prednisolone using vifilcon, etafilcon, and polymacon lenses when placed in fresh saline solution.[75] The more gradual uptake/release (2 hours) of ketotifen fumarate, an amphiphilic histamine, could be related to its low aqueous solubility (0.01 mg/mL), which necessitated the use of very diluted loading solutions and may have had a significant effect on the mass transfer rate of the drug to the surface of the lens. Table II shows the total amounts of drug loaded and released by the different lenses and how these varied with the nature of the material, its ionic or non-ionic character, and the water content. The highest loading capacity observed for cromolyn sodium was related to its high concentration in the loading solution. Although the loading solution of dexamethasone sodium phosphate ranked second in concentration, this drug was poorly loaded by all of the lenses. This was explained by the high solubility (500 mg/mL) of

Table II. Effect of contact lens composition on the amount of drug loaded when immersed in the drug solution, and then released in 2mL borate saline buffer (reproduced from Karlgard et al.,[46] with permission from Elsevier)

Drug (soaking solution concentration)	Lens properties	Average uptake (μg/lens)	Average release (μg/lens)
Cromolyn sodium (20 mg/mL)	Ionic vs non-ionic	7548 vs 8126	390 vs 522
	Silicon vs PHEMA hydrogel	7811 vs 7906	338 vs 517
	High vs low water content	8066 vs 8126	552 vs 349
Ketotifen fumarate (0.20 mg/mL)	Ionic vs non-ionic	198 vs 123	103 vs 77
	Silicon vs PHEMA hydrogel	128 vs 166	84 vs 89
	High vs low water content	170 vs 135	90 vs 85
Ketorolac tromethamine (0.30 mg/mL)	Ionic vs non-ionic	103 vs 99	17 vs 20
	Silicon vs PHEMA hydrogel	85 vs 106	13 vs 21
	High vs low water content	108 vs 90	20 vs 16
Dexamethasone sodium phosphate (0.845 mg/mL)	Ionic vs non-ionic	67 vs 68	NA
	Silicon vs PHEMA hydrogel	57 vs 71	NA
	High vs low water content	74 vs 57	NA

NA = not available; **PHEMA** = poly(2-hydroxyethyl methacrylate).

this drug, which may make it more likely to be found in the outer solution than in the less hydrophilic inner environment of the lenses. With respect to the other two drugs, PHEMA hydrogels with a high water content and ionic character showed the greatest loading capability. It is interesting to note that in the medium used for the release studies (borate saline buffer Unisol® 4) only a fraction of the drug taken up was released: 12% for cromolyn sodium, 1.5–28% for ketorolac tromethamine, and 4–67% for ketotifen fumarate, which indicated that the drugs were irreversibly bound to the lens materials. No correlation was found with drug hydrophilicity nor with its ionic character but, as a general tendency, the higher the water content of PHEMA lenses, the higher the amount of drug released.

When conventional contact lenses are used as drug delivery systems, their rapid drug release makes it necessary to carry out frequent refills, raising problems that have not been adequately resolved as yet. These include:

1. would the reloading be done by the patient or the physician?
2. can the lenses be cleaned before reloading?
3. can the drug solution be prescribed without it containing preservatives (which may cause untoward reactions with the drug) and, if so, how does one avoid infection?[93]

3. Novel Sustained-Release Contact Lenses

Over the last few years, a better understanding of the mechanisms involved in the release of solutes from hydrogels and the application of new technologies for the enhancement of their loading and release performance has led to a revival in interest in soft contact lenses for drug delivery. In relation to the mechanisms involved in drug release from most polymeric systems,[97] the swelling-controlled mechanism can be practically discarded since maintenance of dimensions is an important requirement for the optical function of the contact lenses. In contrast, the following approaches based on diffusion- and chemically controlled release have been successfully applied to improve the performance of the therapeutic soft contact lenses: (i) chemically reversible immobilization of drugs in the hydrogel through labile bonds; (ii) incorporation of drug-loaded colloidal systems into the lens; (iii) copolymerization with functional monomers able to interact directly with the drug; and (iv) molecular imprinting (figure 2). Of course, in all cases, the final system should maintain oxygen permeability, hydrophilicity, and the optical, morphologic, and mechanical properties required for soft contact lenses. These approaches are

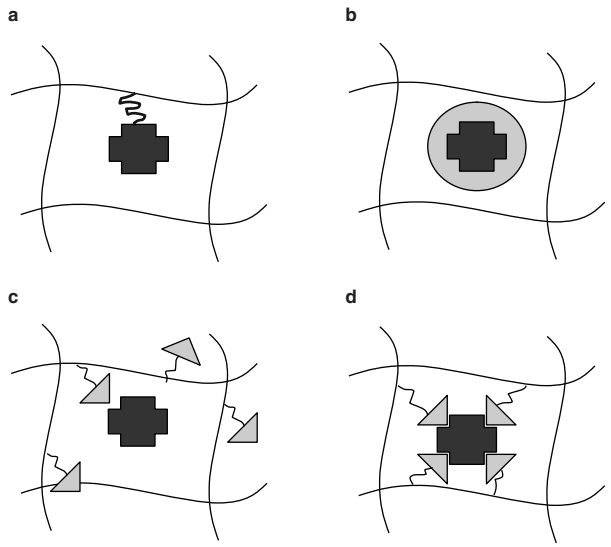

Fig. 2. Different approaches to obtaining contact lenses with high drug loading and controlled release ability. (**a**) Drug fixed by labile bonds; (**b**) drug inside colloidal structures; (**c**) drug noncovalently bound to functional groups; and (**d**) drug noncovalently bound in molecularly imprinted cavities.

explained and discussed in the following sections, together with other approaches that are in a more incipient state of development.

3.1 Soft Contact Lenses with Drugs Immobilized via Labile Bonds

Immobilization of drugs via labile bonds consists of binding the drug to the network through a spacer, the nature of which is carefully chosen to regulate local hydrophilicity and the kinetics of hydrolysis, such that release of the intact drug occurs in a controlled way and preferably following apparent zero-order kinetics.[93] The technique is only useful if the kinetics of bond breakage are slower than the drug diffusion process. Two steps are required to carry out this approach: (i) drug functionalization (i.e. bonding the drug to a polymerizable group through a labile spacer); and (ii) copolymerization with monomers adequate for producing soft contact lenses. Chemical (pH-dependent hydrolysis) or enzymatic (lysozyme-induced) breaking of the labile bonds makes detachment of the drug possible.

When developing indometacin (indomethacin)-loaded lenses, the drug was first reacted with methacrylamide (MAm) phenol to form 1-indomethacinoxy-4-methacrylamide benzene to obtain a monomer that was polymerized with MMA and NVP, or HEMA and NVP. The composition of the lens determines the entrance of the aqueous medium and, therefore, may condition the hydrolysis rate of the ester bonds that immobilizes the drug. Zero-order release profiles were achieved and the rate was able to be accelerated with addition of small proportions of MAA (figure 3). *In vitro*, a lens prepared by this procedure and containing a dose of 30mg was able to release between 5 and 30 µg/day.[98] In rabbits, a mean drug concentration of 1 µg/g of corneal tissue was obtained after 24 hours and remained practically constant for 7 days.[98] These concentrations were similar to those obtained with a >100-fold dose instilled as commercial eyedrops. Higher levels could be achieved by incorporating hydrophilic monomers such as MAA into the network.[98]

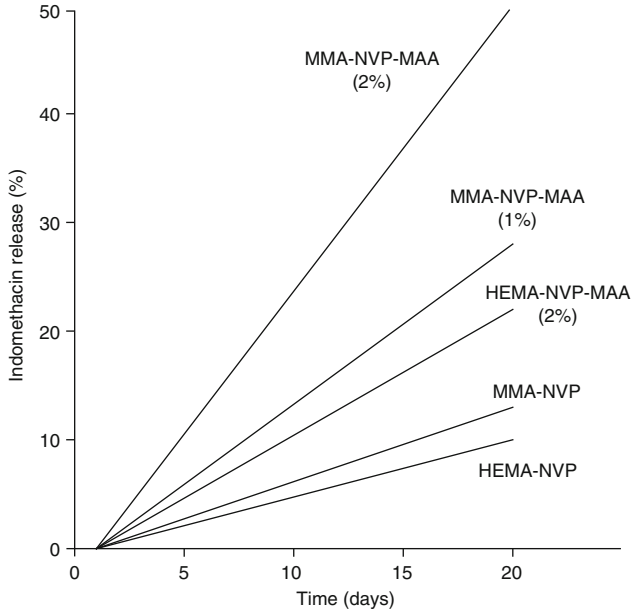

Fig. 3. Indometacin (indomethacin) release in pH 7 phosphate buffer by hydrolysis of the ester bond from MMA-co-NVP and HEMA-co-NVP hydrogels with different proportions of MAA. **HEMA** = hydroxyethyl methacrylate; **MAA** = methacrylic acid; **MMA** = methylmethacrylate; **NVP** = N-vinylpyrrolidone (reproduced from Vairon et al.,[98] with permission from L'Actualité Chimique).

3.2 Soft Contact Lenses with Dispersed Colloidal Systems

Recently, disposable soft contact lenses with nanometric droplets, particles, or vesicles, responsible for drug loading and release, have been developed.[99] The basic concept is to encapsulate the drug in the colloidal structures and to disperse them in the matrix during polymerization. If the number and size of the particles are sufficiently low, the lens stays transparent. Once placed on the eye, the nanoparticles must release the drug, which can then diffuse through the lens to reach the post-lens tear film. Effective control of release by the nanoparticles could provide sustained drug levels on the corneal surface for extended periods of time. Gulsen and Chauhan[99,100] have developed lenses of this type by dispersing oil-in-water microemulsion droplets (10–20nm) in PHEMA hydrogels. Four types of isotropic dispersions thermodynamically stabilized by surfactants were prepared with lidocaine (lignocaine) dissolved in the oil phase (table III). Two of these dispersions also contained octadecyltrimethoxysilane, which accumulates at the oil/water interfaces, forming a silica shell. To obtain the lenses, the microemulsions (7.4mL) were mixed with HEMA monomer (10mL) and the cross-linker ethyleneglycol dimethacrylate (EGDMA) [0.037mL]. The initiator azobisisobutyronitrile was then added and the polymerization carried out inside moulds of thickness ranging from 0.2mm to 1.2mm, at 60ºC for 24 hours. Control hydrogels of 1.25mm thickness were similarly synthesized, but the microemulsion was replaced by an equal volume of water and then loaded by immersion in a lidocaine aqueous solution.

Type 1 and 2 hydrogels were opaque because of the aggregation of the drops that followed the desorption of Tween 80® from the oil drops; therefore, they were not adequate to make lenses. In contrast, the gels prepared with Brij® 97, which is less soluble in the HEMA monomers solution, exhibited a minimal loss of transparency. In the type 4 hydrogels, the distribution of the droplets was irregular and domains with and without the droplets were observed. This could be explained by the lack of interactions between the particles and the network, and because the time

Table III. Composition and optical transparency of lenses (1mm thickness) incorporating different lidocaine (lignocaine) microemulsions (reproduced from Gulsen and Chauhan,[100] with permission from Elsevier)

Hydrogel	Microemulsion composition			Transmittance
	oil phase	aqueous phase	surfactant	(% at 600nm)
Type 1	Canola oil	2% NaCl solution	Tween 80® and Panodan® SDK	4.4
Type 2	Canola oil	2% NaCl solution	Tween 80®, Panodan® SDK, and OTMS	19
Type 3	Hexadecane	Water	Brij® 97	65.6
Type 4	Hexadecane	Water	Brij® 97 and OTMS	79

OTMS = octadecyltrimethoxysilane.

required for the gel to grow was longer than the time needed by the droplets to diffuse away. Therefore, as the network grew, the droplets were pushed towards the bulk solution until, when the medium became very viscous, the droplets were trapped by the hydrogel.[99,100]

The lidocaine profiles showed a release burst of 30–50% of the dose, followed by a much slower release after some hours (figure 4). The burst was due both to the drug absorbed on the surface of the droplets and the drug freely dispersed on the hydrogel network. No significant influence of cross-linking density[99] nor of lens thickness[100] was observed, which indicates that after the burst effect, the droplets inside the network controlled the release. The most challenging issues of this approach may be the optimization of microemulsion composition for each specific drug and stabilization of the drops, which is essential to avoid changes in the optical properties of the hydrogels.

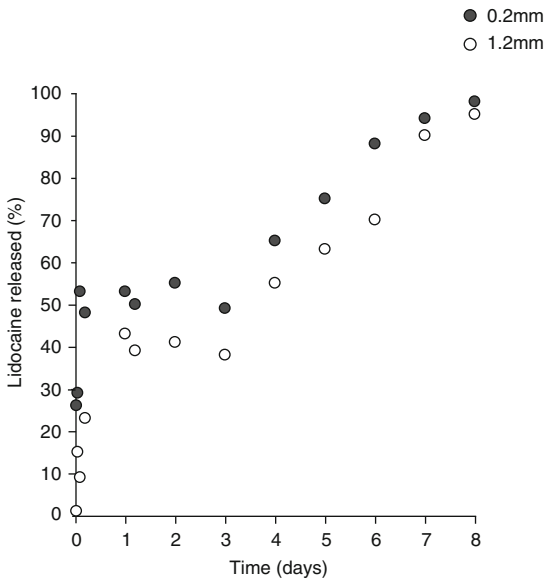

Fig. 4. Lidocaine (lignocaine) release profiles from type 4 hydrogels (see table III) with different thicknesses. Initial drug loading in both hydrogels was 1.2mg lidocaine/g hydrogel (reproduced from Gulsen and Chauhan,[100] with permission from Elsevier).

A similar procedure was developed to disperse dimyristoyl phosphatidylcholine liposomes in PHEMA hydrogels in two steps: (i) preparation of lidocaine-loaded liposomes; and (ii) synthesis of the hydrogel (1mm thickness) in a mixture containing the liposome dispersion.[101] Liposomes can load hydrophobic drugs in the concentric lipid bilayers, or hydrophilic ones in the aqueous cores. At polymerization conditions, liposomes were stable and did not alter the transparency of the hydrogels. In order to maximize the drug loading while maintaining the optical properties, the volume of aqueous dispersion of liposomes incorporated into the polymerization mixture must be equal to the volume of water that the PHEMA hydrogel is able to contain at a fully swollen state (near 40%).[102] In addition, increasing the lipid fraction of the liposomes can increase their ability to incorporate the drug. After a burst (15–30% of the dose) observed during the first 24 hours, the release was sustained for >1 week because of the slow diffusion of the drug across the lipid layers of the vesicles. The liposome-loaded gels showed decaying release rates and required storage in a buffer saturated with the drug to prevent unloading, both of which are important drawbacks. A promising way to overcome these problems is to incorporate smart polymers able to impede the unloading during storage and prompt a controlled release only after the contact lenses have been placed onto the eyes.

3.3 Chemically Modified Soft Contact Lenses

Soft contact lenses with the ability to load drugs and control their release can also be obtained by incorporating functional groups able to interact directly with the drug molecules in the hydrogel and, therefore, able to increase the affinity of the network for the drug. Such an interaction should not be so strong as to cause irreversible binding because of ionic or hydrophobic interactions, as has been reported for epinephrine, fluorescein, and Rose Bengal.[103] The functionalization of hydrogels by addition of monomers of diverse composition is a common way of improving their performance as vision correctors, which is a good starting point for adapting this approach to optimize soft contact lenses as drug vehicles.[104,105] As it is extremely important that the shape of

Table IV. Composition and dimensions of poly(HEMA-co-MAPTAC-co-anionic monomer) lenses before and after the *in vitro* release of azulene. The anionic monomers were MAA and MOEP (data from Uchida et al.,[104] with permission from Elsevier)

MAPTAC (mmol)	MAA (mmol)	MOEP (mmol)	Drug loaded (%)[a]	Diameter (mm)	
				before release	after release
10			105	14.8	Loss of shape
10	10		0.61	14.1	14.1
	7.5		2.03	14.2	14.3
	5.0		11.7	14.5	14.7
	2.5		30.4	14.8	15.1
10		10	7.4	13.3	13.3
		7.5	32.4	13.4	13.4
		5.0	38.4	13.7	13.8
		2.5	48.9	14.1	14.2

a [Incorporated drug (mmol)/MAPTAC (mmol)] × 100.

HEMA = hydroxyethyl methacrylate; **MAA** = methacrylic acid; **MAPTAC** = methacrylamide propyltrimethylammonium chloride; **MOEP** = 2-methacryloxyethyl phosphate.

the lens is not altered by a change in pH, temperature or osmotic pressure, the proportion of functional monomers should be the result of a compromise between achievement of functionality and maintenance of the dimensions of the lens. Also, the nature of the functional monomer should be carefully evaluated to avoid an undesirable adsorption of proteins from the tear fluid.[106]

Contact lenses able to capture/release small molecules based on ion-exchange reactions have been developed by copolymerizing HEMA with ionizable monomers.[104,105] When the lens is immersed in a solution of an ionizable or protonizable drug, the drug can interact with the oppositely charged groups of the lens. Once applied on the eye, the lens releases the drug by an exchange with Cl^- or Na^+ ions of the tear fluid.

To load azulene (used for allergic conjunctivitis) or naphazoline (used to relieve congestion), hydrogels containing, respectively, methacrylamide propyltrimethylammonium chloride (MAPTAC) or 2-methacryloxyethyl phosphate (MOEP) were prepared in moulds 20mm in diameter and 0.3mm thick.[104] Poly(HEMA-co-MAPTAC) hydrogels shrank when azulene was loaded and the positive charge of the hydrogels was counterbalanced by the drug; they swelled as azulene was released in NaCl solutions as a result of repulsion of the cationic groups. An anionic comonomer (MAA or MOEP) was included in the hydrogel to reduce the changes in size. The greater the relative proportion of the anionic comonomer, the lower the change in size but also the lower the amount of drug loaded since the ionic groups in the network neutralized each other (table IV). In order to achieve a high naphazoline-loading efficiency that maintained the dimensions of the lenses, hydrogels were prepared by copolymerization of monomers with phosphate groups (MOEP) and MAm in a proportion ranging between 0.05 and 0.6 mol%.[105] The poly(HEMA-co-MOEP-co-MAm) hydrogels were able to absorb more naphazoline, with smaller changes in size than those prepared without MAm, and to maintain the release profile (figure 5). This behavior is explained by the increase in hydrophilicity of the drug-loaded hydrogel and the role of MAm in the stabilization of the drug-phosphate complexes. When the drug is being released,

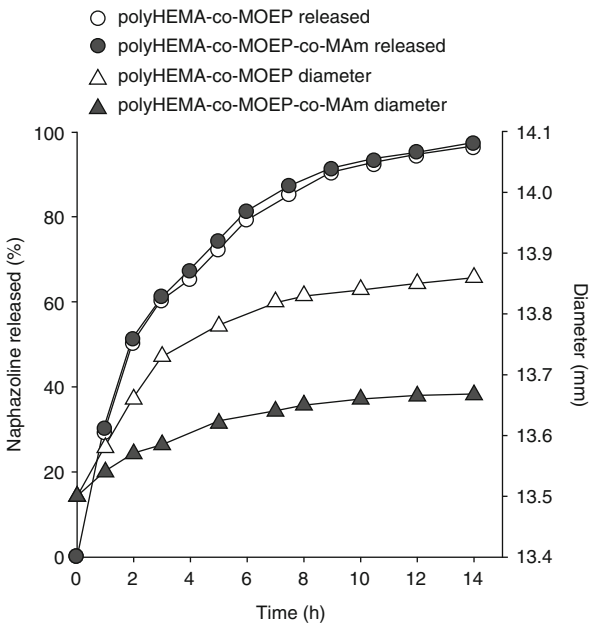

Fig. 5. Naphazoline release profiles (circles) in 0.9% NaCl aqueous solution from polyHEMA-co-MOEP or polyHEMA-co-MOEP-co-MAm lenses, and evolution of their diameter (triangles) during the test. The amount of naphazoline loaded by the polyHEMA-co-MOEP-co-MAm hydrogel was 1.5-fold greater than that by the polyHEMA-co-MOEP hydrogel. **HEMA** = hydroxyethyl methacrylate; **MOEP** = 2-methacryloxyethyl phosphate; **MAm** = methacrylamide (reproduced from Sato et al.,[105] with permission from Wiley Periodicals, Inc.).

the amide groups of MAm partially neutralize the phosphate groups of MOEP, decreasing the repulsive forces and restricting the hydrogel swelling.

3.4 Molecularly Imprinted Soft Contact Lenses

3.4.1 Building High Drug-Affinity Pockets in Polymers

The efficacy of the interactions between the drug and functional groups can be markedly improved by optimizing the spatial distribution of the groups in the polymeric network. One of the most common approaches to the synthesis of host rigid systems, such as highly cross-linked resins that can recognize target guest species, is a polymerization technique known as 'molecular imprinting', which uses the target molecules as templates.[107] This technology has been widely used to create networks with prefabricated 'active sites', i.e. molecular-scale regions with structures that are sufficiently rigid and demonstrate high affinity for target molecules.[108] To control the sequence and the spatial arrangement of the monomers, the template molecule and the functional groups are allowed to associate before polymerization through reversible covalent bonds or noncovalent interactions, such as ionic or hydrogen bonds, or through hydrophobic or charge transfer interactions.[109] These monomers are then polymerized with a cross linker. The 'imprinted pocket' formed in the polymer matrix when the drug is washed out memorizes the spatial features and bonding preferences of the template. As a consequence, when the system enters into contact again with the target molecules, they are efficiently absorbed by accommodation into the high affinity cavities.

The preorganized or covalent approach, introduced in the 1970s by Wulff,[110] consists of using templates covalently bound to the monomers prior to polymerization. These bonds are broken after the synthesis of the networks to obtain the imprinted cavities. In the self-assembly or noncovalent approach, proposed in the 1980s by Arshady and Mosbach,[111] and Sellergren,[112] the template molecules and the functional monomers arrange themselves, prior to polymerization, in the dissolution medium to form stable and soluble complexes of appropriate stoichiometry by noncovalent or metal coordination interactions. In this latter approach, multiple-point interactions between a template molecule and various functional monomers are required to form strong complexes. In general, the noncovalent imprinting protocol allows more versatile combinations of templates and monomers, and provides faster bond association and dissociation kinetics than the covalent imprinting approach.[113] In either case, preparation of conventional molecularly imprinted polymers requires the copolymerization of the functional monomer-template complexes with high proportions of cross-linking agents in a porogen solvent and the subsequent removal of the template molecules in order to create recognition cavities (i.e. specific receptors) that are complementary in shape and functionality to the template molecules.

Mere polymerization in the presence of a drug does not ensure an imprinting effect. The success of the imprinting strongly depends on the stability and solubility of the functional monomers-target assemblies during polymerization. If the molar ratio in the complex is not appropriate[114] or if the assemblies dissociate to some extent during polymerization,[115] the functional monomers will be far apart from both the template and each other, resulting in a small difference between imprinted and non-imprinted (conventional) networks. The polymerization should be carried out at the lowest temperature possible to shift the equilibrium toward the formation of target-monomers complexes.[108,115] From this point of view, polymerization by UV irradiation at room temperature would be preferable to heating whenever the template remains stable.

These highly cross-linked molecularly imprinted polymers are very useful in selectively rebinding target molecules from mixtures of chemical species and, thus, can be utilized as stationary phases for chromatographic separations of molecules, recognition entities in sensors and immunoassays, and as artificial catalysts.[116,117] In the last few years, the molecular imprinting technique has also received increasing attention in the drug delivery field.[118-125] Imprinted materials have enormous potential for providing new and optimized features to the drug dosage forms, and can be particularly useful for the development of more efficient medicated soft contact lenses.

3.4.2 Making Molecularly Imprinted Contact Lenses

In the development of contact lenses, molecular imprinting technology should be adapted to meet the following requirements:

- The drug must be stable under the conditions at which the hydrogel is synthesized and should form complexes with the functional monomers with adequate affinity.
- The functional monomers should be chosen from the limited number of monomers that interact with the drug without altering the optical properties and the biocompatibility of the lens.
- The cross-linking density should be adequate to provide hydrogels with good mechanical properties. This is a critical point since the imprinted cavities should have a structure sufficiently stable to maintain the conformation in the absence of the template and at the same time be sufficiently flexible to facilitate the attainment of a fast equilibrium between the release and reuptake of the template in the cavity. Most imprinted systems are prepared with 50–90% cross-linker agent to obtain high mechanical resistance and chemical stability.[126] By contrast, in the design of soft contact lenses, flexibility is a major

concern and, thus, the cross linker should not be above 10 mol%, at which point the stability of the imprinted cavities in the hydrogel structure may be compromised. Correct design of the hydrogel may allow an optimum balance to be reached between the mechanical properties required for ocular application and the stability of the imprinted cavities in the hydrogel structure, which helps determine both affinity and selectivity.

- The solvent should be carefully chosen since it could interfere or compete with the target molecules for interactions with the functional monomers, resulting in potentially poor affinity and selectivity for the target. Conventional molecularly imprinted polymers are synthesized using organic solvents to give a macroporous structure that allows the target molecules access to the active sites. This is also a drawback not only for the contact lens manufacturing process but also in terms of environmental and worker/patient safety issues. Thus, in the case of soft contact lenses, it would be preferable to avoid the use of solvents and take advantage of the liquid state of the major monomers.

3.4.3 Drug Loading/Release from Imprinted Lenses

Our group adapted the imprinting technique to create medicated contact lenses using three basic components: functional monomer, cross linker, and hydrophilic backbone monomer.[127-132] Each component has a different role. The functional monomer interacts with the target molecules to form active sites with ability to recognize the target molecules. The cross linker makes the hydrogel insoluble in water but is able to swell in aqueous media, and plays an important role in the stabilization of the active sites. The backbone monomer, which is the main component of the polymer network, largely determines the physical and mechanical properties of the hydrogel. Although each component plays a different role, they all contribute markedly to making the molecular imprinting effective in terms of affinity for the target drug and, as a consequence, achieving a high loading capacity and controlled-release properties.[130]

The first studies were focused on timolol. As the permeability of the conjunctiva to this β-adrenoceptor antagonist is very significant and similar to that of the cornea,[133,134] most topically applied timolol is absorbed into the blood stream and can induce severe cardiovascular and pulmonary adverse effects.[135] The use of drug-loaded contact lenses could reduce this nonproductive absorption and minimize adverse effects. Additionally, timolol structure is particularly suitable for providing imprinted systems since it offers multiple sites for interacting with functional monomers through ionic and hydrogen bonds.[127] As a first step, the effect of the proportion of MAA or MMA (0 to 5.12 mol%) and of pH (1.5–10) on timolol loading and release was evaluated for both non-imprinted (conventional) and imprinted (synthesized in the presence of 23 mmol/L of the drug) PHEMA hydrogels of 0.7mm thickness.[127] Once polymerized, the hydrogels were cleaned by immersion in boiling water for 3 minutes. Although only 30% of the timolol dose is lost during boiling, this step can be avoided if the polymerization is complete and no residual monomers are expected, as may happen when polymerization is induced by UV irradiation.[136] The imprinted hydrogels were able to sustain the release of the remaining drug for several hours, with the release rate being mainly determined by the characteristics of the release medium (0.9% NaCl solution pH 5.5, phosphate buffer pH 7.4, or artificial lacrimal fluid pH 8) and the nature of the functional comonomers (figure 6). Despite presenting a similar ionic strength, the differences in the nature of the ions and pH of the medium profoundly conditioned the uptake of water by the hydrogels and the strength of the interactions of the drug molecules with the functional groups. At pH >7, most MAA groups were ionized (cross-linked polyMAA had an apparent pKa [negative logarithm of the acid ionization constant] that increased from 6 to 9 with increasing ionization)[137] and the hydrophilicity of the hydrogels increased; at the same time, the ability to interact with the drug through hydrogen or hydrophobic bonds decreased and, therefore, the drug release rate accelerated. By contrast, the more hydrophobic hydrogels prepared with MMA always showed a slower release rate. Once the drug was released, the imprinted PHEMA hydrogels prepared with the lowest MAA proportion (100 mmol/L) were able to reload 3-fold more timolol than the non-imprinted hydrogels from a pH 5.5 drug solution, showing a release rate similar to that on polymerization. This opens the possibility of preparing reloadable contact lenses.

It should be noted that the hydrogels described previously were polymerized in the absence of a solvent (i.e. in an anhydrous state) and with a very low cross-linking proportion (0.128 mol%). Once the lenses swell in aqueous medium and the template is removed, a significant deformation of the imprinted cavities may be expected. Therefore, when the swollen hydrogels are immersed in timolol solutions, only the high-affinity cavities can recover the same conformation present on polymerization (‘induced fit’), and are thus able to load the drug and, subsequently, to sustain drug release. This behavior was experimentally evidenced with imprinted lenses based on HEMA or N,N-diethyl acrylamide (DEAA), and synthesized with different proportions of MAA (1.28–5.12 mol%) and cross-linker EGDMA (0.32–8.34 mol%). A minimum of 0.9 mol% EGDMA was required to achieve markedly greater loading and sustained release than those achieved by conventional lenses. These lenses could load a therapeutic dose of timolol, sustain its release in lacrimal fluid for more than 12 hours and

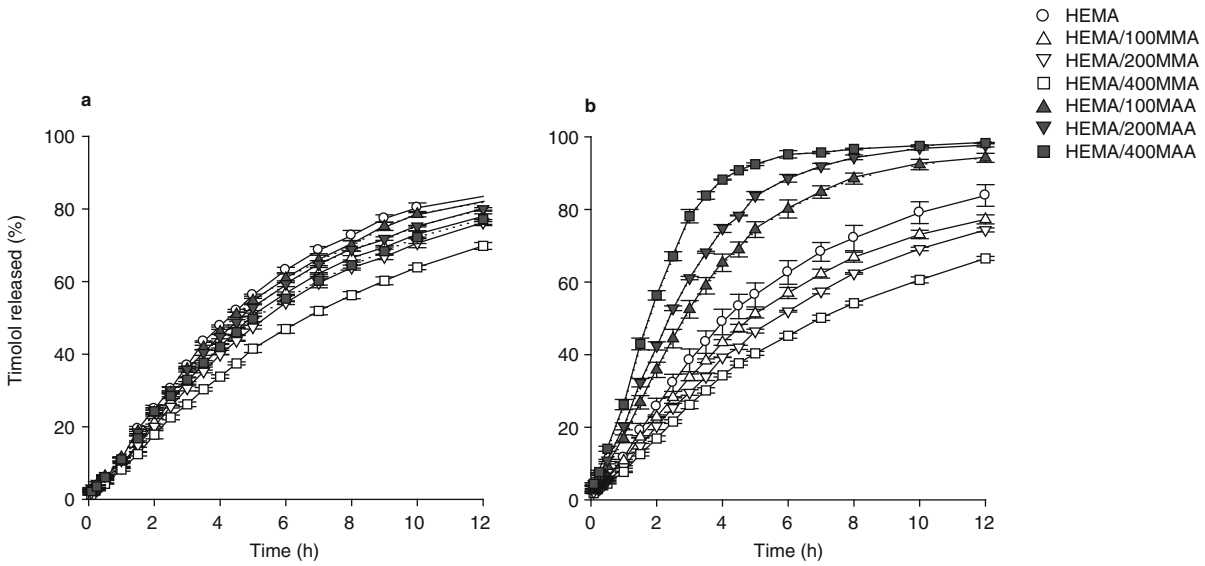

Fig. 6. Timolol release in (**a**) 0.9% NaCl solution (pH 5.5) and (**b**) artificial lacrimal fluid (pH 8) from imprinted hydrogels obtained by copolymerization of 2-hydroxyethyl methacrylate (HEMA) with methyl methacrylate (MMA) or methacrylic acid (MAA) in the presence of timolol maleate. Concentration of MMA or MAA 100, 200, and 400 mmol/L were used to prepare the lenses; values are shown as means ± SD (n = 6) [reproduced from Alvarez-Lorenzo et al.,[127] with permission from Wiley-Liss, Inc. and the American Pharmacists Association].

reload another dose overnight, being ready for use the next day.[127,128]

In order to generalize the applicability of the molecular imprinting technology to the manufacture of therapeutic contact lenses, the influence of the backbone monomers was analyzed keeping the proportions of the functional monomer (MAA; 100 mmol/L) and cross-linker (EGDMA; 140 mmol/L) constant (figure 7).[130] Table V shows the composition of 0.3mm thickness lenses prepared by UV irradiation. The imprinted lenses were synthesized in the presence of timolol maleate (25 mmol/L). The affinity of the lenses for the drug was evaluated by immersion in solutions of different timolol concentrations and fitting the sorption isotherms to the Langmuir model (equation 4):

$$A = SK\frac{C_{eq}}{1 + KC_{eq}} \qquad \text{(Eq. 4)}$$

where A is the amount of timolol absorbed per unit of volume of lens, C_{eq} is the residual timolol concentration in the solution at equilibrium, S is the maximum sorption capacity, K is the affinity of one sorption site, and SK is the overall affinity.

The rank order for timolol overall affinity of the lenses (SK) was: HEMA > 1-(tristrimethylsiloxysilylpropyl)-methacrylate (SiMA)-DMAA > MMA-DMAA > DEAA.[130] These results may be explained as follows: HEMA monomers have an important hydrogen bonding capability (greater than that of the other backbone monomers) to interact with timolol. Although HEMA lenses (without MAA) do not significantly load the drug, the presence of HEMA around the MAA mers may contribute, chiefly in the imprinted systems, to creating an adequate microenvironment for enhancing interactions with timolol. This explains the greater affinity of both non-imprinted and, especially, imprinted HEMA-based lenses for timolol compared with the others. On the other hand, the slightly greater cross-linker molar ratio in SiMA-DMAA lenses (table V) provides greater stability for the conformation of the imprinted sites. MMA-DMAA hydrogels show the highest swelling capacity, which causes the network to have large pores, making timolol diffusion easier, but also disrupts the conformation of the network on synthesis. In the hydrated non-imprinted lenses, MAA groups are too far apart to form binding sites for timolol. Nevertheless, the imprinting procedure provides cavities made of MAA groups spaced close together and considerably increases the loading capacity. Finally, DEAA-based lenses are relatively hydrophobic at 37ºC and have, in general, a slight affinity for timolol. For these lenses, the imprinting effect on the drug-loading capacity becomes particularly relevant. In short, the highest imprinting effect (i.e. the greatest relative increase in SK with regard to non-imprinted systems) was obtained for the MMA-DMAA and DEAA lenses.

All lenses studied showed sustained release in NaCl 0.9% solution for 2–8 hours.[130] Drug diffusion coefficients through the imprinted lenses were 2.2×10^{-9} cm^2/s for DEAA-based lenses, 9.9×10^{-9} cm^2/s for HEMA-based lenses, 66.5×10^{-9} cm^2/s for MMA-DMAA-based lenses, and 71.3×10^{-9} cm^2/s for SiMA-DMAA-based lenses. These values confirmed that timolol mole-

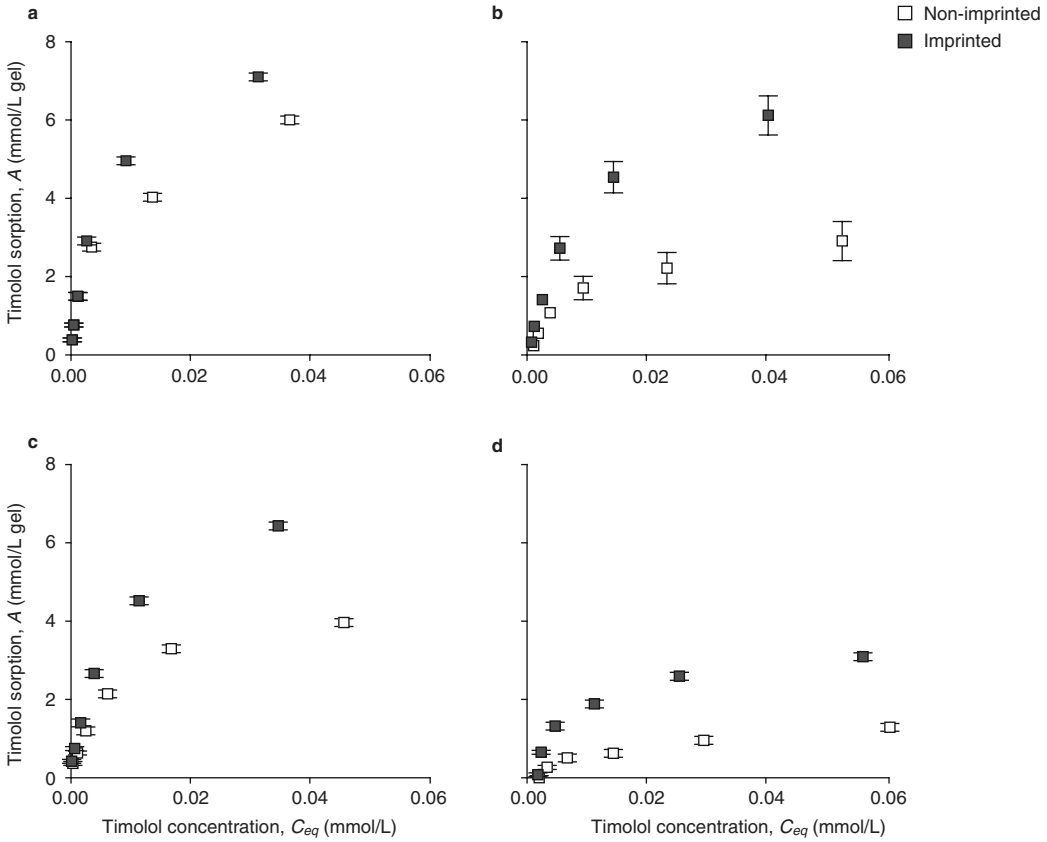

Fig. 7. Timolol sorption isotherms of imprinted and non-imprinted lenses made by photopolymerization of methacrylic acid (MAA, 100 mmol/L) and cross-linker ethyleneglycol dimethacrylate (EGDMA, 140 mmol/L) with (**a**) 2-hydroxyethyl methacrylate (HEMA), (**b**) methyl methacrylate (MMA) and N,N-dimethyl acrylamide (DMAA), (**c**) 1-(tristrimethylsiloxysilylpropyl)-methacrylate (SiMA) and DMAA, or (**d**) N,N-diethyl acrylamide (DEAA) as backbone monomers. Values are shown as means ± SD (n = 6). **A** = amount of timolol absorbed per unit of volume of lens; C_{eq} = residual timolol concentration in solution at equilibrium (reproduced from Hiratani and Alvarez-Lorenzo,[130] with permission from Elsevier).

cules move out more easily from hydrophilic networks with a lower affinity for the drug (i.e. MMA-DMAA and SiMA-DMAA).

The control-release ability of the imprinted ultrathin lenses (14mm diameter and 0.08mm center thickness) has been proved in rabbits by monitoring timolol levels in lacrimal fluid after insertion of imprinted lenses (with a drug load of 34μg) and non-imprinted lenses (20μg drug) or instillation of timolol eyedrop solutions of 0.068% (total dose 34μg) or 0.25% (total dose 125μg) [figure 8].[131] The imprinted lenses were able to maintain the timolol release for 180 minutes, compared with 90 minutes for the non-imprinted lenses. Both displayed the maximum ocular level at around 5 minutes, followed by a monoexponential decay. Irrespective of the initial concentration, timolol applied as drops was flushed out of the eye in <60 minutes. Timolol ocular bioavailability in tear film, as defined by the area under the concentration-time curve (AUC) values, was significantly greater for the imprint-

Table V. Proportions of backbone monomers, functional monomer MAA, and cross-linker EGDMA used to prepare timolol-imprinted lenses (0.3mm thickness) [data from Hiratani and Alvarez-Lorenzo,[130] with permission from Elsevier]

Lens	Monomers (mol%)						
	DEAA	HEMA	MMA	SiMA	DMAA	MAA	EGDMA
A	96.84					1.29	1.87
B		97.10				1.18	1.72
C			47.94		49.55	1.02	1.49
D				17.87	78.17	1.62	2.35

DEAA = N,N-diethyl acrylamide; **DMAA** = N,N-dimethyl acrylamide; **EGDMA** = ethyleneglycol dimethacrylate; **HEMA** = hydroxyethyl methacrylate; **MAA** = methacrylic acid; **MMA** = methylmethacrylate; **SiMA** = 1-(tristrimethylsiloxysilylpropyl)-methacrylate.

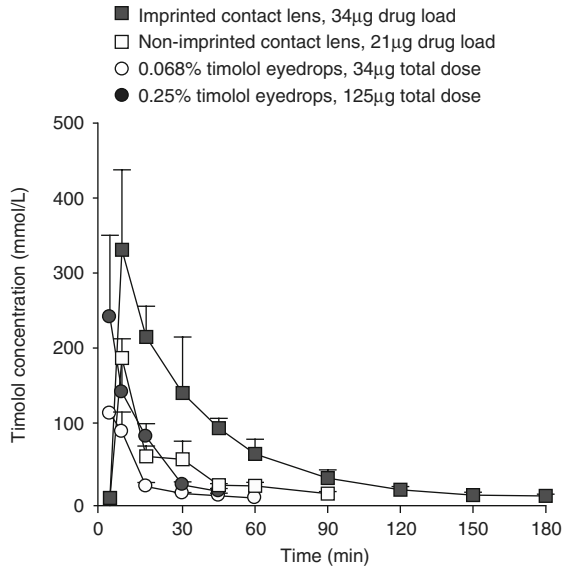

Fig. 8. Timolol tear fluid concentration-time profiles after application of presoaked imprinted and non-imprinted contact lenses and instillation of eyedrops on rabbit eyes. The doses were 34μg for imprinted contact lens, 21μg for non-imprinted contact lens, 34μg for 0.068% timolol eyedrops, and 125μg for 0.25% timolol eyedrops. Each point represents the mean ± SD (n = 3–5) [reproduced from Hiratani et al.,[131] with permission from Elsevier].

ed contact lenses than for the non-imprinted contact lenses, whereas no statistical difference in AUC values was found between non-imprinted contact lenses and commercial eyedrops.

3.4.4 Optimization of Drug-Imprinted Lenses

With the aim of optimizing the affinity of the cavities, the influence of the template **:** functional monomer molar ratio was analyzed in detail. Timolol release rate from lenses prepared with DMAA and SiMA (50:50 v/v) strongly decreased in association with increasing the MAA **:** timolol ratio in the gel recipe from 4 **:** 1 to 16 **:** 1.[132] Lenses (0.3mm thickness) prepared with MAA 400 mmol/L, EGDMA 600 mmol/L and a timolol **:** MAA mole ratio of 1 **:** 16 showed drug diffusion coefficients two orders of magnitude lower than those obtained with non-imprinted hydrogels. This considerable influence of the timolol **:** MAA ratio is related to differences in conformation of the imprinted cavities.[114,115] If a large amount of timolol is present during polymerization, binding sites can be created but these cavities may not have all the MAA units needed to fulfill the interaction capacity of the drug. Therefore, the binding sites show a weaker affinity for timolol, which can accordingly be easily released. In contrast, with a smaller amount of drug in the medium, more MAA units are available to gather during synthesis to form efficient imprinted cavities, which will have greater multiple-point binding constants; that is to say, each binding site is more perfectly constructed and can more effectively retain the drug, hindering the release process (figure 9).

To avoid time- and material-consuming trial and error assays, the optimum template **:** functional monomer ratio can be predicted

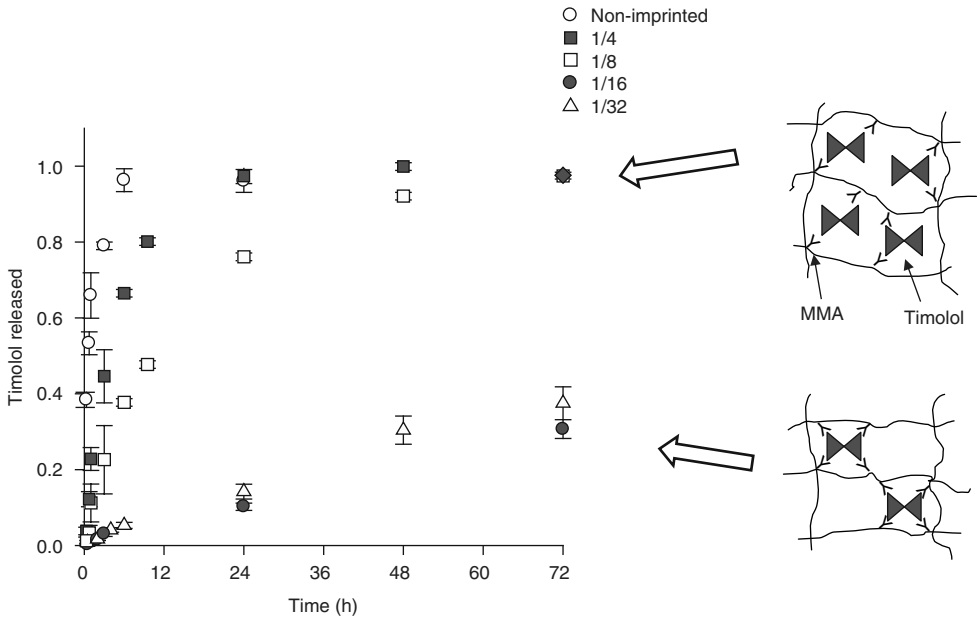

Fig. 9. Timolol (dose fraction) release profiles in 0.9% NaCl from non-imprinted and imprinted lenses prepared with methacrylic acid (MAA, 400 mmol/L), ethyleneglycol dimethacrylate (EGDMA, 600 mmol/L), N,N-dimethyl acrylamide (DEAA), and 1-(tristrimethylsiloxysilylpropyl)-methacrylate (SiMA). The template **:** functional monomer mole ratio (1 **:** 4, 1 **:** 8, etc.) determines the timolol affinity of imprinted hydrogels. With a small proportion of timolol in the polymerization medium, cavities with the maximum multiple-point binding ability are created and hydrogels able to control timolol release are obtained. Values are shown as means ± SD (n = 6) [reproduced from Hiratani et al.,[132] with permission from VCH Verlag GmbH & Co.].

before polymerization by using analytical techniques such as nuclear magnetic resonance, UV spectrophotometry or isothermal titration calorimetry.[138-141] The latter technique has recently been shown to provide accurate information for creating imprinted lenses able to load and control the release of antibacterials such as norfloxacin.[142] Optimization of the imprinted lenses led to a decrease in the drug release rate constant of up to 3.5-fold.

On the whole, investigations conducted to date show that incorporation of adequate functional monomers and application of molecular imprinting technology provide interesting possibilities for the development of soft contact lenses as more efficient drug delivery systems. Additional studies with drugs belonging to various therapeutic groups and different chemical structures are being carried out in our laboratory to extend the scope of the imprinted hydrogels. When a drug cannot be used as a template because it cannot withstand the polymerization conditions or because of the high costs of drug wastage during cleaning of the lenses or their loading, the modality of 'imprinting without a template' may offer interesting possibilities. This basically consists of using pairs of functional monomers directly bonded to each other prior to polymerization.[143,144] An 'imprinter' monomer of this type is, for example, a molecule that has three functional parts, two or more polymerizable double bonds, two or more functional groups, and a link connecting the functional groups that is easily cleaved after polymerization, such as a disulfide bond or a 1,2-glycol structure. This leads to obtaining pairs of functional groups that are closely spaced and simulate the imprinted pockets and, therefore, can efficiently capture target molecules through multiple-point interactions.

3.5 Other Approaches

Among other less developed approaches of enhancing the loading or release control properties of lenses, sandwich-type contact lenses and continuous flow contact lenses have received some attention. The sandwich-type systems consist of placing a drug film between two soft contact lenses, one of which is hydrophilic (in contact with the eye) and the other hydrophobic.[145] Another possibility consists of making a cavity on the inner side of a polymer layer, after which two polymer layers are bonded to each other by melt pressing and then polymerized together to obtain a device similar to a lens. The empty space inside the lens can be filled with a drug solution and act as a reservoir.[146] The continuous flow contact lenses can serve, mostly with experimental aims, as a perfusion system to deliver drugs onto the cornea at a prefixed rate. This device has been reported to achieve higher corneal concentrations of gentamicin than conventional eyedrops.[147]

3.6 Critical Overview

A comparative evaluation of the different approaches for obtaining sustained-release lenses is not easy as none have been assayed in humans as yet and studies using animal models are limited. Additionally, different methodologies have been used in the conduct of *in vitro* release experiments. This is an important issue because, in addition to the structural characteristics of the lenses (cross-linking degree, thickness, water affinity, etc.), the composition of the release medium and conditions of the assays (temperature, volume of the medium, ionic concentration, stirring, etc.) strongly influence the detachment of the drug. Nevertheless, some general assessments can be carried out on the basis of the information presented previously. Table VI summarizes the advantages and limitations of the main approaches to development of sustained-release contact lenses, with emphasis on the technological aspects of each that still need to be investigated and improved. With respect to their potential for clinical use, soft contact lenses with drugs immobilized via labile bonds may be adequate for the treatment of chronic diseases in the extended-wear user, although

Table VI. Advantages and limitations of the main approaches to the development of sustained-release contact lenses

Drug immobilized via labile bond	Dispersed colloidal systems	Chemically modified lenses	Molecularly imprinted lenses
Advantages			
Zero-order release kinetics	Release kinetics modifiable through use of different colloidal carriers	Easy synthesis in the absence of the drug	Well known components
			High drug-loading/reloading ability
		Versatility	
Limitations			
Chemical modification of the drug	Design of carriers must be adapted to each specific drug	Changes in swelling degree during use	Specific design required for each drug
Possible high inter- and intraindividual variability	Risk of destabilization during polymerization	Risk of sorption of proteins	Risk of drug degradation during polymerization
	Limited transparency		

this would seem to be an expensive approach given the need for exhaustive control of drug chemical modification and leaching of residual drug monomers. At present, this approach attracts little interest. The soft contact lenses with dispersed colloidal systems can be particularly useful for relatively hydrophobic drugs, once the problems inherent in industrial scale production are resolved. Chemically modified soft contact lenses are easily adaptable for a wide range of drugs and clinical necessities, although their loading/controlled-release performance is limited. Finally, the molecularly imprinted soft contact lenses, which are the only ones that can be easily reloadable by the patient, are potentially useful for both chronic and acute diseases and could easily be commercialized as they are formed from approved, albeit rearranged, components.

4. Conclusion

The simplicity of use, relative comfort, ease, and low cost of manufacturing make soft contact lenses an attractive as platform for ocular drug delivery systems that can overcome the inherent deficiencies of classical formulations. This approach could be made feasible with the use of preloaded disposable extended-wear lenses or by loading/recharging reusable lenses by immersing them in sterile drug solutions immediately prior to application. Although more research, especially *in vivo* assays, is required to bring medicated contact lens onto the market, recent improvements in the loading and control-release abilities of soft contact lenses indicate that, in the foreseeable future, they will become particularly useful for prolonging the permanence of a drug in the precorneal tear film, reducing systemic absorption through a more efficient corneal penetration and reduction of the administered drug dose, and improving patient compliance. The possibility of both correcting vision and acting as a drug delivery system could remarkably enhance the benefits of soft contact lenses.

Acknowledgments

This work was supported by Ministerio de Educación y Ciencia and FEDER (SAF2005-01930; RYC2001-8), Xunta de Galicia Spain (PGIDT01PX1203014IF; PGIDIT03PXIC20303PN), and Menicon Corporation Ltd, Japan.

Dr Haruyuki Hiratani is an employee of Menicon Corporation Ltd. The other authors have no conflicts of interest relevant to the contents of this review.

References

1. Reddy IK, Ganesan MG. Ocular therapeutics and drug delivery: an overview. In: Reddy IK, editor. Ocular therapeutics and drug delivery. Lancaster (PA): Technomic Publishing Co., 1999: 3-29
2. Myles ME, Neumann DM, Hill JM. Recent progress in ocular drug delivery for posterior segment disease: emphasis on transscleral iontophoresis. Adv Drug Deliv Rev 2005; 57: 2063-79
3. Plazonnet B. Ophthalmic drug delivery. In: Rathbone MJ, Hadgraft J, Roberts MS, editors. Modified-release drug delivery technology. New York: Marcel Dekker Inc., 2003: 289-313
4. Sander B, van Best J, Johansen S, et al. Fluorescein transport through the blood-aqueous and blood-retinal barriers in diabetic macular edema. Curr Eye Res 2003; 27: 247-52
5. Mainardes RM, Urban MCC, Cinto PO, et al. Colloidal carriers for ophthalmic drug delivery. Curr Drug Targets 2005; 6: 363-71
6. Bejjani R, Benezra D, Cohen H, et al. Nanoparticles for gene delivery to retinal pigment epithelial cells. Mol Vis 2005; 11: 124-32
7. Davies NM. Biopharmaceutical considerations in topical ocular drug delivery. Clin Exp Pharmacol Physiol 2000; 27: 558-62
8. Hughes PM, Olejnik O, Chang-Lin JE, et al. Topical and systemic drug delivery to the posterior segments. Adv Drug Deliv Rev 2005; 57: 2010-32
9. Zhu H, Chauhan A. A mathematical model for ocular tear and solute balance. Curr Eye Res 2005; 30: 841-54
10. Tomlinson A, Khanal S. Assessment of tear film dynamics: quantification approach. Ocul Surf 2005; 3: 81-95
11. Robinson JR. Ocular drug delivery mechanism of corneal drug transport and mucoadhesive delivery systems. STP Pharma Sci 1989; 5: 839-46
12. Singh CP, Shah DO. Surface chemical aspects of ocular drug delivery systems. In: Reddy IK, editor. Ocular therapeutics and drug delivery. Lancaster (PA): Technomic Publishing Co., 1999: 31-49
13. Keister JC, Cooper ER, Missel PJ, et al. Limits on optimizing ocular drug delivery. J Pharm Sci 1991; 80: 50-3
14. Wilson CG. Topical drug delivery in the eye. Exp Eye Res 2004; 78: 737-43
15. Ding SL. Recent developments in ophthalmic drug delivery. Pharm Sci Technol Today 1998; 1: 328-35
16. Kaur IP, Kanwar M. Ocular preparations: the formulation approach. Drug Dev Ind Pharm 2002; 28: 473-93
17. Felt O, Einmahl S, Gurny R, et al. Polymeric systems for ophthalmic drug delivery. In: Dumitriu S, editor. Polymeric biomaterials. New York: Marcel Dekker Inc., 2002: 377-421
18. Davis JL, Gilger BC, Robinson MR. Novel approaches to ocular drug delivery. Curr Opin Mol Ther 2004; 6: 195-205
19. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. Adv Drug Deliv Rev 2005; 57: 1595-639
20. Aqil M. Advances in ophthalmic drug delivery systems. Phamainfo.net [online]. Available from URL: http://www.pharmainfo.net/exclusive/reviews/advances_in_ophthalmic_drug_delivery_systems_-_part_ii./ [Accessed 2006 Jul 24]
21. Pandit JC, Nagyova B, Bron AJ, et al. Physical properties of stimulated and unstimulated tears. Exp Eye Res 1999; 68: 247-53
22. Sintzel MB, Bernatchez SF, Tabatabay C, et al. Biomaterials in ophthalmic drug delivery. Eur J Pharm Biopharm 1996; 42: 358-74
23. Vadnere M, Amidon G, Lindenbaum S, et al. Thermodynamic studies on the gel sol transition of some pluronic polyols. Int J Pharm 1984; 22: 207-18
24. Sultana Y, Jha MC, Ali A, et al. A three-way comparative study on the efficacy of twin sol to gel systems and marketed eye drops of pefloxacin mesylate. J Ocul Pharmacol Ther 2004; 20: 363-71
25. Zignani M, Tabatabay C, Gurny R. Topical semisolid drug-delivery: kinetics and tolerance of ophthalmic hydrogels. Adv Drug Deliv Rev 1995; 16: 51-60
26. Schenker HI, Silver LH. Long-term intraocular pressure-lowering efficacy and safety of timolol maleate gel-forming solution 0.5% compared with Timoptic XE 0.5% in a 12-month study. Am J Ophthalmol 2000; 130: 145-50
27. Srividya B, Cardoza RM, Amin PD. Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system. J Control Release 2001; 73: 205-11
28. Herrero-Vanrell R, Fernandez-Carballido A, Frutos G, et al. Enhancement of the mydriatic response to tropicamide by bioadhesive polymers. J Ocul Pharmacol Ther 2000; 16: 419-28
29. Zimmer A, Kreuter J. Microspheres and nanoparticles used in ocular delivery systems. Adv Drug Deliv Rev 1995; 16: 61-73
30. Calvo P, Vila-Jato JL, Alonso MJ. Comparative in vitro evaluation of several colloidal systems, nanoparticles, nanocapsules, and nanoemulsions as ocular drug carriers. J Pharm Sci 1996; 85: 530-6

31. Gavini E, Chetoni P, Cossu M, et al. PLGA microspheres for the ocular delivery of a peptide drug, vancomycin using emulsification/spray-drying as the preparation method: in vitro/in vivo studies. Eur J Pharm Biopharm 2004; 57: 207-12
32. Ebrahim S, Peyman GA, Lee PJ. Applications of liposomes in ophthalmology. Surv Ophthalmol 2005; 50: 167-82
33. Alonso MJ. Nanomedicines for overcoming biological barriers. Biomed Pharmacother 2004; 58: 168-72
34. Aggarwal D, Kaur IP. Improved pharmacodynamics of timolol maleate from a mucoadhesive niosomal ophthalmic drug delivery system. Int J Pharm 2005; 290: 155-9
35. Willoughby CE, Batterbury M, Kaye SB. Collagen corneal shields. Surv Ophthalmol 2002; 47: 174-82
36. Weyenberg W, Vermeire A, Dhondt MMM, et al. Ocular bioerodible minitablets as strategy for the management of microbial keratitis. Invest Ophthalmol Vis Sci 2004; 45: 3229-33
37. Schwarz S, Nick J. Effectiveness of lubricating daily disposable lenses with different additives. Optician 2006; 231: 22-6
38. Peterson RC, Wolffsohn JS, Nick J, et al. Clinical performance of daily disposable soft contact lenses using sustained release technology. Cont Lens Anterior Eye 2006 Jul; 29 (3): 127-34
39. Munoa-Roiz JL, Aramendia-Salvador E. Historia y desarrollo de las lentes de contacto [online]. Available from URL: http://www.oftalmo.com/publicaciones/lentes/cap2.htm [Accessed 2006 Jul 24]
40. Witcherle O, Lim D. Hydrophilic gels for biological use. Nature 1960; 185: 117-8
41. McMahon TT, Zadnik K. Twenty-five years of contact lenses. Cornea 2000; 19: 730-40
42. Yamauchi A. Soft contact lenses. In: Osada Y, Kajiwara K, editors. Gels handbook. Vol. 3. San Diego (CA): Academic Press, 2001: 166-79
43. Nicolson PC, Vogt J. Soft contact lens polymers: an evolution. Biomaterials 2001; 22: 3273-83
44. US FDA. Premarket notification (510(k)) guidance document for daily wear contact lenses [online]. Available from URL: http://www.fda.gov/cdrh/ode/conta.html [Accessed 2006 Jul 24]
45. Shah C, Raj S, Foulks GN. The evolution in therapeutic contact lenses. Ophthalmol Clin North Am 2003; 16: 95-101
46. Karlgard CCS, Wong NS, Jones LW, et al. In vitro uptake and release studies of ocular pharmaceutical agents by silicon-containing and p-HEMA hydrogel contact lens materials. Int J Pharm 2003; 257: 141-51
47. Tighe B. Silicone hydrogel materials: how do they work? In: Sweeney DF, editor. Silicone hydrogels. Oxford: Butterworth Heinemann, 2000: 1-27
48. Donshik PC. Extended wear contact lenses. Ophthalmol Clin North Am 2003; 16: 79-83
49. Hiratani H, Nakajima T, Yamamoto K. The state and prospect of contact lenses. Jpn Soc Biomater 2002; 20: 221-7
50. Vision Council of America [online]. Available from URL: http://www.visionsite.org/s_vision/ [Accessed 2006 Jul 24]
51. Steele CF. Fitting and management of therapeutic contact lenses. Hospital Optometrists Information series, 2000 Nov [online]. Available from URL: http://www.assoc-optometrists.org/uploaded_files/pdf/fm-tcl-info1.pdf [Accessed 2006 Jul 24]
52. Lim L, Tan DTH, Chan WK. Therapeutic use of Bausch & Lomb pure vision contact lenses. CLAO J 2001; 27: 179-85
53. Kanpolat A, Ucakhan O. Therapeutic use of Focus Night and Day contact lenses. Cornea 2003; 22: 726-34
54. Mely R. Therapeutic and cosmetic indications of Lotrafilcon: a silicone hydrogel extended-wear lenses. Ophthalmologica 2004; 218: 33-8
55. Silbert JA. Therapeutic uses of silicone hydrogels [online]. Available from URL: http://www.siliconehydrogels.org/editorials/oct_05.asp [Accessed 2006 Jul 24]
56. Krejci L, Brettschneider I, Praus R. Hydrophilic gel contact lenses as a new drug delivery system in ophthalmology and as a therapeutic bandage lenses. Act Univ Carol Med 1975; 21: 387-96
57. Silbert JA. A review of therapeutic agents and contact lens wear. J Am Optom Assoc 1996; 67: 165-72
58. Zegans ME, Becker HI, Budzik J, et al. The role of bacterial biofilms in ocular infections. DNA Cell Biol 2002; 21: 415-20
59. Wong T, Ormonde S, Gamble G, et al. Severe infective keratitis leading to hospital admission in New Zealand. Br J Ophthalmol 2003; 87: 1103-8
60. Galezowski X. Sur la place cornéenne dans l'extraction de la cataracte et sur les moyens de prévenir la suppuration. Bull Mem Soc Fr Ophthalmol 1886; 4: 217-26
61. Sedlacek J. Possibilities of application of eye drugs with the aid of gel-contact lenses. Cesk Oftalmol 1965; 21: 509-12
62. Gasset A, Kaufman HE. Therapeutic uses of hydrophilic contact lenses. Am J Ophthalmol 1970; 69: 252-9
63. Waltman SR, Kaufman HE. Use of hydrophilic contact lenses to increase ocular penetration of topical drugs. Invest Ophthalmol 1970; 9: 250-5
64. Hillman JS. Management of acute glaucoma with pilocarpine-soaked hydrophilic lens. Br J Ophthalmol 1974, 679
65. Ruben M, Watkins R. Pilocarpine dispensation for soft hydrophilic contact-lens. Br J Ophthalmol 1975; 59: 455-8
66. Marmion VJ, Jain MR. Role of soft contact-lenses and delivery of drugs. Trans Ophthalmol Soc U K 1976; 96: 319-21
67. Rubinstein MP, Evans JE. Therapeutic contact lenses and eyedrops: is there a problem? Cont Lens Anterior Eye 1997; 20: 9-11
68. Hull DS, Edelhauser HF, Hyndiuk RA. Ocular penetration of prednisolone and hydrophilic contact-lens. Arch Ophthalmol 1974; 92: 413-6
69. Matoba AY, McCulley JP. The effect of therapeutic soft contact-lenses on antibiotic delivery to the cornea. Ophthalmology 1985; 92: 97-9
70. Jain MR. Drug delivery through soft contact-lenses. Br J Ophthalmol 1988; 72: 150-4
71. Li CC, Chauhan A. Modeling ophthalmic drug delivery by soaked contact lenses. Ind Eng Chem Res 2006; 45: 3718-34
72. Vandorselaer T, Youssfi H, Caspers-Valu LE, et al. Treatment of traumatic corneal abrasion with contact lens associated with topical nonsteroid anti-inflammatory drug (NSAID) and antibiotic: a safe, effective, and comfortable solution. J Fr Ophtalmol 2001; 24: 1025-33
73. Refojo MF, Leong FL, Chan IM, et al. Absorption and release of antibiotics by a hydrophilic implant for scleral buckling. Retina 1983; 3: 45-9
74. Podos SM, Becker B, Asseff CF, et al. Pilocarpine therapy with soft contact lenses. Am J Ophthalmol 1972; 73: 336-41
75. Lesher GA, Gunderson GG. Continuous drug-delivery through the use of disposable contact-lenses. Optom Vis Sci 1993; 70: 1012-8
76. Kaufman HE, Uotila MH, Gasset AR, et al. The medical uses of soft contact lenses. Trans Am Acad Ophthalmol Otolaryngol 1971; 75: 361-73
77. Salz JJ, Reader AL, Schwartz LJ, et al. Treatment of corneal abrasions with soft contact-lenses and topical diclofenac. J Refract Corneal Surg 1994; 10: 640-6
78. Pinilla-Lozano I, Polo-Llorens V, Larrosa-Poves JM, et al. Medium-water-content contact lenses ciprofloxacin saturation: differences between exposure times [in Spanish]. Rev Esp Contact 1998 [online]. Available from URL: http://www.oftalmo.com/sec/98-tomo-2/02.htm [Accessed 2006 Jul 24]
79. Pinilla-Lozano I, Larrosa-Poves JM, Perez-Olivan S, et al. Quinolones intraocular penetration depending on therapeutic contact lens wear [in Spanish]. Rev Esp Contact 1998 [online]. Available from URL: http://www.oftalmo.com/sec/98-tomo-2/03.htm [Accessed 2006 Jul 24]
80. Tian X, Iwatsu M, Kanai A. Disposable 1-day Acuvue® contact lenses for the delivery of lomefloxacin to rabbits' eyes. CLAO J 2001; 27: 209-15
81. Tian X, Iwatsu M, Sado K, et al. Studies on the uptake and release of fluoroquinolones by disposable contact lenses. CLAO J 2001; 27: 216-20
82. Hehl EM, Beck R, Luthard K, et al. Improved penetration of aminoglycosides and fluoroquinolones into the aqueous humour of patients by means of Acuvue contact lenses. Eur J Clin Pharmacol 1999; 55: 317-23
83. Momose T, Ito N, Kanai A, et al. Adsorption of levocabastine eye drops by soft contact lenses and its effects in rabbit eyes. CLAO J 1997; 23: 96-9
84. Heyrman TP, McDermott ML, Ubels JL, et al. Drug uptake and release by a hydrogel intraocular-lens and the human crystalline lens. J Cataract Refract Surg 1989; 15: 169-75
85. Chapman JM, Cheeks L, Green K. Drug-interaction with intraocular lenses of different materials. J Cataract Refract Surg 1992; 18: 456-9
86. Weiner AL. Polymeric site-specific pharmacotherapy. In: Domb AJ, editor. Polymeric drug delivery systems for the eye. Chichester: Wiley, 1994: 315-46
87. Krejci L. Therapeutic use of scleral gel contact lenses. Cesk Oftalmol 1971; 27: 104-9

88. Krejci L, Brettschneider I, Praus R. Comparative study of fluorescein release from various types of therapeutic hydrophilic gel contact lenses. Cesk Oftalmol 1971; 27: 285-91
89. Praus R, Brettschneider I, Havranek M, et al. Penetration of radioactive sulphate and glucose from hydrophilic gel contact lenses into the eye of rabbit. Ophthal Res 1974; 6: 291-300
90. Ren DH, Yamamoto K, Ladage PM, et al. Adaptive effects of 30-night wear of hyper-O_2 transmissible contact lenses on bacterial binding and corneal epithelium: a 1-year clinical trial. Ophthalmology 2002; 109: 27-39
91. Ladage PM, Ren DH, Petroll WM, et al. Effects of eyelid closure and disposable and silicone hydrogel extended contact lens wear on rabbit corneal epithelial proliferation. Invest Ophthalmol Vis Sci 2003; 44: 1843-9
92. Holden BA, Mertz GW. Critical oxygen level to avoid corneal edema for daily and extended wear contact lenses. Invest Ophthamol Vis Sci 1984; 25: 1161-7
93. Wajs G, Meslard JC. Release of therapeutic agents from contact lenses. Crit Rev Ther Drug 1986; 2: 275-89
94. Kim SW, Bae YH, Okano T. Hydrogels: swelling, drug loading, and release. Pharm Res 1992; 9: 283-90
95. Kunzler JF, McGee JA. Contact-lens materials. Chem Ind 1995; 16: 651-5
96. Lloyd AW, Faragher RGA, Denyer SP. Ocular biomaterials and implants. Biomaterials 2001; 22: 769-85
97. Langer R. Polymeric delivery systems for controlled drug release. Chem Eng Commun 1980; 6: 1-48
98. Vairon JP, Yean L, Meslard JC, et al. Immobilisation reversible sur polymers et liberation controlee: application aux lentilles corneennes reservoirs de medicaments. Actual Chim 1992; Sep-Oct: 330-5
99. Gulsen D, Chauhan A. Ophthalmic drug delivery through contact lenses. Invest Ophthalmol Vis Sci 2004; 45: 2342-7
100. Gulsen D, Chauhan A. Dispersion of microemulsion drops in HEMA hydrogel: a potential ophthalmic drug delivery vehicle. Int J Pharm 2005; 292: 95-117
101. Gulsen D, Li CC, Chauhan A. Dispersion of DMPC liposomes in contact lenses for ophthalmic drug delivery. Curr Eye Res 2005; 30: 1071-80
102. Gulsen D, Chauhan A. Effect of water content on transparency, swelling, lidocaine diffusion in p-HEMA gels. J Memb Sci 2006; 269: 35-48
103. Miranda MN, Garcia-Castineiras S. Effects of pH and some common topical ophthalmic medications on the contact lens Permalens. CLAO J 1983; 9: 43-8
104. Uchida R, Sato T, Tanigawa H, et al. Azulene incorporation and release by hydrogel containing methacrylamide propyltrimethylammonium chloride, and its application to soft contact lens. J Control Release 2003; 92: 259-64
105. Sato T, Uchida R, Tanigawa H, et al. Application of polymer gels containing side-chain phosphate groups to drug-delivery contact lenses. J Appl Polym Sci 2005; 98: 731-5
106. Lord MS, Stenzel MH, Simmons A, et al. Lysozyme interaction with poly(HEMA)-based hydrogel. Biomaterials 2006; 27: 1341-5
107. Maeda M, Bartsch RA. Molecular and ionic recognition with imprinted polymers: a brief overview. In: Bartsch RA, Maeda M, editors. Molecular and ionic recognition with imprinted polymers, ACS Symposium Series 703. Washington, DC: American Chemical Society, 1998: 1-8
108. Ramström O, Ansell RJ. Molecular imprinting technology: challenges and prospects for the future. Chirality 1998; 10: 195-209
109. Wulff G, Biffis A. Molecularly imprinting with covalent or stoichiometric non-covalent interactions. In: Sellergren B, editor. Molecularly imprinted polymers. Amsterdam: Elsevier, 2001: 71-111
110. Wulff G. Molecular imprinting in cross-linked materials with the aid of molecular templates: a way towards artificial antibodies. Angew Chem Int Ed Engl 1995; 34: 1812-32
111. Arshady R, Mosbach K. Synthesis of substrate-selective polymers by host-guest polymerization. Makromol Chem 1981; 182: 687-92
112. Sellergren B. The non-covalent approach to molecular imprinting. In: Sellergren B, editor. Molecularly imprinted polymers. Amsterdam: Elsevier, 2001: 113-84
113. Allender CJ, Brain KR, Heard CM. Molecularly imprinted polymers: preparation, biomedical applications and technical challenges. In: King FD, Oxford AW, editors. Progress in medicinal chemistry. Vol. 36. Amsterdam: Elsevier, 1999: 235-91
114. Andersson HS, Karlsson JG, Piletsky SA, et al. Study of the nature of recognition in molecularly imprinted polymers: influence of monomer-template ratio and sample load on retention and selectivity. J Chromatogr A 1999; 848: 39-49
115. Mayes AG, Whitcombe MJ. Synthetic strategies for the generation of molecularly imprinted organic polymers. Adv Drug Deliv Rev 2005; 57: 1742-78
116. Kandimalla VB, Ju HX. Molecular imprinting: a dynamic technique for diverse applications in analytical chemistry. Anal Bioanal Chem 2004; 380: 587-605
117. Hillberg AL, Brain KR, Allender CJ. Molecular imprinted polymer sensors: implications for therapeutics. Adv Drug Deliv Rev 2005; 57: 1875-89
118. Allender CJ, Richardson C, Woodhouse B, et al. Pharmaceutical applications for molecularly imprinted polymers. Int J Pharm 2000; 195: 39-43
119. Byrne ME, Park K, Peppas NA. Molecular imprinting within hydrogels. Adv Drug Deliv Rev 2002; 54: 149-61
120. Alvarez-Lorenzo C, Concheiro A. Molecularly imprinted polymers for drug delivery. J Chromatogr B 2004; 804: 231-45
121. Hilt JZ, Byrne ME. Configurational biomimesis in drug delivery: molecular imprinting of biologically significant molecules. Adv Drug Deliv Rev 2004; 56: 1599-620
122. van Nostrum CF. Molecular imprinting: a new tool for drug innovation. Drug Discov Today 2005; 2: 119-24
123. Cunliffe D, Kirby A, Alexander C. Molecularly imprinted drug delivery systems. Adv Drug Deliv Rev 2005; 57: 1836-53
124. Alvarez-Lorenzo C, Concheiro A. Molecularly imprinted gels and nano- and microparticles: manufacture and applications. In: Arshady R, Kono K, editors. Smart nano and microparticulates. MML Series Vol. 7. London: Kentus Books, 2005: 279-336
125. Alvarez-Lorenzo C, Concheiro A. Molecularly imprinted materials as advanced excipients for drug delivery systems. In: El-Gewely MR, editor. Biotechnology annual review. Vol. 12. Amsterdam: Elsevier, 2006: 225-68
126. Sibrian-Vazquez M, Spivak DA. Improving the strategy and performance of molecularly imprinted polymers using cross-linking functional monomers. J Org Chem 2003; 68: 9604-11
127. Alvarez-Lorenzo C, Hiratani H, Gómez-Amoza JL, et al. Soft contact lenses capable of sustained delivery of timolol. J Pharm Sci 2002; 91: 2182-92
128. Hiratani H, Alvarez-Lorenzo C. Timolol uptake and release by imprinted soft contact lenses made of N,N-diethylacrylamide and methacrylic acid. J Control Release 2002; 83: 223-30
129. Hiratani H, Alvarez-Lorenzo C. Process for production of hydrogel material enhanced in the intake of drugs and permitting sustained release of drugs. Patent WO03090805, November 6, 2003
130. Hiratani H, Alvarez-Lorenzo C. The nature of backbone monomers determines the performance of imprinted soft contact lenses as timolol drug delivery systems. Biomaterials 2003; 25: 1105-13
131. Hiratani H, Fujiwara A, Tamiya Y, et al. Ocular release of timolol from molecularly imprinted soft contact lenses. Biomaterials 2005; 26: 1293-8
132. Hiratani H, Mizutani Y, Alvarez-Lorenzo C. Controlling drug release from imprinted hydrogels by modifying the characteristics of the imprinted cavities. Macromol Biosci 2005; 5: 728-33
133. Ahmed I, Gokhale RD, Shah MV, et al. Physicochemical determinants of drug diffusion across the conjunctiva, sclera, and cornea. J Pharm Sci 1987; 76: 583-6
134. Ahmed I, Francoeur ML, Thombre AG, et al. The kinetics of timolol in the rabbit lens: implications for ocular drug delivery. Pharm Res 1989; 6: 772-8
135. Nelson WL, Fraunfelder FT, Sills JM, et al. Adverse respiratory and cardiovascular events attributed to timolol ophthalmic solution, 1978-1985. Am J Ophthalmol 1986; 102: 606-11
136. Andrzejewska E. Photopolymerization kinetics of multifunctional monomers. Prog Polym Sci 2001; 26: 605-65
137. Sellergren B, Shea KJ. Correlation between solute retention and a theoretical ion-exchange model using imprinted polymers. J Chromatogr A 1993; 654: 17-28
138. Molinelli A, O'Mahony J, Nolan K, et al. Analyzing the mechanisms of selectivity in biomimetic self-assemblies via IR and NMR spectroscopy of prepolymerization solutions and molecular dynamics simulations. Anal Chem 2005; 77: 5196-204
139. McStay D, Al-Obaidi AH, Hoskins R, et al. Raman spectroscopy of molecularly imprinted polymers. J Opt A Pure Appl Opt 2005; 7: S340-5
140. Fish WP, Ferreira J, Sheardy RD, et al. Rational design of an imprinted polymer: maximizing selectivity by optimizing the monomer-template ratio of a cinchonidine MIP, prior to polymerization, using microcalorimetry. J Liq Chromatogr Relat Technol 2005; 28: 1-15

141. O'Mahony J, Molinelli A, Nolan K, et al. Towards the rational development of molecularly imprinted polymers: 1H NMR studies on hydrophobicity and ion-pair interactions as driving forces for selectivity. Biosens Bioelectron 2005; 20: 1884-93
142. Alvarez-Lorenzo C, Yañez F, Barreiro-Iglesias R, et al. Imprinted PHEMA soft contact lenses as norfloxacin delivery systems. J Control Release 2006; 113: 236-44
143. D'Oleo R, Alvarez-Lorenzo C, Sun G. A new approach to design imprinted polymer gels without using a template. Macromolecules 2001; 34: 4965-71
144. Moritani T, Alvarez-Lorenzo C. Conformational imprinting effect on stimuli-sensitive gels made with an imprinter monomer. Macromolecules 2001; 34: 7796-803
145. Sano K, Tokoro T, Imai Y. A new drug delivery system utilizing piggyback contact lenses. Acta Ophthalmol Scand 1996; 74: 243-8
146. Nakada K, Sugiyama A, inventor. Menicon Co., Ltd, assignee. Process for producing controlled drug-release contact lens, and controlled drug-release contact lens thereby produced. US Patent 6,027,745. May 1998
147. Rootman DS, Willoughby RPN, Bindlish R, et al. Continuous-flow contact-lens delivery of gentamicin to rabbit cornea and aqueous-humor. J Ocul Pharmacol 1992; 8: 317-23

Correspondence and offprints: Dr *Carmen Alvarez-Lorenzo*, Departamento de Farmacia y Tecnologia Farmaceutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782-Santiago de Compostela, Spain.
E-mail: ffrusdog@usc.es