Soft contact lenses for controlled ocular delivery: 50 years in the making

The use of contact lenses as ocular bandages for drug delivery was envisioned nearly 50 years ago by Wichterle and co-workers. Despite the therapeutic advantages that can be obtained, this application has to face up to the poor affinity shown by commercially available contact lenses for most ophthalmic drugs, resulting in small amounts of drug being loaded and short time of therapeutic levels in the eye structures. Novel strategies that appeared in the beginning of 21st century, for example coating lenses with vitamin E, incorporation of drug nanocarriers or application of molecular imprinting technology, are becoming relevant tools for development of true drug/contact lens combination products that may be available for ocular therapy in the foreseeable future.

Although scientific events are not always easy to date with certainty, there is a consensus that the use of contact lenses (CLs) as suitable platforms for controlled delivery of ophthalmic drugs was first postulated by Otto Wichterle and his Czech colleagues in a patent published in 1965 [1–3], soon after the first patent that described a semi-industrial method of preparing hydrogel CLs, filed in 1963 (Figure 1) [4]. In the US Patent 3,220,960 relating to “cross-linked hydrophilic polymers and articles made therefrom”, Wichterle and Lim speculated that “medicinal active substances such as antibiotics may be dissolved in the aqueous constituent of the hydrogels to provide medication over an extended period”. The same year, Sedlacek published first experiments on the application of eye drugs with the aid of gel-CLs [5]. Subsequent research in this field has proved the relevant advantages that medicated CLs can offer in ocular therapy compared with conventional ocular treatments. However, almost 50 years later, the off-label use of CLs as drug depots remains infrequent [6] and the first clinical studies for commercialization of medicated CLs are still ongoing [20]. Delays in the development of these combination products (medical device plus drug) are mainly, but not only, due to the different origin of their parents (if a comparison with animated beings is allowed). Industries specializing in CLs and of pharmaceutical dosage forms have traditionally evolved separately [7]. Thus, production of medicated CLs involves strong efforts of the manufacturers to reorganize research and to find financial returns. Additionally, regulatory issues regarding classification and evaluation of drug-eluting CLs were not clear [8]. The last decade has witnessed a tremendous advance in the numerous challenges that the design of medicated CLs involve, such as: the loading of adequate amounts of the drug without perturbing biocompatibility, optical clarity and comfort; and the release of therapeutic drug concentrations with controlled profiles during the desired timeframe [9]. The large body of scientific research and the implementation of specific evaluation pathways in the regulatory process as a subclass of combination products [8,10] allows forecasting that, finally, there is a hopeful future for medicated CLs 50 years after their postulation. This Review will try to provide the reader an overview of the sequence of improvements in the design of medicated CLs, with particular attention on advances that occurred in the last decade. First, a short general outlook on ocular drug delivery is provided for a better comprehension of the needs in the field. Then, the evolution in CLs for drug release is revisited, not forcedly in a temporal order, but from the simplest combination of independently developed medical devices and drug solutions, to the most elaborated designs of ad hoc combination products.

Ocular drug delivery
Infections, allergies, vascular and degenerative processes, as well as accidental damages are relatively common threats for the eye structures [11,12]. Systemic treatment involves the administration of large doses able to create sufficient serum–ocular tissue concentration gradients and to counteract, at least partially, the blood–ocular barriers (blood–aqueous humor, blood–retina, and blood–vitreous humor) against drug penetration. Even administering high drug doses, systemic delivery only helps in the management of diseases affecting the posterior segment of the
The anterior segment seems to be more accessible via external topical route, although also with notable limitations [14, 15]. Additionally, topical administration may be a patient-friendly alternative to the intravitreal implants and transscleral drug-delivery systems for some diseases affecting the back of the eye [13, 15]. One of the most important challenges of ocular administration is to maintain the optimal drug concentration in the site of action during prolonged periods of time [9, 15]. Eye drops are the most common form to deliver drugs into the eye, but less than 5% of the instilled dose effectively penetrates into the cornea [16]. Nasolachrymal drainage, epithelial membrane barriers and nonproductive absorption lead to poor ocular bioavailability and to undesirable systemic adorption, which could provoke side effects [9]. Eye-drop instillation produces a rapid burst where the drug concentration is well above the therapeutic concentration, followed by a short time of optimal concentration and a subsequent period of subtherapeutic concentration until the next drop is administered [15, 16]. To diminish the burst and prolong the contact time between the drug and the eye surface, many approaches have been proposed, such as the use of penetration enhancers, mucoadhesive and viscous polymers, nanoparticles, suspensions and implants [17–20]. The interest for developing ocular bandages dates back to 1886 when Galewowski successfully applied gelatine discs loaded with different drugs (cocaine and sublimate) to prevent complications after cataract surgery [21]. Nevertheless, the poor optical performance and the limited possibilities of obtaining mechanically stable, sterile bandages limited their ocular application.

The search for systems that combine efficient control of drug release without compromising optical performance (e.g., not causing blurred vision) or patient adherence with drug therapy (e.g., avoiding uncomfortable feeling of foreign body) has been concurrent with the notable development in CLs, as explained in the next section. The feasibility of using CLs as drug platforms opens novel possibilities in eye therapy [6, 9, 22]. Soft CLs are flexible, slightly crosslinked hydrogels that can uptake drugs when soaking in eye-drop solutions and then sustain drug release to the postlens tear film – that is, the lachrymal fluid trapped between the cornea and the lens. Since turnover of the postlens tear film occurs slowly, the greater drug concentration attained should promote the pass through the cornea. Moreover, the release towards the lachrymal fluid that bathes the external surface of the CL is minimized by the dry periods during the blinking interval, and it is estimated to be five-times smaller than the amount of drug that diffuses towards the corneal epithelium [23]. Prolonged stay of the drug on the cornea leads to higher intraocular concentration, which in turn results in remarkable improvements in pharmacological response compared with conventional topical administration [24–27]. In some cases, drug delivery through CLs can even allow a decrease in the dose required to attain the desired therapeutic effect [26, 28]. However, the success of commercial CLs as drug-release platforms was rapidly found to be limited to drugs with medium affinity for the polymer components. If the affinity is too low, the loading is insufficient to attain therapeutic levels; while if the drug–polymer interaction is strong, irreversible binding occurs and the drug is not released to the postlens tear film. These findings meant that interest in developing medicated CLs was kept to a minimum until the beginning of the 21st century, when novel design strategies were implemented (Figure 2).
Medicated CLs

- The origins: CLs as medical devices

Development of poly(methyl methacrylate) in 1928 and commercialization in 1933 under the name Plexiglas® as a lightweight and shatter-resistant alternative to glass opened unprecedented ways of using polymers for industrial and daily tasks. The high biocompatibility of poly(methyl methacrylate) was accidentally discovered during the Second World War, when it was observed that pilots of airplanes having Plexiglas windows did not suffer rejection events when small splinters incrusted in their eyes [29]. The use of poly(methyl methacrylate) for hard CLs began in 1936. Soon after, the introduction of more comfortable poly(2-hydroxyethyl methacrylate) (pHEMA) in 1954 triggered the popularization of CLs for vision correction [30,31]. These acrylic-based polymers combine the high optical clarity of the glass with lower density and better mechanical properties, and served as starting point for designing new copolymers able to improve the quality of the lenses [32]. Conventional CLs could be classified into hydrophilic (-’filcon’) or hydrophobic (-‘focon’) lenses according to their chemical composition and physical properties, mainly to categorize behavior of the lenses in care product solutions and in contact with the proteins in the tear film (Table 1) [33,34,202]. Some hydrophilic CLs were approved in the late 1970s for extended wear (up to 6 nights and 7 days) due to their ability to absorb and retain large amounts of water (>35% w/w), in which the oxygen can dissolve and diffuse towards the cornea. During the 1980s, the search for materials that prevent hypoxia during closed-eye periods led to the development of silicone-based, gas-permeable, hard lenses, with greater oxygen permeability, which maintained the optical clarity and the simplicity of handling of hard lenses [31,32]. To overcome the strong hydrophobicity of these materials, high gas permeable silicone hydrogels were prepared combining the large permeability of silicone components with the ocular biocompatibility and comfort of hydrophilic CLs. Some of them were approved in 2001 for continuous wear (up to 29 nights and 30 days) [35]. The time of permanence allowed on the eye surface is, thus, a critical point to consider when developing drug-eluting CLs, since the release profiles have to be fitted to the daily, weekly or monthly disposable lenses. Until recently, silicone hydrogel CLs were placed into one of the four existing US FDA classes, mostly into group I, with the exception of balafilcon A that was assigned to group III (Table 1). However, their unpredictable way of reacting with disinfectants and care solutions led to the International Standards Organization to recognize that silicone hydrogels do not fit adequately within the existing FDA materials grouping and to propose a specific ‘group V’ for this class of high-oxygen permeability hydrogel materials [203]. Splitting of group V into various subgroups as for the hydrophilic conventional CLs is under study [204,205].

The FDA also classifies CLs according to their intended uses as: nontherapeutic CLs (e.g., for correction of refractive ametropia, aphakia and presbyopia); specialized-use CLs (e.g., for the treatment of keratoconus); and, therapeutic CLs that serve as a tool in the management of a wide variety of ophthalmic disorders refractory to other treatment modalities [38]. Interestingly, drug delivery is included in the list of aims of therapeutic CLs, which are also intended for relief of ocular pain, promotion of corneal healing, mechanical protection and support, or maintenance of corneal epithelial hydration [36–38,206]. Drug release could be pursued for treatment of diseases that occur disregarding the wear of CLs (e.g., seasonal allergies) or are directly associated to their use (e.g., risk of infection or dry-eye syndrome) [39–41].
Table 1. Classification of contact lenses according to the US FDA.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Group</th>
<th>Description</th>
<th>Examples: material (polymer composition; brand name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophilic</td>
<td>I</td>
<td>Nonionic (&lt;1% ionized groups at pH 7.2), low water content (&lt;50%)</td>
<td>Crofilcon A (MMA-GMA; CSI 38), lotrafilcon A (DMA-siloxane macromer; Focus Night &amp; Day™), polymacon (HEMA-NVP-CMA; Optima FW, Plano T, Soflens® 38)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Nonionic (&lt;1% ionized groups at pH 7.2), high water content (&gt;50%)</td>
<td>Alphafilcon A (HEMA-NVP-CMA; Soflens 66); omal filcon (HEMA-phosphorylcholine; Proclear® Compatibles); nefilcon A (PVA; Focus Daily™)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Ionic (&gt;1% ionized groups at pH 7.2), low water content (&lt;50%)</td>
<td>Balafilcon A (Siloxane macromer-NVP; Pure Vision®)</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Ionic (&gt;1% ionized groups at pH 7.2), high water content (&gt;50%)</td>
<td>Etafilcon A (HEMA-MA; Acuvue®-2; HEMA-MA-PVP; 1-Day Acuve Moist), ocufilcon B (HEMA-MA; Biomedics® 1 Day), methafilcon (HEMA-MA; Kontour 55), vi filcon A (HEMA-MA-NVP; Focus® Monthly)</td>
</tr>
<tr>
<td>Hydrophobic</td>
<td>I</td>
<td>Without silicon and fluorine</td>
<td>Porocon (CAB; RX56), arfocon (1-butyl styrene; AirLens)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>With silicon but not fluorine</td>
<td>Pasafocon (silicone acrylate; Boston® II and IV)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>With silicon and fluorine</td>
<td>Itafluorocon A (FSC; Equalens), tsilfocon A (FSC; Menicon Z), paflucon (FSC; Fluoroperm®), flusifocon (FSC; Fluorex), enflucon B (FSC; Boston EO)</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>With fluorine but not silicon</td>
<td>Fluorocon (FSC; 3M Fluoropolymer)</td>
</tr>
</tbody>
</table>

After International Standards Organization 18369-1 (2009) silicone hydrogel materials should be reclassified in a novel Group V. All contact lenses shown as examples of the hydrophilic ones are available for therapeutic use or have been used in an off-label manner as therapeutic lenses [33,34,202]. After International Standards Organization 18369-1 (2009) silicone hydrogel materials should be reclassified in a novel Group V. All contact lenses shown as examples of the hydrophilic ones are available for therapeutic use or have been used in an off-label manner as therapeutic lenses [33,34,202].

The match: commercial CLs & drug solutions
pHEMA hydrogel meant a revolution not only on the poplularization of CLs, but also on the scope of their applications. Since Sedlacek in 1965 [5] and Kaufman and co-workers in 1970 demonstrated that drug-loaded CLs can increase drug concentration in the anterior segment of the eye, many researchers have investigated how to load the CLs commonly used to correct ametropia problems with therapeutic substances [22,42]. Namely, the design of the medical device and the therapeutic substance formulation occur separately, and depending on the pathological process of the CL wearer, the clinician prescribes or prepares certain combinations of both components. Immersion in concentrated solutions of drug (eye drops) [42–46], instillation of the drug solution in the concavity of the lenses before placed on the eye, and instillation of the eye drops on the surface of the CLs after insertion (also named splash or postsoaking) [47-52] have all been evaluated. Some general rules on the variables affecting drug uptake are summarized in the following section [37].

Loading conditions & loading/release efficiency
The time taken for penetration of a drug into a CL depends on the mesh size of the network (determined by the crosslinking density and the degree of swelling), the molecular size of the drug and the concentration of the drug in the loading solution [33]. Drug uptake increases over the course of soaking in the drug solution, rapidly in the first 30–60 min and then more slowly for 24 h [44,53]. Attainment of drug-loading equilibrium throughout the CL is critical for it to perform as a sustained-release device; as the drug diffuses out from the surface, drug molecules localized in deeper parts would progressively replenish the surface layers enabling prolonged release [50,55]. For example, polymacon and alphafilcon A lenses loaded with ciprofloxacin by soaking for 1 hour in commercial eye drop solution led to remarkably greater drug levels in both corneal tissue and aqueous humour at 6 h after application, compared with the direct application of eye drops (polymacon: 8.034 µg; alphafilcon: 6.432 µg, eye drops: 0.451 µg in cornea; polymacon: 0.361 µg; alphafilcon: 0.240 µg, eye drops: 0.0071 µg in aqueous humour) [52,53]. Similarly, etafilcon A (1-Day Acuvue®) CLs loaded by immersion in eye drop solutions provided higher concentrations of antifungals, aminoglycosides and fluoroquinolones in aqueous humour than when the eye drops were directly instilled [56–58]. Wearing of ofloxacin-loaded or ciprofloxacin-loaded lenses for 4–5 h before cataract extraction resulted in aqueous humour concentrations above the MIC90 of Staphylococcus epidermidis at the beginning of surgery [58]. Nevertheless, there are many drugs (chloramphenicol, epinephrine and pilocarpine).
that do not show affinity for pHEMA lenses, and in those cases the soaked lenses hardly led to one tenth of the aqueous humour concentration that can be achieved using eye drops [59–61]. In general, hydrophilic drugs scarcely adsorb on CLs. Cationic substances have some affinity for anionic and hydrated methacrylic acid-based CLs (lens type IV, see Table 1), anionic drugs mainly interact with nonionic and hydrated N-vinylpyrrolidone (NVP)-based CLs (lens type II), and nonionic substances adsorb on hydrophobic silicone-based lenses (lens type III or the new group V) [60].

**Lens thickness**

In the 1970s the increase in the hydrogel thickness was evaluated as a way to enhance the amount of drug loaded and to prolong the release. Thick pHEMA lenses (0.7–1.3 mm) provided sustained release of fluorescein, tetracycline or chloramphenicol up to 24 h [62–64] and prolonged in vitro elution of diethylaminoetrazone, disodium ethylenediamine tetraacetate or cys-tein hydrochloride, shortening the period of corneal burns healing by half compared with eye drops [65]. However, the increase in thickness has negative repercussions on oxygen permeability and patient comfort [66,67].

**Water content**

Drugs that do not interact with polymer components of the CLs are just hosted in the aqueous phase embedded in the network. Once the loading equilibrium is attained, the concentration of drug in the aqueous phase (w/w dry hydrogel) of the CL is the same as that in the loading solution [68]. Therefore, the greater the volume of water in the hydrogel, the greater the amount of drug loaded, as follows [69]:

\[
\text{Drug in aqueous phase} = \left( \frac{W_a}{W} \right) C_p
\]

**Equation 1**

where \( V \) is the volume of the aqueous phase in the hydrogel, \( W \) is the weight of dried hydrogel, and \( C_p \) the drug concentration in the loading solution. This explains that, for example, high water content (71%) Permalens lenses provide greater tobramycin concentrations in corneal tissue when the antibiotic is instilled on the lens, and for longer periods of time, than low water content (38.6%) Plano T therapeutic lenses [49]; although sustained release is general more efficient from low water content lenses [55], as explained in the following. The content in water also has repercussions on the oxygen permeability; large content in water enhances the permeability of hydrophilic CLs, but diminishes that of hydrophobic silicone-based lenses [70,71].

CLs deliver weakly interacting drugs via drug diffusion at a rate that can be predicted, if sink conditions are fulfilled, using the following equation [68]:

\[
\frac{dM}{dt} = \frac{8DM}{l^2} \exp\left(\frac{-\pi^2Dt}{l^2}\right)
\]

**Equation 2**

In this expression, \( M \) represents the total amount of drug released, \( l \) the lens thickness and \( D \) the diffusion coefficient of the drug. In general, the release rate becomes faster for low-molecular-weight drugs and as the water content of the lens increases [68].

A clear example of the influence of the variables mentioned above can be seen by comparing the ability to absorb and release drugs of silicon-containing (lotrafilcon and balafilcon) and pHEMA-containing (etafilcon, alphafil-con, polymacon, visifilcon and omfalicon) commercial CLs (see characteristics in Table 1) [34]. Low molecular-weight drugs, namely cromolyn sodium, ketorolac tromethamine, and dexamethasone sodium, were rapidly loaded and released (<1 h) from any of the lenses (all with a high content in water). Similar kinetics has been reported for cromolyn sodium, ciproflaxa-cin, idoxuridine, pilocarpine and prednisolone using visifilcon, etafilcon and polymacon lenses when placed in saline fresh solution [55]. By con-trast, ketotifen fumarate, a relatively hydrophobic histamine, was more gradually taken up/released (for 2 h) because of the low concentration (0.01 mg/ml) of the soaking solution and the slow mass transfer rate of the drug in and out the lens matrix. As explained above, the amount loaded depends on the content in water of the lenses and on the feasibility of interacting with polymer components (particularly, with ionic groups). Table 2 shows the total amounts of drug loaded and released by the different lenses. In general, pHEMA hydrogels with a high content in water and ionic character showed the greatest loading capability and also released more drug. Interestingly, only a fraction of the drug loaded was released in borate saline buffer unisol 4: 12% for cromolyn sodium, 1.5–28% for ketorolac tromethamine and 46–67% for ketotifen fumarate, indicating that the drugs were in part irreversibly bound to the lens materials.
Greater and faster release from pHEMA-based soft CLs (SCLs; etafilcon A, omafilcon A, vifilcon A and polymacon) compared with silicone hydrogel SCLs (balafilcon A, comfilcon A, galafilcon A, lotrafilcon B and senofilcon A) was also observed when loaded with natamycin by soaking in a solution of the antifungal agent in dimethylsulfoxide for 24 h. No differences were observed in the amount of natamycin loaded between both types of CLs, ranging between 500 and 1200 µg/lens. pHEMA-based CLs released approximately 15–30% drug in 1 h, while silicone hydrogel CLs released 2–10%, except balafilcon A that released 21%. Hydrophobic interactions of the drug with the silicone network are responsible for the greater retention. Although the control of the release was limited to 1 hour, the amount of natamycin released may be enough to attain the MIC₉₀ of Candida spp and Fusarium spp [72].

A further study was carried out with ketotifen fumarate and three conventional CLs (etafilcon A, polymacon and alphafilcon A), four daily disposable CLs (nelfilcon A, omafilcon A, etafilcon A and ocufilcon B), five silicone hydrogels (lotrafilcon B, balafilcon A, comfilcon A, galafilcon A and senofilcon A) and two silicone daily disposable CLs (narafilcon A and filcon II 3) [73]. When immersed in a 0.25 mg/ml ketotifen fumarate solution in unisol 4, all the lenses demonstrated a high loading capacity on the first 2 h. Etafilcon A (both Acuvue® 2 and 1-Day Acuvue Moist), balafilcon A and ocufilcon B – that is, those bearing ionic groups showed the greatest uptake and were also the ones that released more drug (Table 3). Interestingly, all CLs released a fraction of the loaded drug in 1–3 h and then the release stopped due to irreversible binding, failing to provide a sustained profile under sink conditions. The influence of the drug-loading concentration on the total amount loaded and released was studied for ocufilcon B lenses. The concentration gradients between the loading solution and the lens aqueous phase (during soaking) and between the loaded lens and the release medium (during release) can be considered the main driving forces for the total mass transfer. This study [73] and another about loading and release of a phospholipid for management of dry eye syndrome [74] called the attention on two relevant points of the release tests: the volume of the in vitro release medium is usually much larger than that of the postlens tear film, which is in contrast under continuous flow/drainage; this may lead to unreal in vitro gradients that accelerate release compared with the in vivo situation; and the composition of the in vitro release test medium, usually water or a buffer does not resemble the composition of the tear fluid and may cause a delay in the release. In vivo, the interaction of the drug with the lipids, proteins and salts can reduce the concentration of free drug molecules in the medium and, thus, increase the driving force for drug diffusion out of the CLs [74].

### The matchmakers: coadjuvants for drug loading and controlled release

Two different approaches have been explored to enhance the amount loaded and to control drug release of commercial CLs: coating with or incorporation of a drug-containing polymer film on/into the CLs; and adsorption of an amphiphilic molecule that regulates drug interactions with the CL network.
The first approach has been tried with ciprofloxacin- and econazol-impregnated poly(lactic-co-glycolic) acid (PLGA), films that were added to the CL monomers solution before polymerization [75,76]. Since the films are not transparent to UV-vis light, a clear optical aperture should be left in the CLs. After a short burst, the film-containing CLs demonstrated zero-order release kinetics under infinite sink conditions for over 4 weeks, being able to inhibit the growth of sensitive strains of microorganisms. Drug release rate can be modulated by changing either the PLGA molecular mass or the drug/PLGA ratio.

In a comparative study carried out with Acuity CLs, antimicrobial agents were loaded by three different procedures: soaking, application of a coating of fibrin containing the drugs to the inner surface of the CLs, and sealing of the drug-containing fibrin film between two CLs (film-loaded CL) [77]. The CLs coated with or containing the films were able to provide sustained-release profiles, different from the rapid release recorded for the drug-soaked CLs. Once again the films resulted in alteration of the optical performance of the CLs, and the two CLs sandwiched together would have a thickness not valid for practical use. Therefore, only partial coating of the CLs, near to the edges, could be feasible for clinical application in the prevention or treatment of ocular infections [77].

Adsorption of an amphiphilic molecule onto commercial CLs for enhancement of drug interactions and regulation of the release process seems to be a simpler approach, with minor incidence on the optical performance of the CLs. For example, cationic surfactants (e.g., cetalkonium chloride) have been shown to adsorb through hydrophobic interactions on CL networks (1-Day Acuve), while the cationic moieties are free to interact with anionic drugs, such as dexamethasone 21-disodium phosphate used to treat persistent macular edema in retina. The surfactant and the drug were simultaneously loaded in the CLs by soaking in a solution of both components. As the amount of surfactant increased, the drug loading was larger and the release rate became slower [78]. Drug release was prolonged from 2 to 50 h in CLs loaded with 10% surfactant.

The use of vitamin E may be a more physiologically friendly alternative to the use of cationic surfactants. This lipophilic vitamin has been shown to be suitable for protecting the eye from light-induced pathologies [79]. Vitamin E can be loaded in the CLs by soaking before loading of the drug or, alternatively, the loading of both vitamin E and the drug can simultaneously occur. The vitamin increases the CL/loading medium partition coefficient and also acts as a barrier for drug diffusion during release. As a consequence, drug uptake and release performance of both silicon hydrogel and pHEMA-based CLs can be notably improved. For example, loadings of 10% and 40% vitamin E prolonged the release

<table>
<thead>
<tr>
<th>Lens</th>
<th>Total ketotifen uptake after 24 h (µg/lens)</th>
<th>Uptake plateau time (min)</th>
<th>Total ketotifen release after 24 h (µg/lens)</th>
<th>Release plateau time (min)</th>
<th>Release† (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etafilcon A (Acuvue® 2)</td>
<td>461.78 ± 27.45</td>
<td>60</td>
<td>284.51 ± 29.83</td>
<td>120</td>
<td>61.7 ± 7.2</td>
</tr>
<tr>
<td>Polymacon</td>
<td>363.98 ± 41.41</td>
<td>60</td>
<td>114.3 ± 9.84</td>
<td>120</td>
<td>31.7 ± 4.6</td>
</tr>
<tr>
<td>Alphafilcon A</td>
<td>382.52 ± 15.32</td>
<td>20</td>
<td>138.98 ± 7.85</td>
<td>120</td>
<td>36.4 ± 3.3</td>
</tr>
<tr>
<td>Nelfilcon A</td>
<td>223.52 ± 14.33</td>
<td>360</td>
<td>40.36 ± 4.13</td>
<td>5</td>
<td>18.1 ± 1.4</td>
</tr>
<tr>
<td>Omafilcon A</td>
<td>237.56 ± 50.84</td>
<td>30</td>
<td>106.72 ± 6.03</td>
<td>60</td>
<td>48.8 ± 8.1</td>
</tr>
<tr>
<td>Etafilcon A (1-Day Acuve Moist)</td>
<td>502.48 ± 10.19</td>
<td>120</td>
<td>249.93 ± 13.39</td>
<td>180</td>
<td>49.7 ± 2.7</td>
</tr>
<tr>
<td>Narafilcon A</td>
<td>350.81 ± 17.19</td>
<td>30</td>
<td>133.22 ± 13.61</td>
<td>120</td>
<td>38.1 ± 5</td>
</tr>
<tr>
<td>Ocufilcon B</td>
<td>502.94 ± 71.27</td>
<td>120</td>
<td>261.17 ± 13.82</td>
<td>240</td>
<td>47.5 ± 2.4</td>
</tr>
<tr>
<td>Ficon 113</td>
<td>309.03 ± 22.12</td>
<td>25</td>
<td>124.21 ± 12.61</td>
<td>60</td>
<td>40.1 ± 1.7</td>
</tr>
<tr>
<td>Lotrafilcon B</td>
<td>362.29 ± 40.13</td>
<td>180</td>
<td>158.98 ± 11.13</td>
<td>240</td>
<td>44 ± 2.4</td>
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<tr>
<td>Balafilcon A</td>
<td>515.85 ± 47.29</td>
<td>240</td>
<td>227.64 ± 14.71</td>
<td>120</td>
<td>45.4 ± 2.6</td>
</tr>
<tr>
<td>Comfilcon A</td>
<td>373.5 ± 56.33</td>
<td>60</td>
<td>110.38 ± 8.88</td>
<td>120</td>
<td>30.1 ± 5</td>
</tr>
<tr>
<td>Galafilcon A</td>
<td>257.44 ± 57.96</td>
<td>180</td>
<td>139.34 ± 12.33</td>
<td>60</td>
<td>36.1 ± 1.6</td>
</tr>
<tr>
<td>Senofilcon A</td>
<td>339.82 ± 12.71</td>
<td>240</td>
<td>122.49 ± 1.61</td>
<td>240</td>
<td>49 ± 9</td>
</tr>
</tbody>
</table>

†Percentage release is the total ketotifen uptake delivered divided by total release.

of timolol by a factor of about five and 400, respectively, for NIGHT&DAY™ lens. Similar results have been obtained for other drugs including fluconazole, dexamethasone 21-disodium phosphate and cyclosporine A (Figure 3) [80,81]. Vitamin E-loaded silicone CLs (lotrafilcon B; O2OPTIX®) provided continuous anaesthetics release for about 1–7 days and could be very useful for postoperative pain control after corneal surgery, such as the photorefractive keratectomy procedure for vision correction [82].

The success of the use of vitamin E as co-adjuvant of loading and controlled release of timolol in Acuvue® TruEye™ has recently been proved in vivo using Beagle dogs affected by spontaneous glaucoma [83]. The in vivo release experiments were performed for: eye drops (150 µg/drop) placed twice a day; 60 µg drug-loaded control lenses replaced daily; 200 µg drug-loaded control lenses continuously worn for 4 days; and 200 µg drug-loaded vitamin E-containing lenses continuously worn for 4 days. Any CL reduced the intraocular pressure to a greater extent compared with the eye drops using a minor amount of timolol, and vitamin E-containing lenses were the only CLs able to provide a prolonged decrease of the intraocular pressure over the 4 days, in agreement with its most sustained release of the drug [83].

The specific design: CLs prepared ad hoc for drug delivery

Commercial CLs present three important drawbacks to use as drug-delivery systems: the amount of drug loaded by the lenses is limited due to the fact that their affinity for the majority of the drugs is very low; most of the drug contained in the soaking solution is not loaded neither released by the CLs; and the release of the drug is too rapid and the period of time where therapeutic levels are maintained is quite short. Therefore, the design of true combination products comprising a CL and a drug requires novel approaches [6,84]. Below, the three most commonly investigated are described.

Incorporation of drug-loaded nanocarriers into CLs during manufacturing

This approach is based on the capability of nanometric micelles, particles and liposomes to host drugs and to regulate their release. It is expected that, if an adequate proportion of nanocarriers is added to the components of CLs during manufacturing, the nanocarriers will remain trapped in the CL structure, acting as reservoirs for sustained release. If the number and the size of the nanocarriers are sufficiently low, the CL stays transparent. Intensive research carried out in Chauhan’s group has demonstrated the feasibility of this approach for a variety of drugs and nanostructures. Incorporation of microemulsions or liposomes to PHEMA-based hydrogel CLs usually led to biphasic release profiles, with an initial burst of drug that was free in the network followed by a sustained release of drug remaining encapsulated. Microemulsion droplets and liposomes were shown to be responsible for the control of drug release, with minor effects from the crosslinking density and the lens thickness on the kinetics of the process [85,86]. Nevertheless, microemulsion droplets and liposomes exhibited limited physical stability and required the storage of the CLs in a drug-saturated buffer to prevent premature release. Immobilization of liposomes on the surface of the CLs has been tried by other groups, but the many steps involved in the process have prevented the scaling-up to date [87,88]. Drugs tested and their release conditions are specified in Table 4.

Incorporation of drug-loaded micelles and polymeric nanoparticles seems to be more promising. Micelle-containing CLs have been shown to be able to stand autoclaving and packing in multipurpose solution, and still provide extended release of cyclosporine A at therapeutic concentrations.
Table 4. *In vitro* release conditions of tests used to evaluate the performance of some drug-loaded contact lenses.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lens</th>
<th>Medium (volume; ml)</th>
<th>Temperature and motion</th>
<th>Medium replacement</th>
<th>Duration of study</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natamycin</td>
<td>Balafilcon A, comfilcon A, galyfilcon A, senofilcon A, lotrafilcon B, etafilcon A, omafilcon A, polymerac, vifilcon A</td>
<td>Unisol 4 boreuffered saline pH 7.4 (5 ml)</td>
<td>32 ± 1ºC with continuous shaking</td>
<td>Replaced completely at 24 h</td>
<td>48 h</td>
<td>[70]</td>
</tr>
<tr>
<td>Ketotifen</td>
<td>Etafilcon A, polymacon, alphafilcon A, nelfilcon A, omafilcon A, etafilcon A, oculifilcon B, lotrafilcon B, balafilcon A, comfilcon A, galyfilcon A, senofilcon A, narafilcon A, filcon II 3</td>
<td>Unisol 4 boreuffered saline pH 7.4 (6 ml)</td>
<td>34ºC with continuous shaking</td>
<td>30 µl samples were extracted for measurements, without replacement</td>
<td>24 h</td>
<td>[71]</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>PLGA-coated pHEMA</td>
<td>PBS pH 7.4 (15 ml)</td>
<td>37ºC with continuous shaking</td>
<td>Replaced completely at predetermined intervals</td>
<td>4 weeks</td>
<td>[73]</td>
</tr>
<tr>
<td>Vancomycin and gentamicin</td>
<td>Drug in fibrin gel to coat lenses or to be trapped between two lenses</td>
<td>PBS (200 µl) filling the concavity of the lens</td>
<td>37ºC, static</td>
<td>Replaced completely at predetermined intervals</td>
<td>72 h</td>
<td>[74]</td>
</tr>
<tr>
<td>Dexamethasone 21-disodium phosphate</td>
<td>pHEMA</td>
<td>PBS (6 ml)</td>
<td>Room temperature, static</td>
<td>None</td>
<td>400 h</td>
<td>[76]</td>
</tr>
<tr>
<td>Timolol, fluconazol, dexamethasone 21-disodium phosphate</td>
<td>Vitamin E-coated NIGHT&amp;DAY lens</td>
<td>PBS (2.00 ml)</td>
<td>Room temperature, soaking</td>
<td>None</td>
<td>Up to 500 h</td>
<td>[78]</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>Vitamin E-coated 1-DAY Acuvue® and silicone lenses</td>
<td>PBS (1.75 ml)</td>
<td>Room temperature, soaking</td>
<td>None</td>
<td>Up to 50 days</td>
<td>[79]</td>
</tr>
<tr>
<td>Bupivacaine, lidocaine, tetracaine</td>
<td>Vitamin E-loaded lotrafilcon B (O2OPTIX) lens</td>
<td>PBS (2.00 ml)</td>
<td>Room temperature, soaking</td>
<td>None</td>
<td>Up to 500 h</td>
<td>[80]</td>
</tr>
<tr>
<td>Timolol</td>
<td>Acuvue TruEye™ with vitamin E</td>
<td>PBS (2.00 ml)</td>
<td>Room temperature, soaking</td>
<td>None</td>
<td>Up to 500 h</td>
<td>[81]</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Particle-laden pHEMA lens</td>
<td>Water (volume not specified)</td>
<td>Room temperature (movement not specified)</td>
<td>None</td>
<td>10 days</td>
<td>[83]</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Microemulsion-laden pHEMA lens</td>
<td>Water (volume not specified)</td>
<td>Room temperature (movement not specified)</td>
<td>None</td>
<td>10 days</td>
<td>[84]</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Levofloxacin-loaded liposomes immobilized on hioxifilcon B lens</td>
<td>150 mM NaCl at pH 7.4 or a solution of 0.5% w/v Triton X-100 in water (3 ml)</td>
<td>37ºC (movement not specified)</td>
<td>None</td>
<td>140 h</td>
<td>[86]</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>Brij 97 microemulsions or micelles – laden in pHEMA lens</td>
<td>PBS (3.00 ml)</td>
<td>Room temperature, soaking</td>
<td>Replaced every 24 h</td>
<td>20 days</td>
<td>[87]</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>Brij surfactant-laden pHEMA lens</td>
<td>PBS (3.50 ml)</td>
<td>Room temperature, soaking</td>
<td>Replaced every 24 h</td>
<td>20 days</td>
<td>[88]</td>
</tr>
</tbody>
</table>

1VI: 1-vinylimidazole; 4VI: 4-vinylimidazole; AAc: Acrylic acid; AM: Acrylamide; DEA: N,N-diethylacrylamide; DEAEM: Diethylaminoethoxy methacrylate; DMA: N,N-dimethyleclylamide; HEAA: N-hydroxyethyl acrylamide; HEMA: 2-hydroxyethyl methacrylate; MAA: Methacrylic acid; MAPTAC: Methacrylamidopropyltrimethylammonium chloride; MMA: Methylmethacrylate; MOEP: 2-methacryloxyethyl acid phosphate; NVP: N-vinylpyrrolidone; PBS: Phosphate-buffered saline; pHEMA: Poly(2-hydroxyethyl methacrylate); PLGA: poly(lactic-co-glycolic) acid; SIMA: 1-(trimethylsilyloxy)silylpropyl methacrylate; TRIS: Tris(trimethylsiloxy)silylpropyl methacrylate.
Table 4. *In vitro* release conditions of tests used to evaluate the performance of some drug-loaded contact lenses (cont.).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lens</th>
<th>Medium (volume; ml)</th>
<th>Temperature and motion</th>
<th>Medium replacement</th>
<th>Duration of study</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone acetate</td>
<td>Silica shell crosslinked micelles laden in pHEMA lens</td>
<td>PBS (4.5 ml)</td>
<td>37°C (movement not specified)</td>
<td>Replacement or not of aliquots taken for measurement</td>
<td>30 days</td>
<td>[89]</td>
</tr>
<tr>
<td>Timolol</td>
<td>Drug nanoparticles loaded in Acuvue Oasys™ lens</td>
<td>PBS (1.75–3.50 ml)</td>
<td>25–100°C (movement not specified)</td>
<td>None</td>
<td>50 days</td>
<td>[90]</td>
</tr>
<tr>
<td>Azulene</td>
<td>p(HEMA-MAPTAC) optionally with MOEP and MAA</td>
<td>0.9% NaCl (5 ml)</td>
<td>37°C, soaking</td>
<td>Replaced every 2 h</td>
<td>8 h</td>
<td>[91]</td>
</tr>
<tr>
<td>Naphazoline</td>
<td>p(HEMA-MAPTAC) optionally with MOEP and MAA</td>
<td>0.9% NaCl (10 ml)</td>
<td>37°C, soaking</td>
<td>Not specified</td>
<td>40 h</td>
<td>[92]</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>pHEMA with MAA or MOESA and a silyl-containing monomer</td>
<td>0.9% NaCl (2 ml)</td>
<td>Room temperature, soaking</td>
<td>Replaced at 1, 2, 4, 8 and 24 h</td>
<td>72 h</td>
<td>[93]</td>
</tr>
<tr>
<td>Timolol</td>
<td>pHEMA-silicone IPNs</td>
<td>PBS (10 ml)</td>
<td>37°C, 100 rpm</td>
<td>Replaced at certain time intervals</td>
<td>16 days</td>
<td>[95]</td>
</tr>
<tr>
<td>Puerarin</td>
<td>pHEMA/β-CD lens</td>
<td>Water (10 ml)</td>
<td>37°C, 100 rpm</td>
<td>5 ml was replaced at certain time intervals</td>
<td>12 h</td>
<td>[97]</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>pHEMA with pendant β-CD units</td>
<td>Artificial lachrymal fluid (10–20 ml)</td>
<td>25°C, static conditions</td>
<td>None</td>
<td>20 days</td>
<td>[98]</td>
</tr>
<tr>
<td>Timolol maleate</td>
<td>p(DEA-MAA), pDEA, pHEMA, p(SiMA-DMA), and p(MMA-DMA) lenses</td>
<td>0.9% NaCl (10 ml)</td>
<td>37°C, static conditions</td>
<td>None or 0.6 ml was replaced at certain time intervals</td>
<td>13 days</td>
<td>[24,109,110]</td>
</tr>
<tr>
<td>Timolol maleate</td>
<td>pHEMA with MAA or MMA</td>
<td>0.9% NaCl pH 5.5, phosphate buffer pH 7.4 or artificial lachrymal fluid pH 8</td>
<td>37°C, static conditions</td>
<td>None</td>
<td>12 h</td>
<td>[108]</td>
</tr>
<tr>
<td>Timolol maleate</td>
<td>p(DMA-TRIS-MAA) lenses</td>
<td>0.9% NaCl (10 ml)</td>
<td>25°C, static conditions</td>
<td>0.6 ml were replaced at certain time intervals</td>
<td>7 days</td>
<td>[111]</td>
</tr>
<tr>
<td>Timolol maleate</td>
<td>p(HEMA-AAc) lenses</td>
<td>0.9% NaCl (2 or 8 ml)</td>
<td>25°C, static conditions</td>
<td>None</td>
<td>22 days</td>
<td>[112]</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>p(HEMA-AAc) lenses</td>
<td>Artificial lachrymal fluid (10–15 ml)</td>
<td>37°C, static conditions</td>
<td>None</td>
<td>24 h</td>
<td>[113]</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>p(HEMA-DEAEM-PEG200DMA)</td>
<td>Artificial lachrymal fluid (450 ml for infinite sink conditions or microfluidic device)</td>
<td>34°C and 45 rpm for infinite sink conditions; or continuous physiological flow</td>
<td>None/flow conditions (3 µl/min)</td>
<td>140 h</td>
<td>[114]</td>
</tr>
<tr>
<td>Prednisolone acetate</td>
<td>p(HEMA-MAA) lenses</td>
<td>0.9% NaCl or artificial lachrymal fluid (10 ml)</td>
<td>37°C (movement not specified)</td>
<td>None</td>
<td>48 h</td>
<td>[115]</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>p(HEMA-TRIS-AAc) lenses</td>
<td>Artificial lachrymal fluid (2 ml)</td>
<td>34°C, shaking</td>
<td>None</td>
<td>14 days</td>
<td>[116]</td>
</tr>
<tr>
<td>Ketotifen fumarate</td>
<td>pHEMA lenses combining AAc, AM, NVP and PEG200DMA</td>
<td>Water or artificial lachrymal fluid solely or containing lysozyme (30 ml)</td>
<td>120 rpm</td>
<td>None</td>
<td>5 days</td>
<td>[117]</td>
</tr>
</tbody>
</table>

**Table Notes**: 1VI: 1-vinylimidazole; 4VI: 4-vinylimidazole; AAc: Acrylic acid; AM: Acrylamide; DEA: N,N-diethylacrylamide; DEAEM: Diethylaminoethyl methacrylate; DMA: N,N-dimethylacrylamide; HEAA: N-hydroxyethyl acrylamide; HEMA: 2-hydroxyethyl methacrylate; MAA: Methacrylic acid; MAPTAC: Methacrylamidopropyltrimethylammonium chloride; MMA: Methylmethacrylate; MOE: Z-methacryloxyethyl acid phosphate; NVP: N-vinylpyrrolidone; PBS: Phosphate-buffered saline; pHEMA: Poly(2-hydroxyethyl methacrylate); PLGA: poly(lactic-co-glycolic) acid; SMMA: 1-tristrimethyl-siloxypropylmethacrylate; TRIS: Tris(trimethylsiloxy)silipropyl methacrylate.
The hydrophobicity of the micellar core plays a relevant role on the drug partition. For example, in a study carried out with Brij surfactants (C_{18}H_{x}[OCH_{2}CH_{2}]_{y}OH), namely Brij 78 (x = 37, y = 20), Brij 97 (x = 35, y = 10), Brij 98 (x = 35, y = 20) and Brij 700 (x = 37, y = 100), cyclosporine A showed a high partitioning inside the micelles of Brij 78 and Brij 700 (x = 37, y = 100), Brij 97 (x = 35, y = 10), Brij 98 (x = 37, y = 20), Brij 700 (x = 37, y = 10), Brij 98 (x = 37, y = 20) and Brij 700 (x = 37, y = 100), cyclosporine A showed a high partitioning inside the micelles of Brij 78 and Brij 700. By contrast, the micellar partition coefficients of dexamethasone-21-acetate were smaller than the micellar partition coefficients of dexamethasone acetate. The drug was encapsulated in methoxy poly(ethylene glycol)-block-polyacrylate nanoparticles, and then the nanoparticles incorporated to the CLs either during or after synthesis.

Table 4. In vitro release conditions of tests used to evaluate the performance of some drug-loaded contact lenses (cont.).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lens</th>
<th>Medium (volume; ml)</th>
<th>Temperature and motion</th>
<th>Medium replacement</th>
<th>Duration of study</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketotifen fumarate</td>
<td>pHEMA lenses combining AAc, AM, NVP and PEG200DMA</td>
<td>Artificial lacrimal fluid (30 ml for infinite sink conditions or microfluidic device)</td>
<td>120 rpm for infinite sink conditions; or continuous physiological flow</td>
<td>None/flow conditions (3 µl/min)</td>
<td>7 days</td>
<td>[90]</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>pHEMA or p(DMA-NVP) lenses combining 1VI or 4VI and HEAA with a Zn^{2+} source</td>
<td>0.9% NaCl (5–10 ml)</td>
<td>25°C, static conditions</td>
<td>None</td>
<td>8 days</td>
<td>[120,122]</td>
</tr>
</tbody>
</table>

IVI: 1-vinylimidazole; 4VI: 4-vinylimidazole; AAc: Acrylic acid; AM: Acrylamide; DEA: N,N-diethylacrylamide; DEAM: Diethylaminoethyl methacrylate; DMA: N,N-dimethylacrylamide; HEAA: N-hydroxyethyl acrylamide; HEMA: 2-hydroxyethyl methacrylate; MAA: Methacrylic acid; MAPTAC: Methacrylamidopropyltrimethylammonium chloride; MMA: Methylmethacrylate; MOEP: 2-methacryloxyethyl acid phosphate; NVP: N-vinylpyrrolidone; PBS: Phosphate-buffered saline; pHEMA: Poly(2-hydroxyethyl methacrylate); PEGA: poly(lactic-co-glycolic) acid; SiMA: 1-(tristimethylsiloxy)silproplyl methacrylate; TRIS: Tris(trimethylsiloxy)sililpropyl methacrylate.

Since sterilization and conditioning processes may trigger premature leakage of a certain amount of the preloaded drug, incorporation of the nanocarriers after silicone hydrogel CL synthesis has also been recently explored [92]. Timolol was encapsulated in propoxylated glyceryl triacrylate nanoparticles, and then the nanoparticles incorporated to the CLs either during or after synthesis.

**Figure 4.** Dexamethasone release profiles from 200 µm thick hydrogels containing 0, 2, 4 or 6% of silica shell crosslinked micelles. The hydrogel without micelles attained the plateau at 50 h, releasing 90% of the drug loaded. Hydrogels that contained crosslinked micelles loaded with dexamethasone were able to control the release over 30 days. Reproduced with permission from [91] © John Wiley and Sons.
Incorporation of monomers with enhanced affinity for the drug

Copolymerization of the monomers used to fabricate CLs with small proportions of other monomers bearing specific groups to interact with certain drugs has also received some attention. The nature and the proportion of functional monomers should be chosen taking into account the compromise between the achievement of the functionality and the maintenance of the morphology, dimensions, optical clarity and biocompatibility of the CLs. pHEMA hydrogels copolymerized with ionizable monomers, for example, methacrylamide propyltrimethylammonium chloride, 2-methacryloxyethyl phosphate or methacrylic acid (MAA), have been shown to be able to capture/release small molecules using ion-exchange reactions [93,94]. When the CL is immersed in a solution of an ionizable or protonizable drug, for example, azulene or naphazoline, this can interact with the oppositely charged groups of the network. Once applied on the eye, the CL releases the drug by an exchange with Cl⁻ or Na⁺ ions of the tear fluid. As an example, pHEMA-based hydrogels prepared incorporating an anionic monomer (MAA or 2-methacryloyloxyethyl hydrogen succinic acid, MOESA, in 1–10% wt) and a silyl-containing monomer (3-methacryloxypropyltrimethylsiloxy)silane (MPTS), have shown enhanced ability to take up ofloxacin, compared with neutral and cationic (methacrylamide propyltrimethylammonium chloride) hydrogels. The CLs were soaked in 0.3% ofloxacin and 0.85% NaCl pH 6.5 solution for 3 h. The amount of ofloxacin loaded was dependent on the pH, being higher at pH 6.5 and 7 and lower at pH 5 and 8 due to the zwitterionic character of the drug. The release was sustained for several hours in 0.9% NaCl. Anionic hydrogels that did not bear silyl-groups released 85% drug in 4 h (Figure 6), while those having silyl-groups showed a slower release [95]. p(HEMA-MPTS) lenses containing MAA could also uptake other antibiotics (gatifloxacin and moxifloxacin) at a greater extent than...
etaficon A and polymacon, and provided in vivo drug concentrations in the cornea and the aqueous humor that were higher than those attained with commercial eye drops [96].

Interpenetration of hydrophilic pHEMA and hydrophobic silicone networks has been explored as a way to prepare timolol-eluting CLs [97]. Increasing the content in silicone network up to 35%, the oxygen permeability was notably enhanced (40.5–118 barrer) while the content in water (40–26%) and the uptake of timolol decreased (35.2–26 mg/g when soaked in 2 mg/ml, and 16.14–13.30 mg/g when soaked in 1 mg/ml). The release rate (see conditions in Table 4) was also slower for CLs with larger content in silicone network.

An alternative is to increase the affinity of the CL networks for relatively hydrophobic drugs without inducing irreversible binding consists in the use of cyclodextrins. These oligosaccharides form inclusion complexes with a variety of drugs and maintain or even enhance this capability when they are fixed in a polymeric network. The affinity of the cyclodextrins for the drug can then be exploited as the driving-force for the loading and the control mechanism for the release [98]. Cyclodextrins can be incorporated during CL synthesis, as a monofunctionalized β-cyclodextrin [99], or in a second step once the CL has been prepared [100].

pHEMA networks incorporating monofunctionalized β-cyclodextrin have shown improved capability to uptake puerarin, an active substance that may alleviate glaucoma and ocular hypertension. In in vivo experiments (in rabbits), pHEMA/β-CD3 (the CL with the highest cyclodextrin content) exhibited longer mean residence times of puerarin in tear fluid than those provided by pHEMA CLs and 1% puerarin eye drops. The puerarin concentration in the aqueous humour of rabbit reached a maximum of 0.81 µg/ml after wearing the pHEMA/β-CD3 CLs soaked in 0.802 mg/ml solution for 4.81 h (Figure 7) [97]. However, copolymerization of cyclodextrin monomers usually results in an increase in the rigidity of the network and a change in water content [100]. Postfunctionalization with cyclodextrins of already preformed lenses aims to avoid changes in the mechanical and optical features of the starting CLs [100]. Cyclodextrin units can be anchored to pHEMA networks having small proportions of glycidyl methacrylate. To do that, the hydroxyl groups of cyclodextrin react with the epoxy groups of glycidyl methacrylate under mild conditions. Pendant cyclodextrins have been shown to be able to reduce the friction coefficient of the hydrogels, to enhance 15-fold the amount of diclofenac loaded, to prevent a premature discharge of the drug in multipurpose storage liquids and to sustain drug release (Table 4) for 2 weeks [100]. If loaded with miconazole, the cyclodextrin-grafted CL completely prevented Candida albicans biofilm formation in vitro [102].

**Molecular imprinting technique**

The success of the incorporation of monomers with enhanced affinity for the drug can be further improved applying molecular imprinting, which pursues the optimization of the spatial distribution of the functional monomers to achieve the maximum efficiency of the interactions between the drug and the polymeric network. The technique consists of using the drug molecules as templates during polymerization in order to induce the arrangement of the monomers as a function of their affinity for the drug. The conformation of the monomers is fixed during polymerization and, once the drug molecules that acted as templates are removed, cavities (named imprinted pockets) with the size and the most suitable chemical groups to interact with the drug are obtained. Imprinted networks can recognize with greater affinity and specificity the drug molecules during soaking, compared with the networks synthesized in the absence of template (nonimprinted networks).

---

**Figure 6. Ofloxacin release profiles from contact lenses with 0, 1, 3, 5 and 10% wt of methacrylic acid.** 85% of the drug loaded was released from the contact lenses within 4 h. Reproduced with permission from [95] © John Wiley and Sons.

**Figure 7.** Ofloxacin release profiles from contact lenses with 0, 1, 3, 5 and 10% wt of methacrylic acid. 85% of the drug loaded was released from the contact lenses within 4 h. Reproduced with permission from [95] © John Wiley and Sons.
This technology, which was initially developed for endowing rigid highly crosslinked polymeric systems with the ability to recognize target species [103,104], has been successfully adapted to the synthesis of medicated CLs [105,106].

The formation of the imprinted pockets strongly depends on the stability and solubility of the functional monomers–template assemblies during polymerization. If the molar ratio in the complex is not appropriate or if the assemblies dissociate to some extent during polymerization, the functional monomers would not correctly arrange around the template molecule, resulting in a small difference between imprinted and non-imprinted (conventional) CLs [107–109]. Furthermore, the low crosslinking density of CLs and their swelling in the preservation liquids or in the lachrymal fluid may compromise the physical stability of the imprinted pockets. This drawback can be overcome by maximizing the interactions of drugs and the network in terms of number of binding points that can synergistically favor the binding process. Research on drug-imprinted CLs has focused on several therapeutic groups, namely β-adrenergic antagonists (timolol), antimicrobials (norfloxacin), antihistamines (ketotifen), carbonic anhydrase inhibitors (acetazolamide) and anti-inflammatory drugs.

CLs imprinted for timolol were the first successfully proven in vivo (in rabbits) [26]. A detailed study of the influence of the nature of the functional monomer and the backbone monomer, the degree of crosslinking and the drug:functional monomers ratio on loading and release performance of the lenses has been carried out [110–114]. Timolol-imprinted ultrathin N,N-diethylacrylamide-based lenses (14 mm diameter and 0.08 mm center thickness) loaded 34 µg drug per lens, while the conventional lenses took up 20 µg drug per lens. Timolol levels in rabbits’ lachrymal fluid were monitored after the insertion of imprinted and nonimprinted lenses or after the instillation of timolol eye drop solutions of 0.068% (total dose 34 µg) or of 0.25% (commercial solution, total dose 125 µg; Figure 8) [26]. The imprinted and the nonimprinted CLs displayed the maximum ocular level at around 5 min, followed by monoexponential decay, which was prolonged for 180 min in the case of the imprinted CLs, compared with the 90 min of the nonimprinted ones. Timolol applied as drops was flushed out of the eyes in less than 60 min. Furthermore, imprinted CLs led to 3.3-fold and 8.7-fold area under the timolol concentration–time curve than the nonimprinted ones and eye drops, respectively. These results proved that imprinted CLs reduce the precorneal elimination of the drug compared with the eye drops and, as a consequence, a much smaller amount of drug is needed to achieve the desired therapeutic levels.

**Key Term**

**Drug-imprinted contact lenses:** Contact lens in which the monomers adopt a designed spatial arrangement by using drug molecules as templates during polymerization. Such an arrangement allows the creation of pockets (imprinted cavities) with the size and chemical groups suited for hosting with the target drug.
pHEMA-based hydrogels prepared with norfloxacin: acrylic acid (AAc) molar ratios ranging from 1:2 to 1:16 revealed that imprinted hydrogels synthesized using the optimal 1:4 molar ratio (as estimated from calorimetric titration) released norfloxacin at a rate 3.5-times lower than non-imprinted hydrogels, providing a 24-h controlled release. Imprinted hydrogels of various contents in AAc and different thicknesses exhibited similar loading/release behavior, evidencing the robustness of the imprinting technique [115]. The relevance of choosing the adequate template: functional monomer molar ratio has also been demonstrated for CLs imprinted for diclofenac [116], prednisolone acetate [117] and ciprofloxacin [118]. In this later study, imprinted p(HEMA-TRIS) lenses prepared with high functional monomer (MAA): template ratio (8:1 and 16:1) sustained release for longer, although released less drug than those prepared with lower monomer/template ratio (4:1).

The Byrne group has designed ketotifen-imprinted CLs using functional monomers that have chemical groups that resemble the structure of the amino acids present in the physiological histamine H1-receptor [119]. The guiding hypothesis was that if antihistamines have high affinity for the H1-receptor, a hydrogel with similar chemical functionality would bind the antihistamine tightly, increasing the loading and delaying release kinetics. In fact, CLs prepared with pHHEMA (92 mol%), crosslinker (5 mol%) and the most biomimetic monomers (3 mol%), namely AAc, NVP and acrylamide (AM), designed as poly(HEMA-co-AAc-co-AM-co-NVP-co-PEG200DMA), demonstrated six- to three-fold greater loading than conventional CLs and networks containing one or two functional monomers, respectively. Release of therapeutically relevant amounts of ketotifen in artificial lachrymal fluid containing lysozyme (see Table 4 for experimental details) was sustained for several days [120,121]. In vivo studies (in rabbits) carried out with ketotifen-imprinted poly(HEMA-co-AAc-co-AM-co-NVP-co-PEG200DMA) CLs (100 µm thickness, 11.8 mm diameter) evidenced the possibility of attaining a constant tear film concentration of 170 ± 30 µg/ml (well above the effective concentration of 30 µg/ml) for 26 h, after an initial burst in the first 4 h with Cmax of 214 µg/ml. Nonimprinted CLs provided a Cmax of 140 µg/ml in the first hour and then drug concentration decreased exponentially within 10 h (Figure 9). Eye drops quickly provided a Cmax of 143 µg/ml, but the drug disappeared from the tear film in less than 45 min.

![Figure 8. Timolol tear fluid concentration–time profiles after application of drug-loaded imprinted and nonimprinted contact lenses or instillation of eye drops. The doses were 34 µg for imprinted contact lenses, 21 µg for nonimprinted contact lens, and 34 µg and 125 µg when 0.068% or 0.25% timolol eye drops were instilled, respectively. Each point represents the mean ± standard deviation (n = 3–5). Reproduced with permission from [26] © Elsevier.](image)

![Figure 9. In vivo ketotifen fumarate tear fluid concentration profile from imprinted poly(2-hydroxyethyl methacrylate-co-acrylic acid-co-acrylamide-co-N-vinylpyrrolidone-co-PEG200DMA) lenses (squares), nonimprinted lenses (circles) and eye drops (0.035% solution Zaditor®; triangles) in white New Zealand rabbits. Reproduced with permission from [27] © Elsevier.](image)
Therefore, ketotifen-imprinted CLs rendered notably higher mean residence time, area under the concentration time curve and bioavailability than conventional CLs and eye drops [27].

The bioinspired selection of functional monomers has also been applied to the design of CLs imprinted for carbonic anhydrase inhibitors (CAIs; e.g., acetazolamide, ethoxzolamide) [122]. The active site of carbonic anhydrases consists of a cone-shaped cavity that contains a Zn$^{2+}$ ion coordinated to three histidine residues in a tetrahedral geometry with a solvent molecule as the fourth ligand [123]. Acetazolamide inhibits the activity of the enzyme by binding to the Zn$^{2+}$ ion. pHMA-based CLs prepared with 4-vinylimidazole (4-VI) that resembles histidine and a source of Zn$^{2+}$ ions (Figure 10) showed network/water partition coefficient ($K_{N/W}$) values three-times greater than those prepared with 1-vinylimidazole, and also provided a better control of drug release [122]. Similar improvements were observed when pHMA was replaced by other the backbone monomers (NVP/HEMA) maintaining the biomimetic functional groups [124]. Nonbioinspired imprinted networks have also been shown to be useful for loading and release of dorzolamide [125].

**Conclusion & future perspective**

The idea of using CLs as delivery systems of ophthalmic therapeutic agents was postulated 50 years ago, but these combination products can still be considered to be in their early youth. Since the first attempts to use conventional commercial CLs as not only vision correctors but also as platforms for management of ocular pathologies, the CLs have revealed a limited affinity for ophthalmic drugs and consequently poor capability for controlling drug release. Notable advances regarding materials to use as components of CLs have been mainly focused on the improvement of oxygen permeability, visual acuity and wearer comfort, paying little attention to a potential application for drug delivery. Nevertheless, the efforts of clinicians to screen, among the commercially available ones, the CLs with better performance as drug platforms have generated information of great interest for further advances in the field. In fact, certain commercial CLs could behave as interesting bandages, which can be readily loaded just by soaking, for ensuring drug ocular levels up to a few hours, compared with the more limited performance of eye drops and other topically applied drug formulations. Controlled release could be successfully attained for demulcent macromolecules.
that have smaller diffusion coefficients than low molecular weight drugs [126–128].

The last decade has witnessed the dawn of novel approaches for development of true drug/CL combination products. Among others, two approaches have been revealed as the most promising ones since they do not compromise the optical features of the CLs: sequential or simultaneous soaking of commercial CLs in drug solution and vitamin E solution, in such a way vitamin E enhances drug/network partition coefficient and regulates the diffusion in/out of the drug and water; and application of the molecular imprinting approach during synthesis of extended-wear CLs. The first approach could benefit from the fact that the synthesis process of the CLs does not need to be necessarily altered, and thus any CL could be loaded with any drug, although the loading involves several steps and premature discharge in the multipurpose solutions cannot be completely avoided. The second approach requires a detailed knowledge about the interactions of the target drug with the monomer constituents of the CLs to create efficient drug/CL pairs. Imprinted CLs are so far the ones that can most prolong the release profiles.

It is obvious that many questions still remain to be answered before wider clinical use of drug/CL combination products, mainly regarding when and how the CLs should be loaded and, if possible, reloaded and, more importantly, what dose and release rate are the most convenient for each pathology/CL wearer. The popularization of the use of CLs (currently ~125 million wearers: [209]) and the already proven clinical benefits that CLs can provide to ocular therapeutics are undoubtedly strong driving forces for the emergence of the first drug/CL combination products in the market in the very near future.

Financial & competing interests disclosure
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Executive summary

The value of contact lenses as ocular drug-delivery platforms
- Drugs are loaded onto contact lenses (CLs) by soaking in drug solutions.
- Sustained release to the postlens tear film, slower turnover and minimized loss lead to greater and prolonged drug concentrations in aqueous humor compared with topical drug formulations.
- Less dose may be required to attain the therapeutic effects, as well as excellent optical acuity and biocompatibility.

Limitations of commercial CLs
- There is limited loading of hydrophilic, nonionic drugs.
- Irreversible binding of ionic drugs to pHEMA-based CLs and of hydrophobic drugs to silicone hydrogels can occur.
- Drug is delivered too rapidly.

Coadjutants for improving drug loading/release performance of conventional CLs
- Incorporation of the drug as a polymer film during CL synthesis. An optical window is needed due to opacity of the film.
- Adsorption of an amphiphilic molecule, for example, vitamin E, that favors drug interaction with the CL and delays drug release is a simpler and more efficient method.

Novel approaches for drug/CL combination products
- Drug-loaded nanocarriers dispersed in the CL matrix can efficiently regulate drug release. Physical stability of the nanocarrier and avoidance of premature leakage have to be ensured.
- Random copolymerization with ionic monomers or grafting of cyclodextrins to CL components may notably improve drug/network partition coefficient.
- Drug-template polymerization (molecular imprinting) of the CL monomers results in high-affinity domains with the chemical groups more suitable for specific uptake of the drug of interest, this results in high loading and prolonged release.

Regulatory aspects
- The primary mode of action will determine the regulatory process as device (Center for Devices and Radiological Health) or as drug (Center for Drug Evaluation and Research).
References

Papers of special note have been highlighted as:
- of interest


- Early application of hydrophilic contact lenses for drug delivery.

- Addresses specific aspects of the technical, quality and regulatory requirements of drug-eluting medical devices.

- Early application of hydrophilic contact lenses for therapeutic purposes.

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Soft contact lenses for controlled ocular delivery: 50 years in the making


63 Krejci L, Brettschneider I, Praus N. Comparative study of fluorescein release from various types of therapeutic hydrogel contact lenses into the eye of rabbit. Ophthalmic Res. 6, 291–300 (1974).


72 Phan CM, Subbaraman LN, Jones L. In vitro uptake and release of natazymin from conventional and silicone hydrogel contact lens materials. Eye Contact Lens 39, 162–168 (2013).


- Intraocular pressure reduction by daily contact lenses was comparable with that by eye drops, but with only 20% of drug dose, which suggests higher drug bioavailability for contact lenses. Inclusion of vitamin E into continuous wear lenses enables intraocular pressure reduction during a 4-day treatment.


88 Danion A, Arsenault I, Vermette P. Antibacterial activity of contact lenses bearing...


• Contact lenses that include side-chain anionic groups and silyl groups can load sufficient amounts of antimicrobial agents and release them in a sustained way, providing greater and more sustained drug levels in cornea and aqueous humour.


• The first attempt to adapt the molecular imprinting technology to the design of drug-eluting contact lenses.


• Selection of functional monomers for imprinted networks based on bioinspired criteria.


• Relevance of release conditions on the kinetics of drug release is pointed out. A prototype that mimics ocular in vitro flow conditions is proposed for drug-release experiments.


Websites


206 Silbert JA. Therapeutic uses of silicone hydrogels. www.siliconehydrogels.org/editorials/oct_05.asp (Accessed April 2013)

