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Review article

Testing drug release from medicated contact lenses: The missing link to predict *in vivo* performance

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ABSTRACT

Contact lenses (CLs) offer a wide variety of advantages as ocular drug-releasing platforms, but the feasibility of medicated CL development is constrained by numerous scientific, technological, and regulatory challenges. One main difficulty is the setting of release rate specifications for each drug, since at present there are no standardized *in vitro* release models that can appropriately predict the performance of drug-eluting CLs once placed onto the eye. CL-adapted release tests may provide knowledge on how the drug release pattern should perform *in vivo* to trigger and maintain the therapeutic effects for both anterior and posterior ocular tissues. Moreover, *in vitro* release tests are valuable tools for quality assessment during production and to investigate the effect of a change in composition or process variables. This review aims to shed light on biorelevant ways of evaluating *in vitro* drug release from CLs and the feasibility of establishing *in vitro-in vivo* correlations (IVIVC) to predict *in vivo* performance. First, general guidelines and Pharmacopeia release tests for topical ophthalmic formulations as well as *in vitro* release tests implemented for drug-CLs in the last two decades are analyzed. Then, development of an appropriate method to investigate IVIVC is attempted from the few papers simultaneously reporting *in vitro* release profiles and either *in vivo* release or therapeutic response. Finally, key points to be considered for *in vitro* testing drug release from a medicated CL are suggested to pave the way to the clinical arena.

1. Introduction

The world's first drug-releasing contact lens (CL) was recently approved by the appropriate regulatory bodies in both Japan and Canada [1,2]. Although this approval was only specific to a drug (ketotifen)-CL combination, it nonetheless represents a significant milestone in the already long journey to obtain drug-CL combination products. Indeed, 2021 marked the 60th anniversary of the patent by Otto Wichterle and colleagues on the preparation of poly(2-hydroxyethylmethacrylate), pHEMA, soft CLs by the spin casting process [3]. pHEMA hydrogels revealed excellent optical properties and biocompatibility [4,5], and their moderate water content immediately caught the attention of Wichterle and Lim as a suitable compartment to host drugs, as stated in their US Patent 3,220,960 "*medicinally active substances (…) may be dissolved in the aqueous constituent of the hydrogels to provide medication over an extended period*" [6].

In these pioneering patents, the potential for using soft CL materials as drug delivery devices that can both act as an optical correction device and also provide therapeutic treatment for ocular diseases was implicit. However, the commercialization of both applications was not so straightforward. After the patent publication in 1961 it took Bausch + Lomb a further 10 years to bring soft CLs to the market (SofLens in 1971, 50 years ago), and another 50 years for a company to obtain approval for a true drug delivering CL (Johnson & Johnson's ACUVUE Theravision) [1,2]. The enormous amount of time and research efforts invested up to this point are proof of how difficult it is to develop drug-releasing CLs (which are "combo devices" as they are considered both a device and a drug product), as opposed to just a CL device that solely corrects a visual deficit [7].

There are several advantages to using CLs that elute drugs onto the ocular surface over conventional eye drops. It is known that a large number of patients prescribed drops are non-compliant with instilling

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them at the dosing frequency they are advised to, with non-adherence ranging from 5% to 80% for patients prescribed glaucoma medications [8]. A medicated CL that was inserted and worn for an extended period of time would overcome such an issue. Only a small and varying volume of an eye drop effectively contacts the ocular surface, which is then rapidly cleared from the eye due to rapid tear fluid turnover or absorbed through the conjunctiva. Combined with the low permeability of the cornea, it is estimated that less than 5% of the instilled drug is bioavailable [9]. In contrast, a CL may provide more accurate dosing as a known amount of loaded drug (or drugs) is placed on the surface of the eye. The presence of a CL delays tear turnover in the post-lens tear film, thereby creating a higher drug concentration gradient towards the cornea and favoring flux into the tissue. As a result, the CL approach minimizes unproductive drug loss while increasing ocular bioavailability to more than 50% [10]. Personalization of treatments, improved patient compliance, and even stimuli-responsive control of drug release are other potential advantages [11]. Integration of diagnosis components into the CLs may open the door to advanced ocular biosensors that can perceive changes of biorelevant biomarkers in real-time. These theranostic devices would not only alert the patients to potential worsening of their disease, but also be able to adjust the drug release rates to match the therapeutic amounts needed to treat the relevant disease [12–14].

Despite the apparent advantages of a CL-based drug delivering device over topical drops, transforming a CL into a drug-releasing platform faces numerous, formidable scientific, technological and regulatory challenges. To a large extent, these challenges are related to two major issues: a) the aqueous phase of the CL is insufficient by itself to host and control the release of the required dose; and b) the drug release rate to maintain therapeutic levels for an extended period of time is unknown and cannot be directly extrapolated from previous data on eye drops.

Most commercially available CL materials lack affinity for ophthalmic drugs. When these materials are soaked in a drug solution, the drug molecules diffuse towards the aqueous phase of the CL until the concentration in both the loading solution and the aqueous phase of the hydrogel is at equilibrium. If there are no interactions or binding of the drug to the CL polymer network, then the drugs will be released very rapidly when the drug-loaded CL is applied onto the ocular surface. In this situation, there are no real advantages of the drug-CL combination in comparison to an eye drop. Strategies to address poor loading and limited control of drug release have been widely explored and include copolymerization with functional monomers, incorporation of the drug into nanocarriers, and specific diffusional barriers [11,14,15].

The second issue of how to relate the *in vitro* release profiles with *in vivo* performance is even more complex and has been largely unexplored [16]. Even if the *in vivo* requirements for the drug release could be theoretically predicted from pharmacological demands and pharmacokinetic clearance, there are still a lack of standardized *in vitro* release models that can be used to predict the performance of drug-loaded CLs once placed onto the eye.

The purpose of this review is to shed light on biorelevant ways of evaluating *in vitro* drug release from CLs and the feasibility of establishing *in vitro-in vivo* correlations (IVIVC) to predict *in vivo* performance. First, the review will briefly address the regulatory status and specific opportunities and challenges of drug-releasing CLs. Regulatory agency guidelines and drug release tests collected in the Pharmacopoeias and specialized reports are examined and their possible adaptation to medicated CL discussed. The review covers the variety of *in vitro* release tests used to examine drug-CL interactions in the last two decades. Although the information available on *in vivo* drug release profiles from CL materials to tear fluid is still limited, IVIVC are attempted. Papers reporting both *in vitro* release profiles and either *in vivo* release or therapeutic response are analyzed in detail. Finally, key points to be considered for *in vitro* testing drug release from a medicated CL are highlighted. The information reviewed in this paper may serve as a guide to harmonize drug-CLs *in vitro* testing and facilitate the translation of medicated CLs to the clinical arena.

2. Medicated contact lenses as drug-device combination products

2.1. Regulatory status

CLs are ocular prosthetic devices (i.e., ocular medical devices) used by approximately 150 million people worldwide, and they can be worn to correct vision impairment or for cosmetic or therapeutic reasons [17]. Regarding vision correction, CLs have some advantages over spectacles. Some patients report that their visual acuity is better with CLs than with glasses. CLs do not become foggy due to changes in temperature, humidity or when breathing through a protective mask. Additionally, they do not move or fall off during high-intensity activities. In contrast, the use of CLs poses increased risk of ocular infections, inflammation, and dry eyes. Also, as the age of the users increases, the chance of discontinuing lens wear increases due to CL associated dryness complaints [18].

Regulatory agencies, such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), classify CLs according to their intended use:

(1) non-therapeutic CLs – intended for correction of refractive ametropia, aphakia, and presbyopia;
(2) specialized use CLs – these include orthokeratology (ortho-K) lenses that cause a temporary change in corneal curvature to eliminate any refractive error and decorative (plano) lenses for fashion/cosmetic purposes;
(3) therapeutic CLs – these serve as a tool in the management of a wide variety of ophthalmic disorders refractory to other treatment modalities, including pain relief, promotion of epithelial healing, corneal protection from mechanical damage, correction of an irregular corneal surface, and deliver medication [19,20]. Drug release could be pursued for treatment of both general ocular diseases (e.g., seasonal allergies, as is the case for the approved ketotifen-releasing CL) and CL-related disorders (e.g., infection or dry-eye syndrome).

According to the FDA definition, a medical device is "*an instrument, apparatus, implement, machine (…) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes*" [21]. Therefore, a medical device is expected to achieve its purpose by means of physical or electronic actions. In contrast, drugs achieve their action by chemical actions. CLs as medical devices (as well as the lens care solutions) are under strict regulatory oversight from their design to post-marketing surveillance, with the aim to ensure patient safety and device efficacy. According to the risk profile that the patient may be exposed to, daily-wear CLs are labelled as Class II medical devices (moderate risk), while extended-wear CLs and ortho-K CLs are labelled as Class III medical devices (higher risk). Readers interested in a comparative analysis of FDA and European regulation on CLs should refer to a recent review [22].

Overall, the many hurdles that should be solved to achieve the regulatory approval involve largely time (up to 31 months in USA) and investment (up to 77% of the total expenses required to bring the product to the market) [23]. These expenditures cause substantial delays in the time a new product takes to become commercially available and may impede industrial innovations in CL materials and new designs. Transforming a CL into a drug-releasing CL requires changes in the composition and design that necessitate additional regulatory steps.

Furthermore, if a drug-CL only addresses a small market segment, then commercialization may not be financially viable.

Even when CLs are only used as ophthalmic medical devices, the potential interactions of the polymer network to attract oppositely charged or hydrophobic drugs should be taken into consideration when the wearer has to apply eye drops with the lens *in situ*. Some reports have warned about the need to space the time between applying an eye drop and putting the CL onto the surface of the eye to avoid loss of drug by irreversible uptake by the CL [24].

CLs designed for the purpose of drug-releasing platforms are considered as drug-device 'combination products'. As defined in 21 CFR 3.2(e), a combination product is comprised of two or more regulated components (i.e., in this case a drug and a device). Each component retains its regulatory identity, and additionally the combination product as a whole is subject to specialized regulatory requirements [25]. A drug-releasing CL is classified as the type of device coated/ impregnated/otherwise combined with a drug in which the device has an additional function in addition to delivering the drug [26]. In the USA, evaluation of a drug-releasing CL is assigned to a certain agency center depending on which component provides the primary mode of action (PMOA). The agency center with the primary jurisdiction then works together with the other agency centers to carry out the adequate premarket review.

In the case of a drug-releasing CL used for vision correction that simultaneously delivers a drug for an ocular disease (device-led combination product), substantial equivalence to a predicate product (e.g., the CL device solely) does not apply, since the addition of the drug results in a new intended use and/or implies a change in the technological characteristics, which in turn raises additional questions regarding safety and effectiveness [27]. If the drug makes the greatest contribution, for example, a plano power bandage CL that does not correct any residual refractive error but releases a drug onto the ocular surface, then the drug-led combination product would follow the "new drug application" pathway and demonstrate the safety and the effectiveness of the product in the new conditions of use. Although examples of drug-releasing CLs are not included in the FDA guidelines, illustrative examples that refer to related device-led and drug-led combination products may be useful to understand the long regulatory pathway for a drug-CL combination product [27].

2.2. Drug-eluting CLs in clinical trials

The lack of predicate products implies that the safety and efficacy of a drug-releasing CL should be demonstrated in clinical trials. The search in ClinicalTrials.gov of "contact lens AND drug" (April 2021) led to 344 outcomes. Most clinical trials referred to safety studies of new CL or drugs after ocular or oral administration when they were administered sequentially, not as a combination product. Only 16 clinical trials referred to true drug-CL combination products (Table 1). In addition to the antihistamine/mast cell stabilizer ketotifen, other drugs of interest include those intended for the treatment of macular edema (dexamethasone), glaucoma and ocular hypertension (e.g., latanoprost, timolol and dorzolamide), pain management after photorefractive keratectomy, dry eye symptoms, and persistent epithelial defects.

Although in most clinical studies, the changes in CL composition or technologies to prepare the drug-releasing CL are not disclosed, the application of novel technologies is evident in some cases. As an example, NCT04747808 refers to a Phase 2a study of safety, tolerability, and efficacy of CLs that have been loaded with bimatoprost by means of a proprietary printing technology (MediPrint™). The company disclosed that using an FDA approved drug and an FDA approved CL led to a shorter regulatory course via a 505 (b) (2) pathway [28]. Of note, the average age of the five patients in the trial was 77.4 years old and none had previously worn CLs. The bimatoprost-loaded CLs were well tolerated during the seven days of continuous wearing, which supports the short-term safety of these lenses [29].

Patient and practitioner acceptability is a critical issue for the success of drug-releasing CLs in the marketplace. Physiological conditions associated with old age and vision disorders may hinder the insertion and removal of the CLs [30]. In a recent survey, most patients suffering from an ophthalmic disease indicated that they would prefer to use drug-releasing CLs instead of eye drops, if the combination product was less time consuming and reduced the required frequency of application [31]. Another important consideration is that CL-fitters in some countries are licensed to prescribe CLs but not drugs. Therefore, it is not entirely clear who would be permitted to prescribe drug-releasing CLs, and the regulations will differ between various countries. In addition to legal issues, there are still many other issues to be solved, including the stability of the drug once loaded in the CL, the expiration date, the sterilization protocol for labile drugs, assurance of sterility, disposable procedures, and how to reload the drugs [10,32,33].

3. Guidelines and pharmacopoeia methods for testing ocular drug release

The safety and efficacy of a drug product or a drug-device combo product are ultimately demonstrated in a clinical trial. However, studies with human participants are the final step after numerous preclinical studies involving laboratory testing and a variety of *in vivo* tests. *In vivo* testing in animal models should follow very strict ethical rules and adhere to the 3Rś principles; namely, 'replace' (search for alternatives), 'reduce' (minimize the experiments), and 'refine' (avoid distress) [34]. Moreover, animal testing can be expensive and not suitable for early-stage testing. *In vitro* drug release tests are very valuable for quality assurance since they reveal the robustness and reproducibility of a drug product. Additionally, these tests help identify the critical elements of a drug-device that are important for *in vivo* performance [35]. Therefore, *in vitro* models that better predict the performance of these devices may significantly facilitate the research and development process, thereby reducing both time and cost to bring these products to market.

3.1. Determining drug bioavailability from drug-CLs using mathematical models

The advantages of drug-releasing CLs as ocular drug delivery systems are commonly compared with conventional eye drop administration. A simple mathematical model to explain the concentration of drugs on the ocular surface following an eye drop instillation was developed by Lang and Stiemke [36]. This model assumes that the tear fluid layer on the ocular surface behaves as a continuously stirred reactor (Fig. 1A). Once an eye drop is deposited on the eye, the volume that cannot be contained in the tear layer spills over, and the rest of the volume is rapidly mixed with the tear fluid (Fig. 1B).

If no overflow occurs (i.e., drop volume is very small), the initial drug concentration on the ocular surface ($C_R(0)$) can be estimated as the ratio of the dose applied (Q_i) to the volume of the tear fluid layer (V_R). Since there is a hydrodynamic flow of tear fluid from temporal to the nasal segments of the eye ($\dot{V}$, the flow entrance of new tear fluid is the same as the flow of drainage) [37], the total amount of drug in the tear layer decreases exponentially according to

$$Q_R(t) = Q_i \cdot exp\left(-\frac{\dot{V}}{V_R}\bullet \mathrm{t}\right) \quad (1)$$

In this equation Q_R(t) represents the amount of drug at time t in the tear fluid, Q_i the initial amount (dose) instilled, $\dot{V}$ the tear flow, and V_R the volume of tear fluid.

Similarly, drug concentration in the tear fluid layer decreases along time as follows

$$C_R(t) = \frac{Q_R(t)}{V_R} = C_R(0) \cdot exp\left(-\frac{\dot{V}}{V_R}\bullet \mathrm{t}\right) \quad (2)$$

Table 1
Clinical trials of CLs loaded with a drug or an active substance according to a ClinicalTrials.gov search for "contact lens AND drug" after refinement for "not yet recruiting, recruiting, enrolling by invitation, active not recruiting, terminated, or completed" (April 2021).

Clinical study	Status	Study Title	Contact lens	Drug	Drug loading	Condition/outcome measures	Phase
NCT04225611	Not yet recruiting	Therapeutic Contact Lens Drug Delivery System (TCL-DDS) in Patients With Recurrent Cystoid Macular Edema.	Methafilcon (Kontur Kontact Lens Company, Hercules, CA)	Dexamethasone	TCL-DDS consisted of a dexamethasone-polymer film encapsulated inside a CL.	Cystoid macular edema. Occurrence of CL related ocular infection, corneal epithelial defect, and ocular hypertension greater than 28. Changes in OCT macular thickness, and visual acuity.	1/2
NCT00432757	Completed	Evaluation of Efficacy and Safety of an Anti-Allergy Drug With a Contact Lens in Allergic Conjunctivitis.	Etafilcon A (1-Day ACUVUE, Vistakon, Florida, USA)	Ketotifen	CLs loaded 0.019 mg of ketotifen.	Allergic conjunctivitis. Ocular itching; conjunctival, ciliary, and episcleral redness; chemosis and mucous discharge; tearing and lid swelling	3
NCT00445874	Completed	Evaluation of Efficacy and Safety of an Anti-Allergy Drug With a Contact Lens in the Treatment of Allergic Conjunctivitis.	Etafilcon A (1-Day ACUVUE, Vistakon, Florida, USA)	Ketotifen	CLs loaded 0.019 mg of ketotifen.	Allergic conjunctivitis. Ocular itching; conjunctival, ciliary, and episcleral redness; chemosis and mucous discharge; tearing and lid swelling.	3
NCT04500574	Not yet recruiting	Latanoprost Eluting Contact Lens for Treating Glaucoma and Ocular Hypertension.	Methafilcon (Kontur Kontact Lens Company, Hercules, California)	Latanoprost	Latanoprost eluting CLs consisted in a thin film of latanoprost-polymer film encapsulated within the periphery of the lens.	Glaucoma. Ocular hypertension. Adverse events as assessed by ocular infection, corneal epithelial defects, or cystoid macular edema; changes in intraocular pressure; tolerability and comfort.	1
NCT04747808	Completed	Study of LL-BMT1 in Patients With Elevated Intraocular Pressure.	7-days continuous wearing CLs	Bimatoprost	Drug-printed CLs.	Primary open angle glaucoma and ocular hypertension. Adverse event rate; IOP elevation and changes.	2
NCT00889252	Completed	Safety Study of a Contact Lens With Ketotifen in Healthy, Normal Volunteers.	-	Ketotifen	-	Allergic conjunctivitis. Ocular itching; conjunctival, ciliary, and episcleral redness; chemosis and mucous discharge; tearing and lid swelling	3
NCT00569777	Completed	Safety Study of a Contact Lens With Ketotifen in Healthy, Normal Volunteers.	-	Ketotifen	-	Allergic conjunctivitis. Ocular itching; conjunctival, ciliary, and episcleral redness; chemosis and mucous discharge; tearing and lid swelling.	3
NCT02852057	Recruiting	Effectiveness and Safety of Timolol and Dorzolamide Loaded Contact Lenses.	Senofilcon A (ACUVUE Oasys, Vistakon, Fl, USA)	Timolol maleate and dorzolamide hydrochloride	CLs contained vitamin E as an additive for achieving extended release of the drugs.	Glaucoma IOP changes	1
NCT03848221	Completed	Direct Application of Systane Complete to Contact Lenses.	Daily disposable contact lens	Systane Complete; Sensitive Eyes Rewetting Drops.	Direct application of Systane Complete to CL.	Dry eye Contact lens complication Ocular surface damage; identifying dry eye disease	4
NCT03026257	Completed	Clinical Assessment of a HYDRAGLYDE® Regimen.	Lotrafilcon B (AIR OPTIX® plus HYDRAGLYDE®, Alcon, A Novartis Division)	Polyoxyethylene-polyoxybutylene; EOBO.	CLs were packaged in a blister solution containing the wetting agent polyoxyethylene-polyoxybutylene.	Myopia Hypermetropia Refractive errors *Ex vivo* total cholesterol uptake	-
NCT03392532	Completed	Comparison of Two Silicone Hydrogel Toric Contact Lenses.	Lotrafilcon B (AIR OPTIX® plus HYDRAGLYDE®, and AIR OPTIX® for Astigmatism, Alcon, A Novartis Division)	Polyoxyethylene-polyoxybutylene; EOBO.	-	Astigmatism. Percentage of lenses with axis orientation within ±30 degrees from the 90 degree axis.	-
NCT01918410	Completed	Effect of Contact Lens With Alginic Acid in Dry Eye Patients.	SEED 1dayPure moisture and SEED 2weekPure (SEED Co., Ltd., Tokyo, Japan)	Alginic acid	CLs were stored in a solution of alginic acid.	Dry eyes Difference of visual analogue scale for the ocular discomfort; tear lipid layer thickness; schirmer and tear breakup time tests; corneal fluorescein staining, and tear proteomic analysis.	-

(*continued on next page*)

Table 1 (*continued*)

Clinical study	Status	Study Title	Contact lens	Drug	Drug loading	Condition/outcome measures	Phase
NCT04283331	Recruiting	Anesthetic Impregnated Bandage Soft Contact Lens (BSCL) in Pain Management After Photorefractive Keratectomy (PRK).	Bandage contact lens (BCL)	Proparacaine	The BSCL were soaked in proparacaine hydrochloride 0.5%.	Myopia Hypermetropia Refractive errors Astigmatism Daily pain score; complete re-epithelialization and final refraction at post-operative	4
NCT03388138	Completed	Clinical Evaluation of Etafilcon A With Ketotifen.	Etafilcon A (1-Day ACUVUE, Vistakon, Florida, USA)	Ketotifen	CLs loaded 0.019 mg of ketotifen.	Visual acuity Monocular contact lens-corrected distance visual acuity; eyes with clinically significant slit lamp findings and with unacceptable lens fitting.	2
NCT03653650	Recruting	Autologous Platelet-rich Plasma in the Treatment of Persistent Epithelial Defects	Bandage contact lens (BCL)	Autologous platelet-rich plasma	Bandage CLs plus autologous platelet-rich plasma eye drops.	Persistent epithelial defect Persistent epithelial defect healing time; change in corneal sensitivity; uncorrected visual acuity, best corrected visual acuity; ocular pain; ocular surface symptoms, and frequency of adverse effects.	-
NCT04553432	Recruting	Dry Eye OmniLenz Application of Omnigen Research Study (DOORS).	OmniLenz® (NuVision®, Nottingham, UK)	Omnigen (Amnionic membrane)	OminLenz allows easy delivery and comfortable retention of Omnigen at the ocular surface.	Dry eye Change in dry eye symptoms, visual acuity, meniscus height, non-invasive tear breakup time, ocular surface staining and ocular redness.	4

In addition to drainage through the lacrimal puncta, tear film losses occur due to evaporation and absorption through the cornea, but the contributions of these two factors under healthy conditions are limited to 15-20% of total tear fluid losses [38]. In other words, the amount of drug that is transported from the eye mostly enters into the nasolacrimal duct at a rate of

$$Q_{out}(t) = Q_i \cdot \left(1 - exp\left(-\frac{\dot{V}}{V_R}\bullet \mathrm{t}\right)\right) \tag{3}$$

These equations do not consider drug penetration into eye tissue, but for most drugs that show poor ocular bioavailability, the model is still valid. Assuming that the drug penetrates through all ocular tissues by diffusion, the flux of drug from the tear fluid layer (J) depends on drug diffusion through the eye tissue (D), the oil-water partition coefficient (K), the drug concentration (C_R(t)), and the thickness of the diffusional barrier (h) as follows

$$J = \frac{DK}{h}\bullet \mathrm{C_R(t)} \tag{4}$$

Thus, the rate of absorption can be calculated as

$$\dot{Q}_A(t) = J\bullet \mathrm{A} = \frac{\mathrm{DKA}}{\mathrm{h}}\bullet \mathrm{C_R(t)} \tag{5}$$

The amount absorbed at a given time is estimated by integration to be

$$\frac{Q_A(t) = \frac{DKA}{h\bullet V}\bullet \mathrm{Q_{out}(t)} = \mathrm{P}\bullet \mathrm{A}}{\dot{V}\bullet \mathrm{Q_{out}(t)}} \tag{6}$$

The typical values of the permeability coefficient, P, of ophthalmic drugs are quite low [39], and therefore the fraction absorbed is predicted to also be minimal.

An example simulating the fate of the drug after instillation of 50 μL of a 0.1% drug solution is shown in Fig. 1A. Assumptions included that only 10 μL are effectively mixed with the tear fluid ($Q_i = 0.01$ mg), the drug has a quite high permeability coefficient ($0.5{\cdot}10^{-6}$ cm/s), the corneal surface available for absorption is 0.5 cm^2 [40], and that the tear flow is 1.2 μL/min [36]. Fig. 1A evidences the rapid clearance of the drug from the tear fluid layer and the small amount that can penetrate the ocular tissues. This model also explains that a drug-induced tearing (e.g., tear flow 2.4 μL/min) causes a faster decrease in the drug levels in the tear fluid, consequently resulting in less drug being absorbed. In contrast, an excipient that increases the viscosity of the eyedrop may decrease the flow (e.g., tear flow 0.6 μL/min) and thus favors drug permanence on the ocular surface and subsequent drug absorption (Fig. 1 B1).

Using microparticles that perform as drug-binding resins can notably prolong the time of permanence of the drug on the surface of the eye (Fig. 1 B2). An equilibrium between the drug that is inside the resin and the drug that is free in the tear fluid is established. The fraction of free drug (F, not bound to the microparticles) can vary depending on the affinity of the resin for the drug. In Fig. 1 B2, the F value was assumed to be 0.2; i.e., at each time point 20% of the drug is free and 80% of the drug remains in the formulation. The total amount of drug in the tear fluid layer is the sum of both free and bound drug, but the drug that can be absorbed or drained is only the free drug. Therefore, the equations should be modified accordingly, as follows

$$Q_{out}(t)_{resin} = Q_i \cdot \left(1 - exp\left(-\frac{F\bullet\dot{V}}{V_R}\bullet \mathrm{t}\right)\right) \tag{7}$$

$$\frac{Q_A(t)_{resin} = \frac{DKA}{h\bullet V}\bullet \mathrm{Q_{out}(t)_{resin}} = \mathrm{P}\bullet \mathrm{A}}{\dot{V}\bullet \mathrm{Q_{out}(t)_{resin}}} \tag{8}$$

Sustained drug release attenuates the decrease in Q_R(t), but also slows down the amount absorbed and the amount drained. Therefore, the therapeutic advantage of formulating a drug into microparticles is not related to an increase in the concentration of drug available for absorption (which decreases if the dose remains constant), but due to the prolonged residence of the drug in the tear fluid. Assuming that the formulation does not alter drug permeability, it is clear that a decrease in free drug concentration diminishes the flux of drug into eye tissues

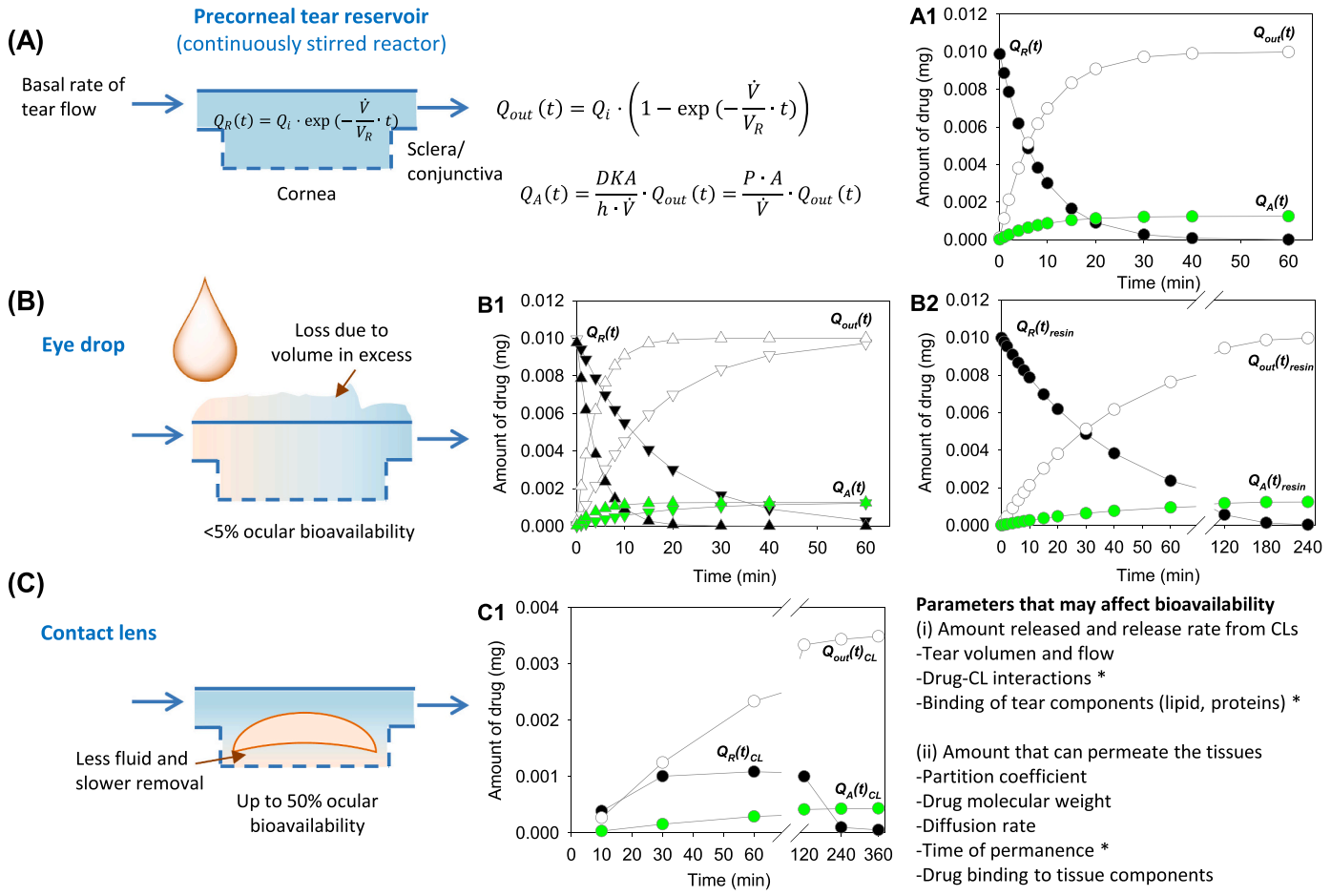

Fig. 1. (A) Modeling of the precorneal tear reservoir as a continuously stirred reactor consisting in a chamber with capability to contain a certain volume of tear fluid, V_R, which is under continuous flow, $\dot{V}$; and equations that predict, after one drop instillation, the amount of drug that remains in the precorneal tear reservoir, $Q_R(t)$ (black symbols), and the amount that is cleared in total, $Q_{out}(t)$ (white symbols), and through tissue permeation, $Q_A(t)$ (green symbols), at a certain time point. Equations adapted from Lang and Stiemke [36]. Plot A1 simulates the evolution of the drug levels after instillation of one drop (50 μL) of a 0.1% drug solution; assuming that only 10 μL are effectively mixed with the tear fluid (Qi = 0.01 mg), the drug has a quite high permeability coefficient ($0.5 \cdot 10^{-6}$ cm/s), the corneal surface available for absorption is 0.5 cm^2, and tear flow is 1.2 μL/min. (B) Plot B1 depicts the effect of a change in the tear flow from 0.6 μL/min (e.g., a decrease induced by a thickening excipient; down triangles) to 2.4 μL/min (e.g., tearing induced by the drug itself; up triangles). Plot B2 depicts the effect of formulating the drug in microparticles that perform as drug-binding resins and that during the release the fraction of drug released at each point (free drug) is 20% of the drug remaining in the microparticles. Only the free drug released to the tear fluid is absorbed or drained, which decreases both the rate of absorption and the clearance, but notably increased the time of permanence of the drug in the tear fluid for the same dose instilled as compared to A1. (C) The use of drug-loaded CL alters the tear volume and slows down the flow beneath the lens. Also, the sustained release of the drug (in the plot $Q_R(t)_{CL}$ represents real data of free drug levels recorded *in vivo* by some of the authors) notably slows down drug clearance (attenuating the risk of collateral systemic effects) and may facilitate sustained absorption through ocular tissues. If the absorption rate is sufficient to induce pharmacological effects, the therapeutic efficiency of the treatment may be notably enhanced and prolonged. Among the listed parameters that may affect ocular drug bioavailability, CLs may preferentially act on those marked with *.

(Equation 5) and thus the absorption rate. Therefore, the improvements in ocular bioavailability recorded for microparticle-based formulations are not due to an increase in permeability, but to a change in the pharmacokinetic profile. Slow drug release from microparticles means more contact time of the drug with the eye tissue. If the absorption rate is sufficient to reach the pharmacological threshold, i.e., the minimum therapeutic concentration in the target tissue, then the pharmacological effects could be notably prolonged compared to eye drop instillation.

It seems clear that ocular drug absorption benefits from a decrease in tear flow and a sustained drug release. Interestingly, CLs may simultaneously achieve both of these conditions. In the case of CLs, an equilibrium between free and bound drugs may not occur since the strength of the binding is less than for the ionic resins. F is expected to increase with time. Therefore, in the following equations F is not a constant and may be a function of the release kinetics. Q_R(t) depends also on the release kinetics. Additionally, placing a CL on the eye causes the tear film to divide into two layers, an outer 'pre-lens tear film' closest to the air and a layer beneath the CL and in front of the cornea designated as the 'post-lens tear film'. Drug release mainly occurs toward the post-lens tear film because, in the time interval between successive blinks, the external surface of the CL dries and thus drug diffusion stops. Therefore, an initial consequence of placing a CL on the surface of the eye is that the volume available for drug release is less than in the case of eye drops. Tear film thickness in the absence of a CL is estimated to be 6 μm, and the thickness below a CL is 1-2 μm [41].

A second consequence is that the exchange of tear fluid beneath the CL, i.e., the hydrodynamic flow of the post-lens lachrymal fluid ($\dot{V}_{CL}$), is smaller than in the absence of the CL, particularly for soft CLs [42]. Moreover, the dynamics of tear flow under the CL may follow a non-constant rate, since blinking causes deformation of the CL, which in turn ejects the fluid when the CL is under pressure and suctions more fluid when the pressure vanishes [43]. Thus, $\dot{V}_{CL}$ should be considered as a mean value, and the blinking pressure may also alter drug release kinetics from the CL.

$$Q_{out}(t)_{CL} = Q_i \cdot \left(1 - exp\left(-\frac{F' \bullet \dot{V}_{CL}}{V_R} \bullet t\right)\right) \quad (9)$$

$$Q_A(t)_{CL} = \frac{DKA}{h \bullet \dot{V}_{CL}} \bullet Q_{out}(t)_{CL} = \frac{P \bullet A}{V_{CL}} \bullet Q_{out}(t)_{CL} \quad (10)$$

The complex dependence of the release rate, $Q_R(t)$ and F' on $\dot{V}_{CL}$ explains the difficulties in designing *in vitro* release tests for drug-eluting CLs that can mimic the physiological conditions on the eye surface, or at least that can provide values useful to predict *in vivo* behavior. It should be noted that CLs are not expected to increase drug permeability, because this parameter mainly depends on the drug-tissue pair, but CLs may notably enhance ocular bioavailability (at least $Q_A(t)_{CL}$) by regulating the concentration of drug in the tear fluid and the time of permanence. These two latter parameters can be tuned through an adequate design of the CL that considers not only drug-network interactions, but also the potential competitive binding of the drug to tear components (lipid, proteins) and also the binding of various tear components to the CL [44].

3.2. Current official methods for testing drug release from topical ophthalmic medicines

In the development of a drug product (medicine), drug release tests provide valuable information for quality control during manufacturing and regulatory review process and as predictive tools of *in vivo* performance. Particularly, for ophthalmic non-solution products, traditional systemic pharmacokinetics studies (using blood sampling) do not inform on bioavailability at the site of action (inner eye structures) [45]. Regulatory bodies have published recommendations on bioequivalence studies that involve clinical endpoint studies (mostly for glaucoma, ocular hypertension, and pain), pharmacokinetic studies in aqueous humor (e.g., topical corticosteroids prior to cataract extraction), microbial kill rate assay (e.g., antimicrobial drugs) and *in vitro* release studies [46]. Clinical endpoints provide semiqualitative information and may be affected by the patient health conditions. Since their capability to discriminate similar products is low, clinical endpoint assessment requires a fairly large sample size. Pharmacokinetic studies in the aqueous humor offer quantitative data of transcorneal ocular bioavailability, but usually only one sampling per patient is feasible. Moreover, drug levels in the aqueous humor may be affected by several interindividual differences (e.g., age, ethnicity, ocular illness) and thus a very large sample size is required for statistical significance [45]. Therefore, so far, *in vitro* studies are considered more reliable to assess differences among ophthalmic formulations.

Researchers and regulatory bodies have been attempting to establish methods for in *vitro-in vivo* correlations (IVIVC). Strong efforts are being made to develop ocular physiologically relevant pharmacokinetic (PBPK) *in silico* models (i.e., via computer simulation) that can predict drug ocular bioavailability and tear film breakup time based on the physicochemical properties of the drug and the formulation. For instance, GastroPlus™ has recently been implemented with an Ocular Compartmental Absorption and Transit (OCAT™) model [47]. Various other modeling approaches to simulate drug transport through the cornea are also currently under investigation [48].

Some product-specific guidances are available for ophthalmic non-solution products, such as suspensions and ointments. A great deal of attention has been focused on identifying drug release tests that can detect changes in formulation or manufacturing process having the same drug and the same inactive ingredients. The most common apparatus to monitor drug release from non-solution ophthalmic products are those included in official pharmacopeias for oral dosage forms, with some modifications to be adapted to semisolid products. Some key examples of the apparatus include the Franz diffusion cell, USP apparatus 2 with enhancer cells, and USP apparatus 4 with semisolid adapters (described in Fig. 2) [49]. Nevertheless, non-compendial dissolution methods that can be more biorelevant are under investigation, such as devices simulating low-volume flow-through [45].

There is an increasing number of reports devoted to identifying the apparatus and the release conditions that allow for improved discrimination among similar ophthalmic formulations of a given drug [50]. *In vitro* release tests in simulated lachrymal fluid and *ex vivo* transcorneal flux correlations have also been attempted. As an example, four loteprednol etabonate ophthalmic ointments considered as qualitatively and quantitatively equivalent formulations (the same components in the same concentration; Q1/Q2) were evaluated in terms of rheological behavior, *in vitro* drug release in artificial lachrymal fluid and *ex vivo* (rabbit) transcorneal flux [51]. The USP apparatus 4 (1.54 cm^2 exposed area, 50 mL medium capacity, flow rate 8 mL/min) clearly showed differences in release rate among the formulations, which were not detected or were less evident using the Franz diffusion cells (1.77 cm^2 exposed area, 12 mL receptor medium, 600 rpm) or the USP apparatus 2 with enhancer cells (4 cm^2 exposed area, 40 mL release medium, 150 rpm). The highest release rates, but the less reproducible ones, were recorded in the Franz diffusion cells. Inverse correlations were found between the rheological properties (crossover modulus and power law consistency index) and the release rate (Higuchi model) of the four ointments. Moreover, *ex vivo* transcorneal permeation coefficients recorded in Franz diffusion cells also revealed differences among the formulations, which correlated with their rheological features (Fig. 2A). Compared to the drug release rates calculated *in vitro*, the drug permeation rates were lower, but the rank order of the formulations was the same; namely, a direct correlation was found between *in vitro* release rate and *ex vivo* release flux (Fig. 2B). This study demonstrated the usefulness of the *in vitro* release tests as predictive tools of *ex vivo* drug transcorneal flux, which may correlate with the flux *in vivo*, although this has not been demonstrated yet. Additionally, particular attention should be paid to the preservation of corneal structure and epithelium integrity during the test [51]. In any case, such *in vitro- ex vivo* correlations are particularly useful when a predicate product has already demonstrated safety and effectiveness, and a generic product is intended to be developed. Nevertheless, prediction of *in vivo* performance does not depend only on the release rate, but also on other formulation properties, such as retention time on the ocular surface.

Release tests carried out with solid ophthalmic formulations, namely inserts to be placed in the conjunctival fornix, are also quite heterogeneous [52–55]. Ocusert-like inserts prepared with poly(lactic co-glycolic) acid and polyethylene glycol (PEG) and loaded with brimonidine tartrate showed almost constant release rate for one month when placed in phosphate buffered saline (PBS) solution at 37 °C [56]. The release medium was completely replaced at each sampling point, but total release medium volume and stirring conditions were not disclosed. There are few other inserts for drug delivery that are under preclinical or clinical phase. A bimatroprost ocular ring (formerly Helios™), which contains the drug onto a non-biodegradable support and coated with silicone, was reportedly 'safe' in preclinical tests, but the *in vitro* release profiles were not disclosed [54]. Ciprofloxacin release from OphthaCoil inserts (stainless steel coated with SlipSkin®) was evaluated by placing the insert in a silicon tube (inner diameter of 1 mm), through which simulated lachrymal fluid was pumped at a rate of 100 μL/min. Fractions of 150 μL were collected for release kinetics evaluation. In general, the profiles showed fast release in the first minutes and decreased amount released in the next few hours [57]. Pradofloxacin-loaded OphthaCoil inserts were similarly tested *in vitro* and compared with the release *in vivo* in a dog model after insertion in the lower conjunctival fornix of the eye [58]. The *in vivo* release was notably slower and thus more prolonged, which was attributed to the *in vitro* high flow of release medium (100 μL/min) compared to physiological tear turnover (1-5 μL/min). Overall, the information reported for topical ocular solid formulations also reveals a disparity of release media and testing conditions, without conclusive proposals on the *in vitro* test setup that may

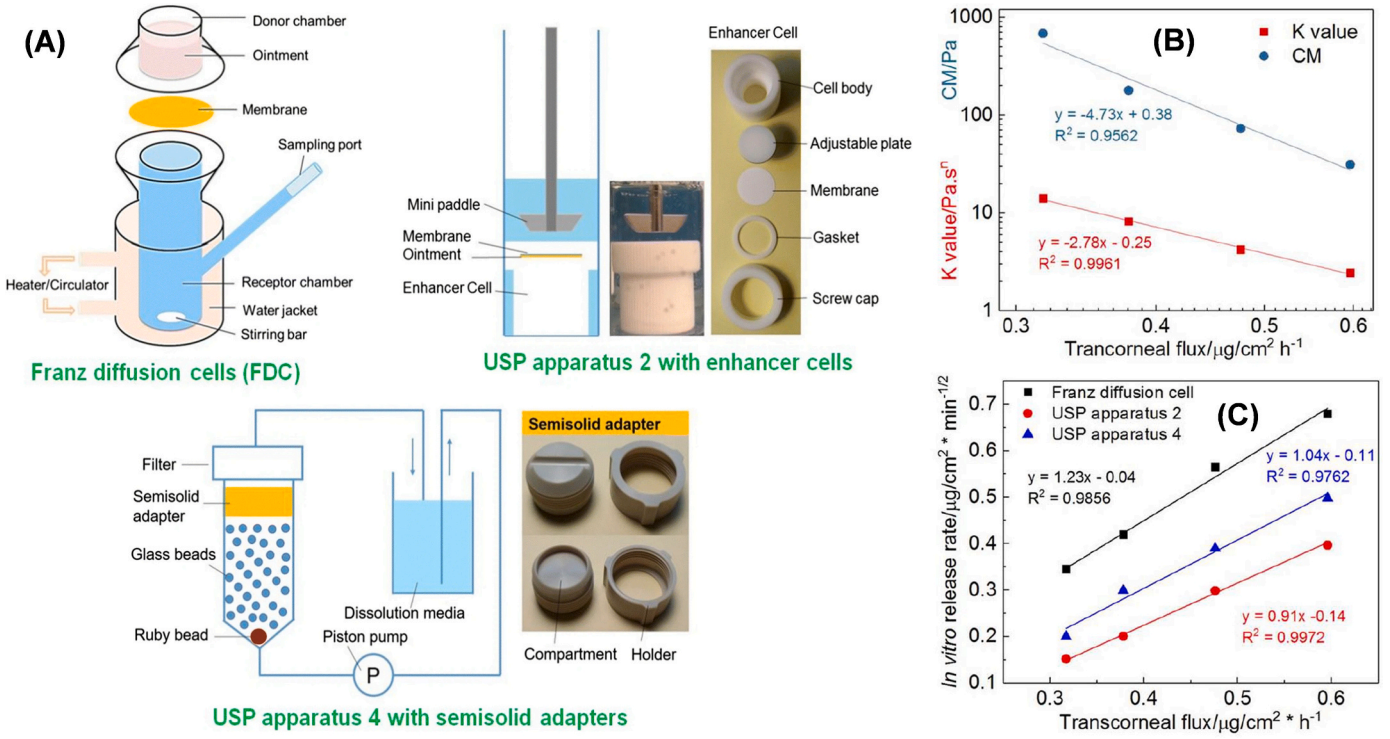

Fig. 2. (A) Scheme of some of the apparatus considered in the USP chapter <1724> for *in vitro* drug release from semisolid drug products. Franz (vertical) diffusion cells consists of two compartments (donor and receptor) separated from each other by a membrane onto which, typically, 200 mg of the product under test is placed. A heating jacket is used to regulate the temperature and the experiment is carried out for 4-6 h. The modified USP apparatus 2 consists of a cell filled with the product (300 mg - 2 g covered with a permeable membrane) which is placed at the bottom of the glass flat vessel. The release medium is added and maintained under stirring with the help of a small paddle positioned at a certain distance from the product. The flow-through cell USP apparatus 4 consists of a reservoir (semisolid adapter) filled with the product (also covered with a permeable membrane) through which a sinusoidal flow of release medium is impelled. Reprinted from Bao and Burgess [49] by permission from Springer Nature; (B) Linear correlation (semi-logarithmic mode) between critical parameters of loteprednol etabonate ophthalmic ointments (crossover modulus CM and power law consistency index K) and drug transcorneal flux; and (C) linear correlation between in vitro release rate recorded using the three apparatus described in (A) and *ex vivo* transcorneal flux (receptor filled with 5 mL of artificial lachrymal fluid with 9% hydroxypropyl-β-cyclodextrin, 600 rpm). Reprinted from Bao et al. [49] with permission from Elsevier.

mimic *in vivo* release.

The lack of standardized *in vitro* test models has also been pointed out as a relevant concern for the development of ocular implants for posterior eye segment [59]. A variety of setups, including configurations similar to those depicted in Fig. 2, have been tested, but finding IVIVC remains elusive. The high complexity of the ocular tissues, comprising a diversity of metabolic and physiological barriers, makes the *in vitro* mimicking of the *in vivo* processes of drug release, absorption and distribution much more challenging than for any other route.

4. *In vitro* testing of drug release from medicated CLs

Since there is not an officially approved method for testing drug release from CLs, authors have used a myriad of different approaches. A search was performed in Web of Science database with the keywords "drug AND contact lens" within the 2000 to 2021 time frame. The search was further refined using the word "release" and to papers published in English. In total, 455 results were generated. This search included ocular drugs and macromolecular demulcents. Further refinement manually removed contributions that did not match the appropriate outcomes searched for, resulting in 251 original papers being analyzed.

The *in vitro* setups can be categorized into three main groups: (i) release in a beaker with or without replacement of the release medium at a pre-stablished time; (ii) release under fluid flow in specially designed microfluidic chambers; and (iii) release under blinking-mimic conditions (Fig. 3). Most reports refer to *in vitro* release profiles recorded in small beakers, but using widely variable volume, medium composition, stirring and replacement. For exhaustive information the reader is referred to Table S1 (Supporting Information file) [60–199]. Although analysis of this non-harmonized data is not easy, beakers in which the release medium is not replaced are usually filled with more volume than those that undergo partial or complete replacement of the release medium at each sampling time (Fig. 3 A1). The selection of the release medium volume is a highly relevant issue, as evidenced in a previous comprehensive report [106]. If too small a volume is chosen, then the release process may become controlled by drug solubility, and therefore the capability of the CL to regulate drug release is overestimated. In comparison, if too large a volume is chosen or a small volume is frequently replaced, then a sink effect accompanied by a large concentration gradient may forcedly accelerate the release process, and the CL may become exhausted much more rapidly than under *in vivo* conditions. Clearly, CLs that are able to sustain the release under the *in vitro* more challenging conditions are also expected to control the release under *in vivo* conditions. However, as evidenced in section 5, these *in vitro* conditions do not ensure IVIVC because the release *in vivo* may be slower. Interestingly, an overall analysis of the time that CLs sustain drug release *in vitro* suggests that, disregarding whether the release medium is replaced or not, conventional commercially available CLs release the drug much faster than CLs designed ad hoc or coated with components that exhibit affinity for the drug. According to the data compiled in Table S1 (Supporting Information file), for these latter CLs, the duration of the release could be prolonged for 149 (s.d. 99), 319 (s.d. 338), 226 (s.d. 278) and 290 (s.d. 328) hours in PBS without replacement, in PBS with replacement, in artificial tears without replacement, and in artificial tears with replacement, respectively. The box plot showing the median values and the upper and lower quartiles are

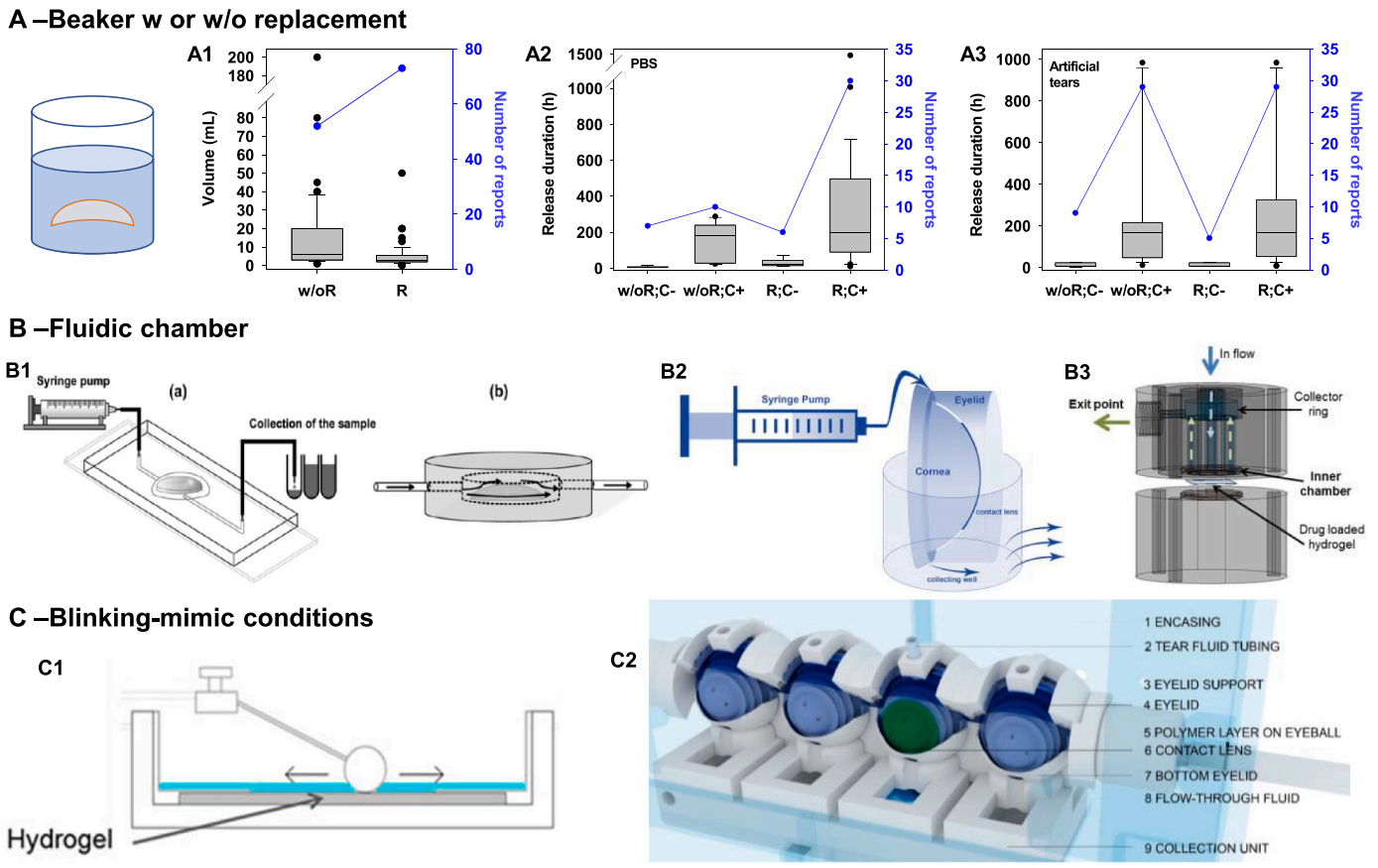

Fig. 3. Main setups used to evaluate *in vitro* drug release from CLs. (A) Beaker of variable volume (from small well to large tube) with (R) or without (w/oR) replacement of the release medium at a pre-established time. The box plots constructed from the data compiled in Table S1 demonstrate that (A1) tests made without replacement of the release medium (w/oR) usually involve large volumes, and (A2 and A3) CLs designed to control drug release (code C+) are more efficient in providing sustained release than conventional CLs (code C-) disregarding whether the release medium (PBS or artificial tears) is replaced or not during the *in vitro* test. (B) Devices proposed to evaluate drug release under fluid flow showing different configurations for inlet and outlet ports; (B1), (B2) and (B3) reprinted, respectively, from Tieppo et al. [201] with permission from Elsevier, Bajgrowicz et al. [204] with permission from ARVO, and Pimenta et al. [206] with permission from Springer Nature. (C) Advanced prototypes in which CLs can be subjected to normal forces that may mimic the blinking conditions; (C1) reproduced from Galante et al. [208] by permission of Taylor & Francis Ltd., and (C2) reproduced from Phan et al. [210] (Creative Common CC BY license).

depicted in Fig. 3 A2 and A3. No *in vivo* release profiles are available for reports collected in Table S1.

Attempts to better mimic the complex scenario of *in vivo* release have mainly focused on the design of microfluidic chambers that allow for regulation of both the flow and the total volume of medium that bathes the CL (Fig. 3B). The microfluidic device depicted in Fig. 3 B1, which may hold 175 μL in the inner chamber and pumps the release medium at a flow rate of 3 μL/min, has been shown to be useful for discrimination of the capability of silicone hydrogel CLs to sustain dexamethasone release [200]. Compared to the release in a large-volume beaker, CLs loaded with a variety of drugs and demulcents showed slower release profiles when tested in the microfluidic device, which were prolonged for weeks [201–203]. The microfluidic device depicted in Fig. 3 B2 consisted of two 3D printed molds resembling the corneal/scleral curvature and the eyelid. The CL is placed between these structures, and the space available for the release medium is 100 μL. For a flow rate of 3.3 μL/min, commercially available CLs sustained the release of ciprofloxacin, moxifloxacin and fluconazole for several hours compared to the few minutes recorded when the test was carried out in a vial with 4.8 mL PBS, partially replaced at each sampling time [204,205].

The microfluidic device depicted in Fig. 3 B3 is the one with the lowest volume in the inner chamber (45 μL, which is quite close to the maximum tear film volume in the eye) and has 8 outlets that converge in a common collector [206]. Once again, release profiles recorded using this microfluidic device showed remarkably slower rates than the release in a beaker [156,207]. At this time, the microfluidic devices are still to be validated with appropriate *in vivo* data.

The reports on devices that can mimic the pressure exerted by the eyelid on the CL are still incipient (Fig. 3 C). Repetitive load and friction cycles (16 kPa) onto CLs placed in a Simublink device (Fig. 3 C1) have been shown to accelerate the release of levofloxacin when directly loaded in the bulk of the CL [208], but the effect was negligible when the drug was encapsulated in liposomes coating the CL [209]. A whole *in vitro* eye model device constructed using 3D printing has recently been proposed to evaluate the effects of air exposure, flow rate, and blinking frequency on drug release rate (Fig. 3 C2) [210–212]. The model considers the coating of the front surface of the eyeball with a silicone material to prevent unspecific binding of the tested drug and allows for quantifying the amount of drug that penetrates into the polyvinyl alcohol (PVA)-mimicking eyelid [212].

5. *In vivo-in vitro* relationships

There is an increasing interest in using *in vitro* profiles to predict *in vivo* performance. Nearly 50 papers have been published since 2000 reporting *in vitro* release profiles from CLs together with either *in vivo* levels in tear fluid or therapeutic response (Table 2). Most studies have relied on the rabbit eye model, which has structural similarities with the human eyes. However, it is important to note that there are also marked differences in lacrimal fluid turnover (~7.1%/min in rabbits *vs.* ~16%/

Table 2
Drug-loaded CLs evaluated *in vivo* (animal model) in terms of drug release to tear fluid. Some studies also include the measurement of drug accumulation in eye tissues or therapeutic outcomes.

Entry	Drug	Lens material	Loading protocol	In vitro test	In vivo test	Outcome	Ref
1	Timolol maleate	N,N-Diethylacrylamide (DEAA), Methacrylic acid (MAA) and Ethylene glycol dimethacrylate (EGDMA)	Soaking of imprinted and non-imprinted CLs in 10 ml of 1 mM timolol solution for 3 days. Then, autoclaved.	10 ml of 0.9% NaCl at 37 °C	Male Nippon albino rabbits. Imprinted (21 μg dose) and non-imprinted (34 μg) were applied on cornea. Timolol solutions (34 and 125 μg) were used as control. Drug levels in tear fluid were monitored.	*In vitro* release sustained for 24 h. *In vivo* release prolonged for 90 min.	215
2	Ketotifen fumarate	Poly(HEMA-co-AA-co-AM-co-NVP-co-PEG200DMA)	Soaking of imprinted and non-imprinted CLs in 3 ml of 0.3 mg/mL drug solution. Then, autoclaved.	300 mL of artificial lacrimal solution, at 30 rpm and 34 °C.	Male New Zealand white rabbits. Imprinted (110 μg dose) and non-imprinted (39 μg) were applied on right cornea. As control, one drop (50 μL) of commercially available 0.025% ketotifen eye drops was instilled in left cornea. Drug levels in tear fluid were monitored.	*In vitro* release from imprinted CLs was sustained for 72 h (85% released in 24h). *In vivo* release prolonged for 26 h.	216
3	Ketotifen fumarate	MA-PDMS-MA macromonomer, DMA, TRIS, EGDMA	Soaking in 5 mL of 1.945 mg/mL drug solution for 5 days.	5 mL of PBS, at 100 rpm and 37 °C	Rabbits. One CL per animal (amount loaded ranged from 25 to 31 mg/g). As control, one drop (50 μL) of commercially available 0.050% ketotifen eye drops was instilled in the other cornea.	*In vitro* release from more hydrophilic CLs was prolonged for 5 h, while less hydrophilic ones sustained the release for 12 h. These later CLs sustained *in vivo* release for 24 h.	218
4	Bimatoprost	Dimethylacrylamide (DMA, 200 μL), Siloxane (50 μL); MAA (50 μL); EGDMA (10 μL), and HEMA (up to 1 mL)	Immersion of imprinted and non-imprinted CLs in 2 ml of 10, 20 or 30 μg/mL drug solution in simulated tear fluid pH 7.4. The systems were autoclaved and soaking was prolonged for 10 days.	2 mL simulated tear fluid at 34°C and 50 rpm; complete replacement of the release medium at each sampling point.	New Zealand white rabbits of either sex. Imprinted (14.8) μg dose) and non-imprinted (16.2 μg) were applied on right cornea. As control, one drop (15 μg) of commercially available 0.025% ketotifen eye drops was instilled in left cornea. Drug levels in tear fluid were monitored.	*In vitro* release from imprinted CLs was sustained for 36 h. *In vivo* release prolonged for 12 h.	219
5	Puerarin	Poly(2-hydroxy-ethyl methacrylate–co-N-vinylpyrrolidone–co-methyl acrylate) (pHEMA–NVP–MA) (0.05 mm)	Soaking in 5 mL of 0.802 mg/mL drug solution in PBS at 37 °C until equilibrium.	5 mL PBS at 100 rpm and 37°C. At each sampling time, 100 μL of the volume was replaced by fresh medium.	Rabbits. One CL per rabbit. In contralateral eye, one drop (50 μL) of 1% puerarin was instilled.	*In vitro*, drug release was complete in 4 h. *In vivo*, CLs with higher content in NVP (28 mg puerarin/g) showed MRT of 77.45 min, with quantifiable drug levels for 6 h. Eye drops had MRT of 12.88 min, with quantifiable drug levels for 90 min.	220
6	Puerarin	Copolymers of HEMA with mono-MA-β-CD and trimethylolpropane trimethacrylate	Soaking in 50 mL of 0.334 or 0.802 mg/mlof puerarin solution for 24 h.	10 mL distilled water at 37 °C and 100 rpm. At each sampling time, 5 mL of the volume was replaced by fresh medium.	Rabbits. One CL per rabbit. In contralateral eye, one drop (50 μL) of 1% puerarin was instilled.	CLs with MA-β-CD loaded more drug (32.6 mg/g) than without comonomer (13.3 mg/g). *In vitro* release profiles from both CLs showed a burst of ca. 60% in the first hour. CLs with MA-β-CD sustained the release for few hours more. *In vivo*, CLs with MA-β-CD sustained the release in tear fluid for 6 hours. They also provided relevant drug levels in aqueous humor for more than 12 h, with a maximum at 4-6 h. Eye	221

(*continued on next page*)

Table 2 (*continued*)

Entry	Drug	Lens material	Loading protocol	In vitro test	In vivo test	Outcome	Ref
						drops were cleared in 50 min. from tear fluid.	
7	Diquafosol	Commercially available silicone hydrogel CLs (comfilcon A and balafilcon A)	Soaking in 1 mL of 1 mM drug solution for 12 h.	1 mL NaCl 0.9%; complete replacement of the release medium every 24 h.	Male New Zealand white rabbits. One loaded CL (approx. 0.02 mg) in one eye, and non-loaded CL in contralateral eye. As control, one drop (10 μL) of 0.1 mM drug was instilled.	*In vitro* release completed in 24 h. *In vivo*, eyedrops were completely drained in 5 min. CLs had maximum level at 30 min in tear fluid, but drug levels were detected for 240 min. *In vivo* CLs increased tear secretion for 300 min, while the effects of topical instillation were maximum at 15 min and lasted for 90 min.	222
8	Ketotifen	HEMA (up to 1 mL) with dimethacrylate acid (250 μL), siloxane (5 μL) and NVP (100 μL)	The drug directly or previously encapsulated in pegylated solid lipid nanoparticles (pSLNs) was added to monomer mixture before polymerization. Some hydrogels were loaded by soaking in drug solution or drug-encapsulated pSLNs for 10 days. After autoclaving, drug remaining in the CLs was quantified.	2 mL of simulated tear fluid at 34 °C and 100 rpm; complete replacement of the release medium at each sampling time.	New Zealand rabbits of either sex. One CL, either directly loaded with p-SLN (70.2 μg drug) or soaked in p-SLN (48.5 μg drug), placed on one eye. As control, two drops (25 μg) were instilled on one eye. Contralateral eyes were referred as control.	Directly loaded CLs provided lower Cmax (445.7 ± 85.3 μg/mL but higher drug levels in tear fluid along time than CLs that were loaded by soaking in ketotifen-encapsulated p-SLNs (581.6 ± 152.7 μg/mL).	223
9	Ketotifen	HEMA (48 %w/w), MAA (1 %w/w), EGDMA (0.5 %w/w) and water (50.5 %w/w) mixed with 10 %w/w silica shell nanoparticles	The drug directly or previously encapsulated in silica shell nanoparticles was added to monomer mixture before polymerization.	2 mL of simulated tear fluid at 35 °C and 100 rpm; complete replacement of the release medium at each sampling time.	New Zealand white rabbits. One CL on one eye. Contralateral eyes were referred as control.	*In vitro*, CLs loaded with the drug encapsulated in nanoparticles showed minor burst and sustained release for 9 days. Sustained drug levels in tear fluid were also recorded for a similar period of time.	224
10	Cyclosporine A	HEMA with MAA (25:1 mol/mol)	The drug directly or previously encapsulated in a microemulsion was added to monomer mixture before polymerization. After boiling and autoclaving, drug remaining in the CLs was quantified.	2 mL of simulated tear fluid at 34 °C and 100 rpm; complete replacement of the release medium at each sampling time.	New Zealand rabbits of either sex. One CL (100 μg drug) in one eye.	*In vitro* and *in vivo*, CLs loaded with the drug itself or encapsulated in unstable microemulsions showed more sustained release, but the release rate was too slow to provide therapeutic levels after few days. Differently, CLs with the drug encapsulated in stable microemulsions released the drug faster *in vivo* and provided therapeutic drug levels in tear fluid for some weeks. IVIV correlations were observed.	226
11	Cyclosporine A	HEMA (60 %), MAA (2 %), EGDMA (0.5 %), NVP (1%), water (36.5 %)	The drug directly or previously encapsulated in Eudragit S100 nanoparticles was added to monomer mixture before polymerization. After boiling and autoclaving, drug remaining in the CLs was quantified.	2 mL of simulated tear fluid at 34 °C and 100 rpm; complete replacement of the release medium at each sampling time.	New Zealand rabbits of either sex. One CL (50 μg drug) in one eye.	*In vitro* and *in vivo*, CLs with the drug directly added showed a burst and completed the release in few days. CLs with the drug encapsulated in nanoparticles had lower burst and sustained for more time the release both *in vitro* and *in vivo*.	227
12	Bimatoprost	Siloxane (100 μL), EGDMA (15 μL), DMA (300 μL), and HEMA (up to 1 ml)	Soaking in bimatoprost microemulsion (ME) or solution (SM) containing 25, 50 or 75 μg drug per mL of simulated tear fluid for 7 days.	2 mL of simulated tear fluid at 34 °C and 50 rpm; complete replacement of the release medium at each sampling point.	New Zealand rabbits (male and female). SM (32.6 μg) and ME (46.4 μg) CL on one eye. As control, one drop (50 μL) of 0.03% w/v bimatoprost eye drop solution was instilled on	*In vitro*, SM and ME CLs showed a relevant burst and sustained drug release for 24 h and 48 h, respectively. *In vivo*, the release in tear fluid was prolonged for 12 and 24 h,	228

(*continued on next page*)

Table 2 (*continued*)

Entry	Drug	Lens material	Loading protocol	In vitro test	In vivo test	Outcome	Ref
					one eye. Contralateral eyes were referred as control.	respectively. The eye drop was cleared in less than 1 hour.	
13	Travoprost	Silicone hydrogel CLs made of DMS (250 μL), siloxane (150 μL), EGDMA (10 μL), and HEMA (up to 1000 μL).	Soaking in drug microemulsion (T-ME) or solution (T-SM) containing 25, 50 and 75 μg drug per mL of simulated tear fluid for 10 days.	2 mL of simulated tear fluid at 34 °C and 100 rpm; complete replacement of the release medium at each sampling point.	New Zealand rabbits (male and female). T-SM (13.9 μg) and T-ME (26.9 μg) CL on one eye. As control, one drop (50 μL) of 0.003% w/v travoprost eye drop solution was instilled on one eye. Contralateral eyes were referred as control.	*In vitro* and *in vivo*, T-SM CL and T-ME CL sustained drug release for 24 and 48 h, respectively. Eye drops showed a rapid decay in drug levels in the first two hours.	229
14	Olopatadine	EGDMA (10 μL), siloxane (100 μL), and HEMA (up to 1 mL).	Soaking (SM-OL), drug directly added during polymerization (DL-OL), or drug encapsulated in ethylcellulose microprarticles in doughnut CLs (DNT-OL).	2 mL of simulated tear fluid at 34 °C and 100 rpm; complete replacement of the release medium at each sampling time.	New Zealand rabbits of either sex. One DNT-OL CL (260 μg dose). As control, one drop (50 μg olopatadine HCl) was instilled on one eye. Contralateral eyes were referred as control.	*In vitro*, DNT-OL CL attenuated the burst but most drug was still released in the first 12 h. *In vivo*, olopatadine levels in tear fluid lasted few hours after eye drop instillation and were prolonged for 24 h with the CLs.	230
15	Betaxolol HCl	Silicone hydrogel CLs made of HEMA:NVP:TRIS 20:40:40 w/w/w.	Drug loaded pH-responsive film (cellulose acetate-Eudragit S100) embedded in the CL.	10 mL of simulated tear fluid or PBS at 35 °C and 100 rpm; 2 mL replacement of the release medium at each sampling point.	Male Nippon albino rabbit. Soaked CL (121 μg dose), film-embedded CL (700 μg dose), or one eye drop (100 μg dose) on one eye. Contralateral eyes were referred as control.	*In vitro*, drug release was minimum in PBS pH6.8 and prolonged for 10 h in simulated tear fluid. *In vivo*, drug levels in tear fluid were measurable for several days. IVIVC found.	231
16	Diclofenac sodium	HEMA and EGDMA (0.5 %)	Drug loaded pH-responsive film (ethylcellulose-Eudragit S100) embedded in the CL.	10 mL of simulated tear fluid or PBS at 35 °C and 100 rpm; 2 mL replacement of the release medium at each sampling point.	Male Nippon albino rabbit. Soaked CL (100 μg dose), film-embedded CL (121 μg dose), or one eye drop (150 μg dose) on one eye. Contralateral eyes were referred as control.	*In vitro*, drug release was minimum in PBS pH6.8. The release rate in simulated tear fluid depended on thickness and molecular weight of polymer film. *In vivo*, drug levels in tear fluid were measurable for 12 h. IVIVC found.	232
17	Betaxolol HCl	Silicone hydrogel CLs made of HEMA:NVP:TRIS 20:40:40 w/w/w.	Drug loaded ion-responsive film (poly (styrene-divinyl benzene) in cellulose acetate) embedded in the CL.	10 mL of simulated tear fluid at 35 °C and 100 rpm; 2 mL replacement of the release medium at each sampling point.	Male Nippon albino rabbit. Film-embedded CL (700 μg dose), or one eye drop of drug-resin complex (100 μg dose) on one eye. Contralateral eyes were referred as control.	*In vitro*, drug release was sustained for one week. *In vivo*, drug levels in tear fluid were measurable for several days. The resin eye drops remained for 8h in tear fluid. IVIVC found.	233
18	Timolol	ACUVUE® TruEye™ (narafilcon A) silicone hydrogel contact lenses.	Soaking in 3 mL of 20 or 50 mg/mL vitamin E in ethanol for 24 h, washed with water, and then placed in 3.5 ml of 8.0 mg/ml timolol maleate-PBS solution for 21 days. CLs without vitamin E were soaked in 2.5 mg/mL drug solution for 7 days.	2 mL of PBS (room temperature).	Beagle dog model of glaucoma. One eye drop (150 μg) was applied to one eye twice a day for 4 days (total amount of timolol delivered 1200 μg). The other eye was referred as control. One control CL (60 μg dose) to be worn for 24 h, and replaced daily with a freshly drug-loaded CL for 4 days. One control CL (200 μg dose) to be worn for 4 days. One drug-loaded vit E-pretreated CL (200 μg dose) to be worn for 4 days.	*In vitro*, vit E-pretreated CLs sustained drug release up to 84 h compared to the 4 h of control CLs. *In vivo*, vit E-pretreated CLs were more efficient in regulating IOP than control CLs wore for 4 days.	236
19	Timolol and dorzolamide	Senofilcon A	Soaking in 3 mL of 40 mg/mL vitamin E in ethanol for 24 h, washed with water, and then placed in 3.5 ml of 0.8 mg/ml timolol maleate-PBS solution or 3.5 ml of	2 mL of PBS (room temperature).	Beagle dog model of glaucoma. One eye drop (205 μg of timolol and 670 μg of dorzolamide) was applied to one eye twice a day for 4 days. The	Dually-loaded commercial CLs released 90% timolol in 1.2 h, and 90% dorzolamide in 3 h. Vit E-pretreated CLs sustained drugs release for 42 h.	237

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Table 2 (*continued*)

Entry	Drug	Lens material	Loading protocol	In vitro test	In vivo test	Outcome	Ref
			0.75 mg/ml dorzolamide hydrochloride solution (4 days). For dual loading, vit E pretreated CLs were soaked in 3.5 ml of PBS containing timolol (12.75 mg/ml) and dorzolamide (20 mg/ml).		other eye was referred as control. One drug-loaded commercial CL (non-pretreated with vitamin E) (60 μg of timolol and 220 μg of dorzolamide) was worn for 24 h and replaced daily for 5 days. One drug-loaded vit E-pretreated CL (200 μg of timolol and 680 μg of dorzolamide) was worn for 48 h and replaced once with a similar CL. The treatment was stopped at 96 h.	Dually loaded CLs exhibited superior IOP reduction compared to eye drops with 4- to 6-fold lower drug loading. Continuous wear of dually-loaded vitamin E-pretreated CLs reduced IOP during the 4 days of wear time and for another 8 days after removal of the CLs.	
20	Timolol and bimatoprost	EGDMA (10 μL), DMA (310 μL), NVP (10 μL), siloxane (100 μL), and HEMA (up to 1 mL).	Three small implants loaded with timolol (100 mg), bimatoprost (75 mg) and HA (60 mg), respectively, were included in the CLs.	2 mL of simulated tear fluid at 34 °C and 100 rpm; complete replacement of the release medium at each sampling time.	New Zealand rabbits of either sex. One CL on one eye (50 μg bimatoprost and 85 μg timolol). As control, one drop (15 μg bimatoprost and 250 μg timolol) was instilled on one eye. Contralateral eyes were referred as control.	*In vitro* and *in vivo*, implant-loaded CLs sustained drug release for 24 h and lowered IOP for 72 h. CLs loaded by soaking showed higher burst release both *in vitro* and *in vivo*, although therapeutic levels were recorded in tear fluid for 12 h and low IOP was maintained 48 h.	238
21	Timolol	Acuvue Oasys	Soaking for 24 h in 3% (w/w) dispersion of timolol-loaded propoxylated glyceryl triacrylate nanoparticles in ethanol.	Storage in 1 ml of packaging solution (PBS) for 2 weeks at 4 °C. Release was then tested in 1.75-3.5 mL PBS at room temperature and 40°C.	Beagle dog model of glaucoma. One CL in one eye. The other eye was referred as control.	*In vitro*, freshly loaded CLs sustained drug release for two weeks. CLs stored in packaging solution evidenced leakage of drug-loaded nanoparticles, which led to lower amount released. *In vivo*, decrease in IOP was observed on days 2, 3 and 4 of wearing.	239
22	Timolol	HEMA-based ring containing timolol-ethyl cellulose nanoparticles and sandwiched in HEMA-CL	During synthesis.	2 mL of simulated tear fluid at 34 °C under shaking; complete replacement of the release medium at each sampling time.	New Zealand rabbits of either sex. One CL with ring (150 μg dose) placed on one eye. As control, one drop (250 μg) was instilled on one eye. Contralateral eyes were referred as control.	*In vitro*, the CLs sustained drug release for two days. *In vivo*, CL showed Cmax of 6.79 μg/mL in 5 min, followed by steady release for several days. The drop led to Cmax of 132.6 μg/mL in 5 min and rapid decrease of drug in tear fluid.	240
23	Timolol and hyaluronic acid	HEMA (669 μL), EGDMA (5 μL), DMA (310 μL), TRIS (1 μL), NVP (10 μL).	Semi-circular implants containing timolol or HA.	2 mL of simulated tear fluid at 34 °C and 100 rpm; complete replacement of the release medium at each sampling point.	New Zealand white rabbits of either sex. One CL (148 μg timolol) for 7 days wearing. One drop of 0.5% timolol maleate (250 μg timolol). Contralateral eyes were referred as control.	CLs sustained the release of timolol and HA for 96 h *in vitro* and 72 h *in vivo* and decreased IOP during 144 h.	241
24	Timolol base and latanoprost	HEMA (580 μL) and EGDMA (15 μL)	Micelles containing both drugs (0.4 mL) were added to the monomers.	Franz diffusion cell. Donor compartment with one CL and 1 mL STF, and receptor with 7 mL STF at 35 °C and 50 rpm; 1 mL replacement of the release medium at each sampling point.	Male Nippon albino rabbits, healthy and glaucoma model. One CL (100 μg timolol and 1 μg latanoprost) on one eye. As reference, 50 μL of Xalacom® eye drops (250 μg timolol and 2.5 μg latanoprost) were instilled. Contralateral eyes were referred as control.	*In vitro*, CLs sustained timolol and latanoprost release for up to 120 h and 96 h, respectively. *In vivo*, CLs increased MRT (79.6-fold and 122.2-fold) and bioavailability (2.2-fold and 7.3-fold) for both timolol and latanoprost compared with eye drops. IOP reduction over 168 h.	242
25	Timolol base	Silicone hydrogel CLs made of DMA (350 μL), siloxane (100 μL), and HEMA (up to 1000 μL).	Soaking in timolol microemulsion (TB-ME-SM) or timolol solution (TB-SM) containing 1, 2	2 mL of simulated tear fluid at 34 °C and 50 rpm; complete replacement of the	New Zealand rabbits (male and female). TB-SM (234.3 ± 18.5 μg) and TB-ME-SM (215.3 ±	*In vitro*, TB-SM CL and TB-ME-SM CL released more than 90% drug in 12 h and in 48 h,	243

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Table 2 (*continued*)

Entry	Drug	Lens material	Loading protocol	In vitro test	In vivo test	Outcome	Ref
			or 3 mg drug per mL of simulated tear fluid for 10 days.	release medium at each sampling point.	9.1 μg) CL on one eye. As control, one drop (50 μL) of 0.5% w/v timolol eye drop solution was instilled on one eye. Contralateral eyes were referred as control.	respectively. *In vivo*, TB-SM CL and TB-ME-SM CL had Cmax at 5 min and provided measurable drug levels in tear fluid for 24 and 72 h, respectively. Eye drops showed a rapid decay in timolol levels in the first two hours. *In vivo* efficacy was evaluated regarding intraocular pressure (IOP). TB-ME-SM CL showed prolonged reduction in IOP values.	
26	Sparfloxacin	EGDMA (10 μL), siloxane (100 μL), and HEMA (up to 1 mL)	Immersion in 2 mL of drug solution (2-6 mg/mL) in 0.5% PVP-simulated tear fluid medium, autoclaving and soaking for 7 days. Alternatively, a drug-loaded ring was adapted to the CL.	2 mL of simulated tear fluid at 34 °C under shaking; complete replacement of the release medium at each sampling time.	New Zealand rabbits of either sex. One CL with ring (129 μg drug) placed on one eye. As control, one drop (150 μg) was instilled on one eye. Contralateral eyes were referred as control. Efficacy in conjunctivitis model.	*In vitro*, the ring-loaded CLs were the only able to sustain drug release for two days. *In vivo*, the ring-loaded CLs provided therapeutically useful drug levels in tear fluid for 12 h and favored conjunctivitis treatment.	244
27	Ofloxacin	Silicone hydrogel CLs made of DMA (250 μL), siloxane (100 μL), and HEMA (up to 1000 μL).	Soaking in ofloxacin microemulsion (Of-ME) or ofloxacin solution (Of-SM) containing 1, 2 or 3 mg drug per mL of simulated tear fluid for 7 days.	2 mL of simulated tear fluid at 34 °C and 100 rpm; complete replacement of the release medium at each sampling point.	New Zealand rabbits (male and female). Of-SM (191 μg) and Of-ME (358 μg) CL on one eye. As control, one drop (50 μL) of 0.3% w/v ofloxacin eye drop solution was instilled on one eye. Contralateral eyes were referred as control.	*In vitro*, Of-SM and Of-ME CLs showed a relevant burst and sustained drug release for 24 h and 72 h, respectively. *In vivo*, the release in tear fluid was prolonged for 24 and 48 h, respectively. The eye drop was cleared in less than 1 hour. *In vivo* efficacy was tested against *Staphylococcus aureus*-induced conjunctivitis. Of-ME CL improved the symptoms in 24 h. Complete healing was observed after 4 days of treatment with either one CL or 0.3% w/v ofloxacin eye drop solution instilled every 4 h.	245
28	Gatifloxacin	HEMA with methacrylic acid (MAA) (25:1 mol/mol)	Soaking in 0.5 mg/L drug solution in 0.9% NaCl medium at 37 °C until equilibrium.	Non-disclosed volume of 0.9% NaCl medium.	Sprague Dawley rats. Keratitis was induced on the right eye. Drug-loaded CLs (50 mg) were placed on the cornea and the eyelids were sutured. Saline and drug drops (5 μL; unknown concentration) were instilled every 4 h and used as controls.	*In vitro* P(HEMA-co-MAA) (11.8 μg/mg) released 70% drug in 24 h. *In vivo* efficacy in a rat model of bacterial keratitis. Wearing for 48 h of P(HEMA-co-MAA) favored the healing of cornea lesions caused by epithelial erosion and stromal ulceration, more efficiently than drug drops.	246
29	Gatifloxacin	Dimethyl acrylamide (31%), siloxane (2.5%), NVP (1%), EGDMA (1%) and hydroxyl ethylmethacrylate (HEMA, up to 1000 μL).	Drug directly added to the monomers solution, following by autoclaving and storage in 0.3% drug solution in Pluronic micelles packaging solution (GT-PL-CL). For comparison, CLs were soaked in the drug-containing packaging solution.	2 mL of simulated tear fluid at 34 °C and 100 rpm; complete replacement of the release medium at each sampling point.	New Zealand rabbits (male and female). GT-PL-CL (92 μg dose), SM-CL (53 μg dose) or one eye drop (150 μg dose) on eye. Contralateral eyes were referred as control.	*In vitro*, all CLs showed more than 60% burst release in the first 1 h. SM-CL completed 90% release in 6 h, while GT-PL-CL extended the release for 48 h. *In vivo*, SM-CL and GT-PL-CL prolonged the release 12 h and 24 h, respectively.	247
30	Hyaluronic acid						248

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Table 2 (*continued*)

Entry	Drug	Lens material	Loading protocol	In vitro test	In vivo test	Outcome	Ref
		HEMA (46.7%), MAA (0.08%), EGDMA (0.5%) in water(52%) (0.1 mm)	Direct addition of HA to the monomer solution.	2 mL simulated tear fluid at 100 rpm at 35 °C; complete replacement of the release medium at each sampling point.	New Zealand white rabbits. CL was placed on right eye. As control, one drop (50 μL) of 0.1% HA was instilled on the right eye. Left eye was referred as control.	*In vitro* release from CLs (200 μg HA) was prolonged for 10 days, without burst. *In vivo* showed a burst in the first day followed by therapeutically useful values for 10 days (MRT 128 h). Eye drops disappeared in the first 3 h of treatment (MRT 0.74 h).	
31	Hyaluronic acid	DMA (200 μL), EGDMA (10 μL), siloxane (100 μL), HEMA (up to 1 mL).	HA and reduced graphene oxide (rGO) were added before polymerization in silicone CLs (HA-GO-DL) or loaded by soaking in 2 mg/mL HA in simulated tear fluid (HA-GO-SM).	2 mL simulated tear fluid at 100 rpm; complete replacement of the release medium at each sampling point.	White New Zealand rabbits of either sex. CL was placed on right eye. As control, one drop (50 μL) of 0.1% HA was instilled on the right eye. Left eye was referred as control.	*In vitro* HA-GO-DL (10 μg HA loaded) sustained HA release for 96 h. *In vivo*, HA-GO-DL provided therapeutic levels for 48 h and promoted the production of tear fluid.	249
32	Hyaluronic acid	DMA (200 μL), EGDMA (10 μL), siloxane (100 μL), HEMA (up to 1 mL).	HA and Pluronic F127 were added before polymerization to obtain DL-HA-Pl CLs containing 20, 40 or 60 μg of HA and 20 μg of Pluronic F127. Alternatively, CLs were soaked in 1-3 mg/mL HA in simulated tear fluid for 7 days (HA-SM CLs).	2 mL simulated tear fluid at 50 rpm; complete replacement of the release medium at each sampling point.	White New Zealand rabbits of either sex. DL-HA-Pl CL (22.5 μg HA) and HA-SM CL (17.6 μg HA) was placed on right eye. As control, one drop (50 μL) of 0.1% HA was instilled on the right eye. Left eye was referred as control.	*In vitro*, HA-SM CL showed high burst and completed the release in 12-36 h. DL-HA-Pl CL sustained HA release for 48-96 h. *In vivo*, HA-SM CL and DL-HA-Pl CL provided therapeutically useful values for 4 and 48 h, respectively.	250
33	Prednisolone and beclomethasone	Lidofilcon (HEMA-based)	Soaking in 1 mL of prednisolone (5 mg/mL) or beclomethasone (1 mg/mL) for 18 h at 4 °C.	1 mL of saline medium for injection (unknown temperature or stirring); complete replacement of the release medium every 3 h.	New Zealand white rabbits. Drug-loaded CL on both eyes and the eyes were closed with surgical tape for four hours. The treatment was applied on days 1, 2, 5, 8 and 10. The amount of drug in plasma and anterior and posterior segment tissues was analyzed on day 11.	*In vitro*, CLs sustained drug release for 6 h. Both drugs were preferentially found in posterior segment tissues, with lower levels in vitreous humour.	251
34	Pirfenidone	11 commercially available CLs	Soaking in 2 mL of 0.05%-0.5% drug solution.	2 mL of PBS under shaking; complete replacement of the release medium at each sampling time.	New Zealand rabbits. One polymacon CL on the right eye (1147 μg dose), one eye drop (30 μL of 0.5%; 150 μg dose) in the left eye.	*In vitro*, polymacon CL showed sustained release for 30 min. *In vivo*, significant levels in tear fluid were recorded for 60 min. CL wearing provided measurable drug levels in cornea, aqueous humor and sclera.	252
35	Pirfenidone	Silicone hydrogel CLs (Acuvue Oasys®) pre-treated with vitamin E	Soaking in 0.1% drug solution in PBS for 72 h.	3 mL of PBS without replacement of the release medium.	New Zealand White rabbits of either sex. An alkali burn was induced in one eye. One group received CLs.	*In vitro*, CLs sustained drug release up to 260 min. Gene expression of inflammatory cytokines IL-1β, TNF-α, and TGF-β1 was reduced.	253
36	Pirfenidone	Silicone CLs made of silicone elastomer MED-6015 embedding a drug-containing polyvinyl alcohol insert	Loading during CLs preparation.	2 mL of PBS under shaking at 37 °C; complete replacement of the release medium at each sampling time.	Female New Zealand white rabbits. One CL on right eye (15.4 μg dose), one eye drop (30 μL of 0.5%; μg dose) in the left eye.	*In vitro*, CLs released 52 % dose in the first hour, followed by ten-times lower release rate in the next 15 hours. *In vivo*, CLs provided lower but more sustained drug levels in tear fluid and aqueous humor than eye drops.	254
37	Epalrestat	HEMA (up to 1 mL) with dimethacrylate acid (250 μL), siloxane (5 μL) and NVP (100 μL)	The drug directly or previously encapsulated in pegylated solid lipid nanoparticles (pSLNs) was added to monomer mixture before polymerization. Some	2 mL of simulated tear fluid at 34 °C under shaking; complete replacement of the release medium at each sampling time.	New Zealand rabbits of either sex. One CL, either directly loaded with p-SLN (98.1 μg drug) or soaked in p-SLN (110.8 μg drug), placed on one eye. As control, two	*In vitro*, CLs loaded during synthesis with the drug encapsulated in pSLNs showed more sustained release, which led to measurable drug levels in tear fluid for	255

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Table 2 (*continued*)

Entry	Drug	Lens material	Loading protocol	In vitro test	In vivo test	Outcome	Ref
			hydrogels were loaded by soaking in drug solution or drug-encapsulated pSLNs for 7 days. After autoclaving, drug remaining in the CLs was quantified.		drops (100 μg) were instilled on one eye. Contralateral eyes were referred as control.	prolonged time. CL wearing provided measurable drug levels in lens, cornea, aqueous humor and retina.	
38	Ofloxacin	HEMA (99.5 wt%) and EGDMA (0.5 wt%) in the form of corneal CL, scleral/corneal CL (S/CL) and rings.	Soaking in ofloxacin ophthalmic solution of 0.3% drug in 0.85% NaCl medium at 100 rpm for 24 h.	*_In vivo_* release. Japanese albino rabbits without nictitating membrane. Each device was worn for 0.25, 0.5, 1, 2, 4 and 8 h and the amount of drug remaining was quantified.	Japanese albino rabbits without nictitating membrane. Each device was worn for 1 h and the amount of drug accumulated in ocular tissues was quantified. As control, 50 μL of ophthalmic solution was instilled. Ofloxacin concentration data collected from each rabbit were converted from actual tissue concentrations to ratios with respect to the administered drug dose. Contralateral eyes were also investigated.	CLs released the drug faster and favored drug accumulation in cornea. S/CL led to high drug levels both in anterior and posterior segment tissues. Rings facilitated drug accumulation in the posterior segment.	256
39	Timolol	HEMA (62.5 %), DMA (31 %), TRIS (2.5%) and NVP (1 %) with and without gold nanoparticles (up to 0.1 mM).	Soaking in timolol base (2 mg/mL and 4 mg/mL; 2 mL) solution in simulated tear fluid containing or not gold nanoparticles (up to 0.1 mM), for 72 h.	2 mL of simulated tear fluid at 34 °C and 100 rpm; complete replacement of the release medium at each sampling time.	New Zealand white rabbits. One CL with or without gold nanoparticles (277 and 253 μg of timolol, respectively) on one eye. As control, one drop (50 μL) of 0.5% w/v timolol maleate eye drop solution was instilled on one eye (250 μg of timolol). Contralateral eyes were referred as control. IOP was also recorded.	*In vitro* all hydrogels released most dose in less than one hour. *In vivo*, timolol was detected in tear fluid for 60 h when administered in CLs and only for 2 h when instilled as eye drops. Timolol was quantifiable in eye tissues for 24 h.	257
40	Latanoprost	Latanoprost and PLGA 65:35 or 85:15 (high molecular weight) film was covered with methafilcon monomers. After polymerization, CLs were lathed.	Three sets of CLs were prepared containing films of thickness 20, 40 and 45 μm.	5 mL of PBS under shaking at 37 °C; complete replacement of the release medium every 24 h.	New Zealand rabbits of either sex. One CL under the nictitating membrane for one month wearing. One drop (30 μL) of 0.005% latanoprost solution.	*In vitro*, $CL_{65:35,\ 20}$, $CL_{65:35,\ 40}$ and $CL_{85:15,\ 45}$ released 90%, 48% and 45% drug dose in the first three days. *In vivo*, drug levels in aqueous humor were sustained for 4 weeks.	259
41	Dexamethasone	PLGA 85:15 (high molecular weight) film loaded with dexamethasone was covered with methafilcon monomers. After polymerization, CLs were lathed.	One drug-loaded PLGA film ring was encapsulated in the CL (Dex-DS CL). Alternatively, CLs were soaked in dexamethasone base or phosphate solutions for 24 h.	10 mL PBS and incubating at 37 °C; complete replacement of the release medium at each sampling time.	Female New Zealand White rabbits. One CL (1.5 mg dose) for 7 days wearing. One drop of 0.1% dexamethasone solution every hour for 8 h.	*In vitro*, soaked CLs completed the release in less than 4 h. Dex-DS CL sustained drug release for 7 days. *In vivo*, continuous wearing of Dex-DS CL provided higher drug levels in all ocular tissues than the eye drops.	261
42	Cyclosporine A	HEMA with MAA	The drug was impregnated into nanoporous silica using supercritical CO_2 and then added to the monomers solution.	2 mL of PBS at 37.8 °C; complete replacement of the release medium at each sampling time.	Female New Zealand rabbits health and dry eye model. CL wearing in both eyes applied daily, or 0.05% drug eyes drops.	*In vitro*, CLs sustained drug release for 8 h. *In vivo*, high levels of drug were detected for 48 h in cornea and conjunctiva. CLs increased tear volume and stabilized tear film.	263

min in humans) and blinking frequency (every 15 min in rabbits *vs.* every 5 s in humans) [213,214]. Thus, drug release may be faster and drug residence time may be shorter in human eyes. Potential *in vivo-in vitro* (co-)relations are discussed in detail in this section as they can provide key information on the true potential of CLs as drug carriers, as well as feedback for improvements.

5.1. Comparison of in vivo and in vitro release profiles

Drug-containing molecularly imprinted CLs were among the first investigated CL *in vivo*. In 2005, Hiratani et al. [215] pioneered the optimization of soft CLs with an ability to load timolol (Table 2, entry 1). Imprinted CLs loaded 34.7 (s.d. 0.3) μg while non-imprinted ones only

hosted 21.2 (s.d. 0.2) μg. In 0.9% NaCl medium (*in vitro* tests) both CLs sustained the release for more than 24 h in spite of being extremely thin (Fig. 4 A1). *In vivo* release (rabbit model) was monitored by measuring timolol levels in the tear fluid (Fig. 4 A2). Topically instilled eyedrops were rapidly cleared (either 34 μg or 125 μg dose), and timolol levels in the tear fluid decreased exponentially in the first 30 min and disappeared within 60 min. In contrast, CLs enhanced the mean residence time (MRT) by two-fold. Imprinted CLs provided measurable timolol levels in tear fluid for 180 min, which was 2-fold longer than the time recorded for non-imprinted CLs. Remarkably, the area under the curve (AUC) obtained with the imprinted CLs was 8 and 3 times higher than those recorded for the eye drop containing the same dose and for the non-imprinted CLs, respectively. The sustained timolol levels in the tear fluid provided by the imprinted CLs are the result of an enhanced affinity for the polymer network by the drug, which in turn facilitates higher loading and more controlled release [215]. However, the capability of these CLs to sustain timolol release *in vivo* was remarkably lower than *in vitro*, probably as a consequence of both the continuous replacement of the tear fluid and blinking. It should be noted that the composition of the CLs tested in this work was chosen in such a way that the main structural component had very low affinity for the drug, and thus the main drug binding site was formed by only the functional methacrylic acid (MAA) moieties [190], which may be too weak for efficient drug retention under the competitive *in vivo* environment.

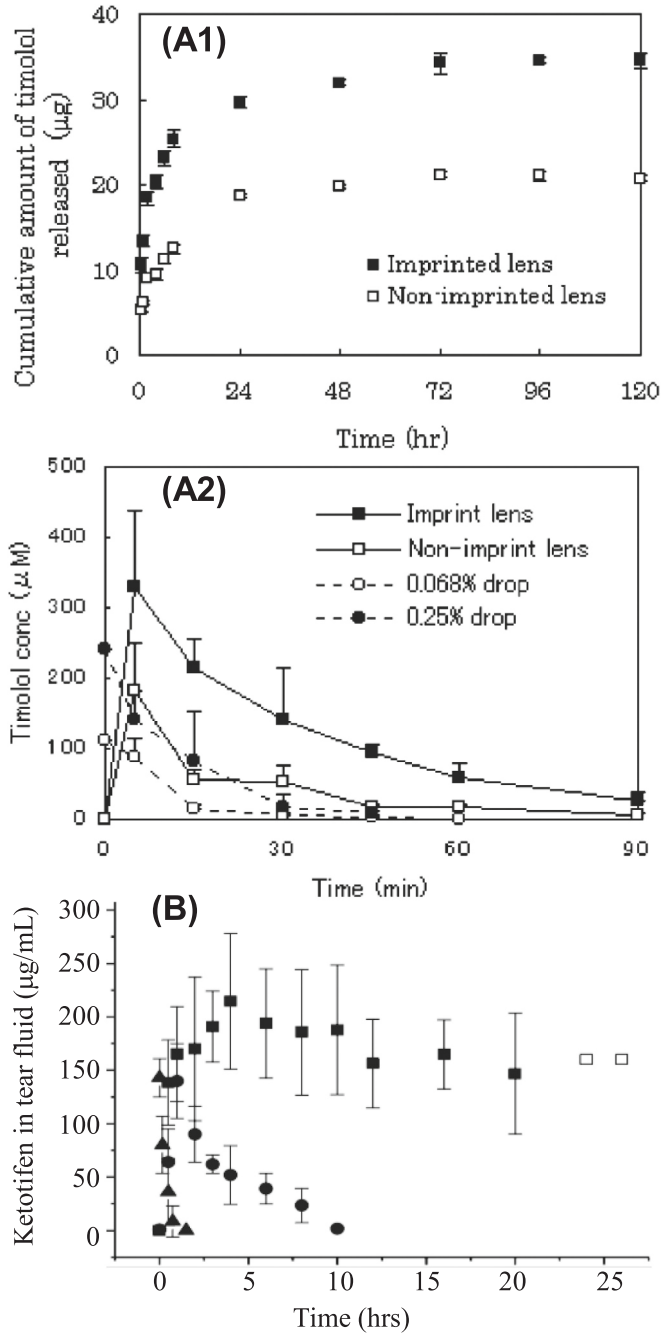

Fig. 4. (A1) *In vitro* timolol release profiles (0.9% NaCl; 10 mL) and (A2) *in vivo* timolol levels in tear fluid after application of drug-loaded imprinted and non-imprinted CLs (0.08 mm center thickness). Timolol doses applied in each eye were 21 μg for non-imprinted CLs, 34 μg for imprinted CLs and 0.068% timolol eye drop, and 125 μg for 0.25% timolol eyedrop (n= 3-5). Reprinted from Hiratani et al. [215] with permission from Elsevier. (B) Ketotifen fumarate levels in tear fluid during wearing of poly(HEMA-co-AA-co-AM-co-NVP-co-PEG200DMA) imprinted (■, □) and non-imprinted (●) CLs and after instillation of eye drops (0.035% solution;▲) (n=3–5; hollow data points represent single run). Reprinted from Tieppo et al. [216] with permission from Elsevier.

More prolonged *in vivo* release profiles were reported by Tieppo et al. [216] for ketotifen-imprinted CLs (Table 2, entry 2). The multi-monomer composition of the CLs was chosen to attempt to mimic the human receptor of the drug. Ketotifen-imprinted poly(HEMA-co-AA-co-AM-co-NVP-co-PEG200DMA) showed 4 times higher loading than non-imprinted hydrogels and 19 times slower transport. Under dynamic infinite-sink *in vitro* release conditions, imprinted CLs released 85% of the drug in 24 h, while non-imprinted CLs completed the release in less than 6 h. Remarkably, imprinted CLs provided sustained release *in vivo* for an entire day (MRT 12.6 h) (Fig. 4 B). Non-imprinted CLs provided therapeutic drug levels (~ 30 μg/mL) for 7 h (MRT 3.4 h), and the eye drops only remained for a few minutes (MRT 0.25 h). The high capability of these drug-imprinted CLs to sustain ketotifen release may pave the way to clinical studies in humans [217]. Compared to conventional (non-imprinted) silicone hydrogel CLs (Table 2, entry 3) [218], the ketotifen-imprinted CLs provided higher drug levels for a more prolonged time. In the case of silicone hydrogel CLs, an increase in DMA enhanced ketotifen loading, but led to faster drug release both *in vitro* (complete release in 5 h) and *in vivo* (also 5 h with levels above the therapeutic concentration; MRT 1.9 h). Interestingly a clear correlation between capability to prolong drug release *in vitro* and *in vivo* was observed, although only two different compositions were evaluated [218]. Also for ketotifen, it was confirmed that an increase in the concentration of the drug in the eye drops does not prolong the MRT.

Bimatoprost-imprinted silicone hydrogel CLs (Table 2, entry 4) showed minor improvements in drug loading compared to non-imprinted CLs, but more prolonged release *in vitro* (up to 36 h vs. 24 h) and slightly higher drug levels in tear fluid *in vivo* (rabbits) for 12 h [219]. Once again, although the capability of the CLs to sustain drug release *in vivo* was shown to be shorter than *in vitro*, the increase in residence time in tear fluid compared to eye drops was remarkable.

Comonomers with affinity for the drug, such as N-vinylpyrrolidone (NVP), have been used to improve the capability of HEMA-based CLs to uptake puerarin and to prolong its release *in vitro* and in tear fluid for 4 h (Table 2, entry 5) [220]. Extended *in vitro* release up to 10 h was observed when β-cyclodextrin was copolymerized with HEMA, which in turn allowed for prolonged permanence in tear fluid, up to 6 h (Table 2, entry 6) [221]. Favorable drug-CL interactions may also occur when using commercially available CLs, particularly silicone hydrogels, which are more prone to stablish hydrophobic interactions. As an example, diquafosol, a secretagogue for dry eye treatment, can be taken up by comfilcon A and balafilcon A (up to 0.02 mg) (Table 2, entry 7). In *in vivo* studies, CLs sustained drug release in tear fluid for 240 min and increased tear secretion for 300 min, while the effects of topical instillation only lasted for 90 min [222].

Loading of hydrophobic drugs can be enhanced if the drug is encapsulated in lipid nanoparticles or microemulsions. Ketotifen was encapsulated in solid lipid nanoparticles, which were pegylated (p-

SLNs) or not (SLNs) and then used for the drug loading of HEMA-based hydrogels (Table 2, entry 8) [223]. Some hydrogels were loaded with ketotifen by addition of SLNs (DL-K-SLN-100) or p-SLNs (DL-K-p-SLN-100) to the monomer solution before polymerization. Another batch of hydrogels was loaded by soaking into either ketotifen solution (SM-K-50 and SM-K-100) or ketotifen-encapsulated SLNs (SM-K-SLN-100) or p-SLNs (SM-K-p-SLN-100). All hydrogels were autoclaved before testing drug release. Hydrogels loaded by soaking showed a very intense burst in the *in vitro* release tests (Fig. 5 A1). Directly loaded CLs contained more drug and released it at slower rate. Interestingly, *in vivo*, these latter CLs (DL-K-p-SLN-100) provided lower C_{max} (445.7 ± 85.3 μg/mL vs. 581.6 ± 152.7 μg/mL) but more prolonged drug levels in tear fluid along time than CLs that were loaded by soaking in ketotifen-encapsulated p-SLNs (SM-K-p-SLN-100) (Fig. 5 A2). This finding was related to stronger retention of the p-SLNs when they were incorporated into the bulk of the hydrogel. Similarly, prolonged ketotifen release in both *in vitro* and *in vivo* was recorded from CLs loaded with silica shell nanoparticles encapsulating the drug (Table 2, entry 9) [224]. From a safety perspective, it should be noted that direct loading, in which the drugs are incorporated into a CL material before polymerization, has the inherent risk of leakage of unreacted monomers when the CL is inserted in the eye.

In vitro-in vivo correlations (IVIVC) have been attempted through Levy plot analysis. Mainly, the percentage of drug released *in vitro* at a certain time is reported on the X-axis, and the percentage of drug released in the tear fluid at the same time on the Y-axis. The methodology for the estimation of this latter parameter was not disclosed in most papers, but it can be assumed that the percentage of drug released *in vivo* was estimated as [225]

$$\text{Drug released } \textit{in vivo}\ (\%) = \frac{\textit{Cumulative release amount}_{0-t}}{\textit{Cumulative release amount}_{0-last}} \times 100\% \quad (11)$$

which can be calculated as

$$\text{Drug released } \textit{in vivo}\ (\%) = \frac{AUC_{0-t}}{AUC_{0-last}} \times 100\% \quad (12)$$

In the case of ketotifen, the Levy plot suggests moderate IVIVC (Fig. 5 A3) [223], although this plot should be read with caution, since only four data points of drug levels in tear fluid were used for the analysis.

CLs loaded with drugs encapsulated in microemulsions have also been investigated in detail. As an example, the effect of surfactant chain length (C8-sodium caprylate, C12-Tween 20, C18-Tween 80) and the molecular weight of Pluronic block copolymers (8400-PF68 and 12600-PF127) was investigated to elucidate how the stability of the microemulsion may determine cyclosporine A release kinetics from hydrogel CLs (Table 2, entry 10) [226]. CLs loaded with cyclosporine A during polymerization (DL-100) were opaque due to drug precipitation. CLs loaded with cyclosporine A encapsulated in stable PF127-T80 microemulsions were transparent and released the drug *in vitro* faster than DL-100 and non-stable PF68-SC CLs (Fig. 5 B1). In this case, a prolonged release profile was not synonymous of prolonged efficacy since the release rate from drug-precipitated CLs was too slow to achieve therapeutic levels (Fig. 5 B2). Indeed, *in vivo* release tests showed that PF127-T80-containing CLs may supply higher drug levels and for more prolonged time than the other tested CLs. Although a dependence of the percentage of drug released to tear fluid on the percentage of drug released *in vitro* was observed (Fig. 5 B3), the correlation coefficients of Levy plots were far from 1, mostly because the cumulative amount released *in vivo* in the first time period was larger than that predicted from the *in vitro* release values. The authors pointed to the presence of lipophilic proteins in tears as a cause of the Levy plot deviations, since they bind and solubilize hydrophobic drugs, promoting the release from the CL [226]. Prolonged levels of cyclosporine A in tear fluid were also found when the drug was encapsulated in Eudragit S100 nanoparticles (Table 2, entry 11), but IVIVC were not investigated [227].

Soaking in microemulsions has also been demonstrated as a useful

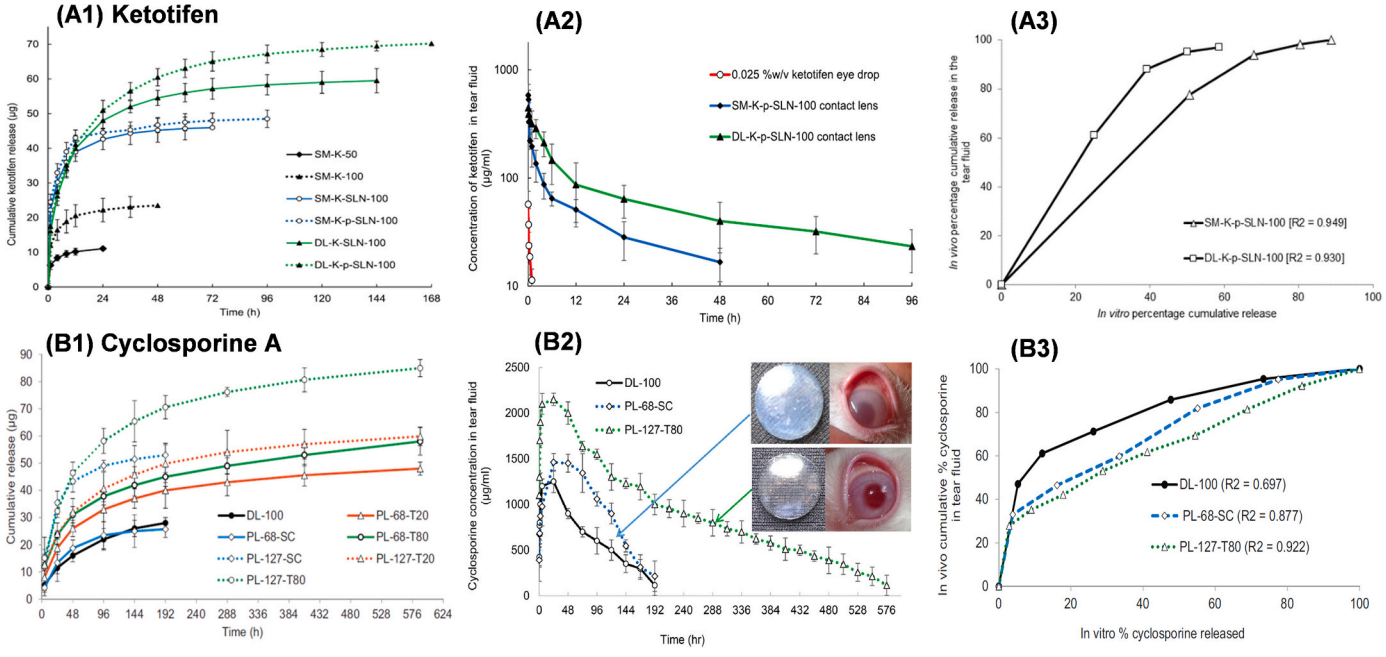

Fig. 5. (A1) *In vitro* ketotifen release profiles from CLs loaded by soaking in drug solutions (SM-K-50 and SM-K-100) or drug-encapsulating non-pegylated solid lipid nanoparticles (SM-K-SLN-100) or pegylated solid lipid nanoparticles (SM-K-p-SLN-100), and CLs loaded by adding the drug-encapsulating nanoparticles directly to the monomer solution (DL-K-SLN-100 and DL-K-p-SLN-100), (A2) *in vivo* ketotifen profiles in tear fluid during CLs wearing and after eye drop instillation (n = 6), and (A3) Levy plot depicting the percentage of ketotifen released *in vivo vs. in vitro*. Reprinted from Zhang et al. [223] with permission from Elsevier. (B1) *In vitro* cyclosporine A release profiles from CLs prepared with the drug directly added (DL-100) or previously encapsulated in a microemulsion, (B2) *in vivo* release profiles (n = 6) and, in the insert, the appearance of the CLs that were transparent when loaded with the drug encapsulated in stable microemulsions, and opaque when the drug was encapsulated in unstable microemulsions and precipitated in the CL network, and (B3) Levy plots for percentage of drug released *in vivo vs. in vitro*. Reprinted from Maulvi et al. [226] with permission from Elsevier.

method to load bimatoprost and to prolong both *in vitro* and *in vivo* drug release from CLs (Table 2, entry 12). Compared to the loading by soaking in a bimatoprost solution, the microemulsions doubled the amount loaded and the time required for complete release both *in vitro* (48 h vs. 24 h) and *in vivo* (24 h vs. 12 h) [228]. Similar results were reported for travoprost (Table 2, entry 13) [229].

Hydrophobic polymeric microparticles have been tested to encapsulate olopatadine and then applied as a doughnut ring on CLs (Table 2, entry 14). Compared to CLs loaded by soaking (SM-OL) or to which the drug was directly added during polymerization (DL-OL), the doughnut CLs (DNT-OL) avoided burst release *in vitro*, but still released most of the drug in the first 12 h. *In vivo*, DNT-OL CLs provided therapeutic levels in tear fluid for 24 h, but once again the Levy plot showed poor IVIVC as *in vivo* release was faster than predicted [230]. Also, bioinspired strategies for choosing the CL monomers have been shown able to enhance the affinity of CLs for olopatadine increasing the loading and providing 24-h almost constant rate release *in vitro* [166]. Although these CLs were not tested *in vivo*, in cell culture they were able to efficiently inhibit the release of histamine and TNF-α from sensitized mast cells.

A variety of film-embedded CLs have also been designed. For example, pH-responsive films made of cellulose acetate and Eudragit S100 containing betaxolol hydrochloride were integrated into silicone hydrogels (Table 2, entry 15). The film prevented premature discharge during storage in PBS at pH 6.8 and provided sustained drug release for 10 days in simulated lachrymal fluid. Since the films enhanced drug loading (700 μg dose) compared to commonly soaked CLs (100 μg) remarkably higher $AUC_{0\text{-}240h}$ (599 vs. 26 μg·h/mL) and MRT (88 vs. 1.7 h) were recorded in tear fluid (Fig. 6 A1). Improvements compared to eye drops were also evident ($AUC_{0\text{-}240h}$ 10.5 μg·h/mL and MRT 0.4 h). The Levy plot revealed that after a lag time, good IVIVC was obtained (R^2 0.9708) (Fig. 6 A2) [231]. In a related study, the same group evidenced the effects of the film components and thickness in controlling the release of diclofenac (Table 2, entry 16) and showed that for a similar amount of drug loaded, the film-embedded HEMA-based CL (121 μg dose) sustained the release both *in vitro* and *in vivo* for 12 h (Fig. 6 B1). In comparison, soaked CL (100 μg dose) rapidly discharged in 4 h. The improvement in the IVIVC according to the Levy plot was notably better in the case of the film-embedded CLs (Fig. 6 B2) [232]. The films were further modified to respond to ionic strength, preventing premature discharge when stored in water (Table 2, entry 17) [233] or to respond to both ionic strength and pH [234]. Once again, the film-embedded CLs showed sustained release *in vivo* (Fig. 6 C1), which correlated quite well with the release pattern *in vitro* (Fig. 6 C2) [233].

5.2. Comparison of in vitro release profiles and therapeutic outcome

Regulation of intraocular pressure (IOP) using timolol-loaded CLs has been the aim of various studies. Since most commercially available CLs lack sufficient affinity for ocular drugs, Chauhan and coworkers developed the strategy of creating biocompatible and optically transparent diffusion barriers that rely on the hydrophobic features of vitamin E [235,236]. Both vitamin E-pretreated and non-pretreated silicone hydrogel CLs were loaded with 200 μg timolol with the aim of continuous wearing for 4 days (Table 2, entry 18). *In vitro*, non-pretreated CLs released 80% of the drug in the first 4 h, while vitamin E-pretreated CLs extended drug release for up to 84 h [236]. The CLs were tested in a Beagle dog model of glaucoma. Daily-replaced non-pretreated CLs (60 μg timolol) led to a significant decrease in IOP from the first day of treatment until one day after. A similar pattern was observed for the eye drops, but the IOP decrease was more pronounced with the daily CLs in spite of containing only 20% of the drug dose instilled with the eye drops. Non-pretreated CLs worn for 4 days (200 μg timolol) caused a decrease in IOP during the first two days only, as expected from the limited capability of the CLs to sustain drug release *in vitro*. In comparison, vitamin E-pretreated CLs wore for 4 days (200 μg timolol) caused a progressive decrease in IOP from day 1 to day 4, and

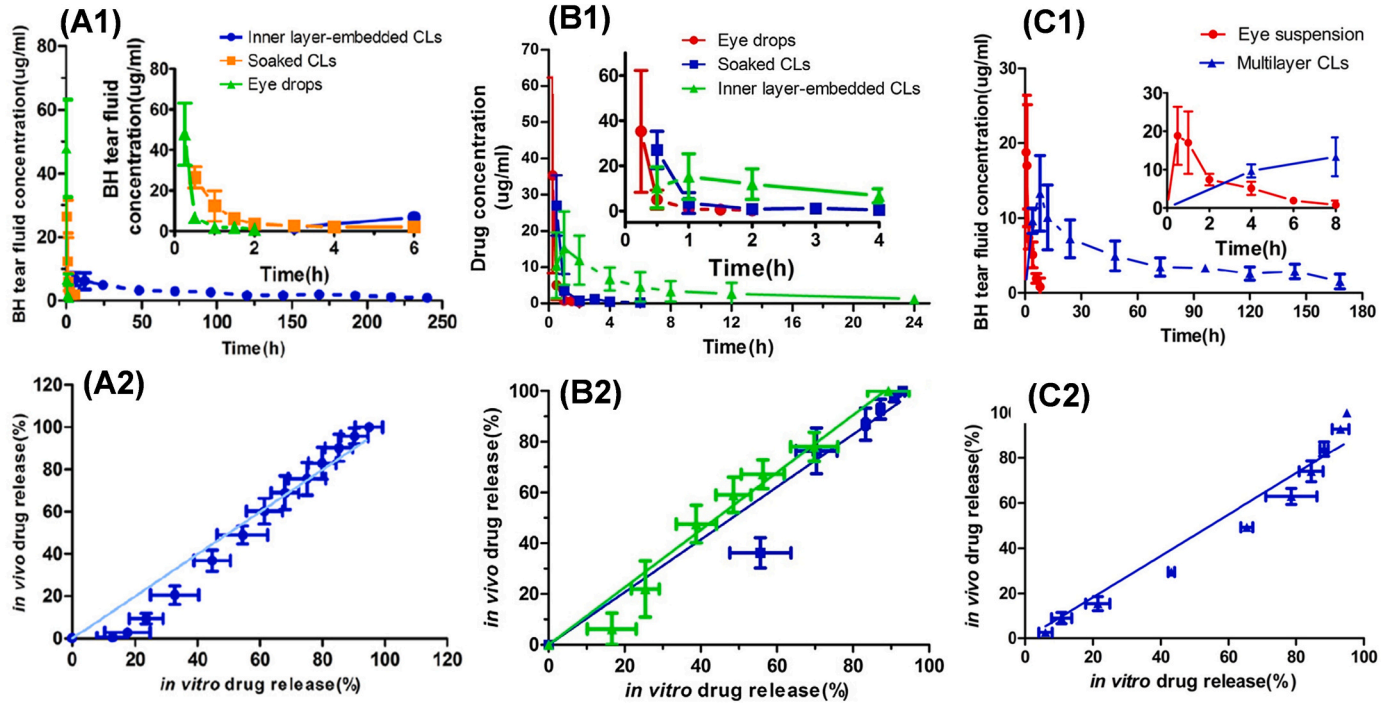

Fig. 6. (A1) Betaxolol hydrochloride (BH) levels in tear fluid after instillation of eye drops (100 μg dose) or wearing of soaked CL (121 μg dose) and film-embedded CL (700 μg dose), and (A2) Levy plot for IVIVC (R^2= 0.9708). Reprinted from Zhu et al. [231] with permission from Elsevier. (B1) Diclofenac sodium levels in tear fluid after instillation of eye drops (150 μg dose) or wearing of soaked CL (100 μg dose) and film-embedded CL (121 μg dose), and (B2) Levy plot for IVIVC of soaked CL (R^2= 0.9019) and film-embedded CL (R^2= 0.9230). Reprinted from Zhu et al. [232] with permission from Elsevier. (C1) Betaxolol hydrochloride (BH) levels in tear fluid after instillation of suspension eye drops (100 μg dose) or wearing of dug-resin complex film-embedded CL (700 μg dose), and (C2) Levy plot for IVIVC obtained for the CL (R^2= 0.9406). Reprinted from Zhu et al. [233] with permission from Elsevier.

the decrease was maintained 24 h after CL removal. These findings clearly demonstrated the advantages of sustained drug release from CLs and their capability to enhance ocular bioavailability compared to eye drops.

Interestingly, commercially available senofilcon A CLs showed distinct release profiles depending on whether they were loaded with one antiglaucoma drug or simultaneously with two drugs (Table 2, entry 19) [237]. In separate, senofilcon A CLs loaded 20 μg timolol and sustained the release over 0.7 h, or loaded 122 μg of dorzolamide and sustained the release for 2.5 h. When both drugs were simultaneously loaded, the loading increased up to 60 μg timolol and 218 μg dorzolamide, and the release was extended to 1.2 h for timolol and 3.0 h for dorzolamide. The increase in drug affinity could be due to favorable drug-drug interactions through hydrogen bonding. Pretreatment of CLs with vitamin E increased drug uptake and led to more controlled release (Fig. 7 A). Timolol release was sustained for 24.6 h in single loaded CLs (18 μg dose) and for 42.2 h in dually loaded CLs (193 μg). Similarly, dorzolamide release was prolonged for 36.0 h in single loaded CLs (122 μg dose) and for 42.3 h in dually loaded CLs (680 μg) [237]. *In vivo* efficacy was evaluated in terms of decrease in IOP in a Beagle dog model of glaucoma. Compared to eye drops that required frequent administration to maintain low IOP values in the treated eye and that altered the IOP values in the contralateral eye (Fig. 7 B), dually-loaded CLs showed more pronounced and sustained decrease in IOP using a lower dose (4- to 6-fold lower) and avoiding effects on the control eye (Fig. 7 C and D). Dually-loaded vitamin E-pretreated CLs maintained the therapeutic effect for two days and, after treatment, the decrease in IOP was maintained for approx. one week after the CLs were removed (Fig. 7 D). These findings confirm once again that CLs can increase ocular drug bioavailability and decrease systemic absorption of drugs through the conjunctiva and nasolacrimal duct, potentially avoiding side effects. These results also suggest a correlation between the time the drug can be released *in vitro* for a sustained period and the time that therapeutic effects can be maintained *in vivo*. It has been hypothesized that the prolonged IOP reduction may be a consequence of the creation of drug depots in the ocular tissues and, in particular, drug partition into corneal epithelial cells [237]. When hydrophilic drugs are administered as eye drops, the precorneal residence time is very short and the drug molecules may penetrate the epithelium by diffusion in between the cells (through the tight junctions), reach the stroma and then diffuse across the endothelium to the aqueous humor. In contrast, the transcellular pathway is slow and requires prolonged contact time for the drug to partition into the epithelium cells. Therefore, sustained release from CLs for several days may facilitate drug accumulation into epithelium cells, which may subsequently act as drug depots. Once the CL is removed, the accumulated drug molecules may slowly release from the cells, maintaining the therapeutic effect.

Dual delivery of timolol and bimatoprost has been investigated in the form of small implants (partial rings) attached to the outer periphery of silicone hydrogel CLs [238]. This approach had the drawback of rapid discharge during wet sterilization. Therefore, omplant-containing CLs could only be sterilized using radiation sterilization and then hydrated for 24 h before wearing. The advantages of implant-containing CLs referred to attenuation of burst release and slow-release rate both *in vitro* and *in vivo* compared to CLs loaded by soaking in the solutions of both drugs (Table 2, entry 20) [238]. Implant-containing CLs provided therapeutic levels in tear fluid for 24 h and maintained IOP decrease for 72 h, while in the case of soaked CLs these times were limited to 12 h and 48 h, respectively.

Timolol encapsulation in nano or microstructures may also provide sustained release from extended wear (overnight) CLs. Nanoparticles of propoxylated glyceryl triacylate containing timolol linked through ester bonds could regulate drug release through the hydrolysis of the bond. CLs containing 5% nanoparticles sustained drug release *in vitro* for several weeks (Table 2, entry 21). *In vivo* testing in Beagle dogs revealed an efficient decrease in IOP on days 2, 3 and 4 of wearing, which means that the CLs required at least 24 h to supply therapeutic amounts of drug, and after 5 days of wearing they were exhausted [239]. An acrylate ring loaded with timolol-ethyl cellulose nanoparticles (150 μg dose) coupled to HEMA-based CLs has also been shown to enhance drug residence on the ocular surface and to decrease IOP levels for several days (Table 2, entry 22) [240]. In this context, semi-circular rings of hyaluronic acid (HA) and timolol coupled to CLs sustained the release of both components for 96 h *in vitro* and 72 h *in vivo* and decreased IOP for 144 h (Table 2, entry 23) [241].

Co-delivery of timolol and latanoprost has been attempted by

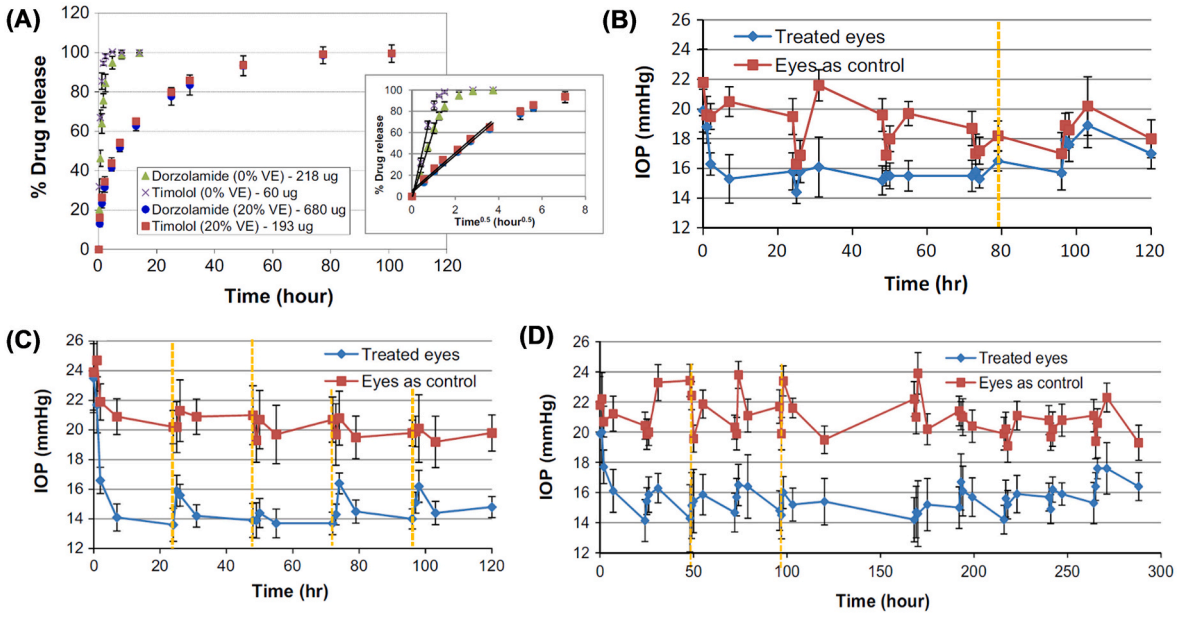

Fig. 7. (A) Timolol and dorzolamide release profiles from dually loaded senofilcon A CLs that were pretreated (20% VE) or not (0% VE) with vitamin E. In the insert the solid lines represent the fitting to the square root kinetics (n = 3). (B, C and D) Measurement of IOPs of 10 beagle dogs treated with (B) Cosopt® eye drops (one eye twice a day for 4 days) for 79 h (indicated by the dash line); (C) dually-loaded CLs worn for 24 h and replaced daily for 5 days; and (D) dually-loaded vitamin E-pretreated CLs worn for 48 h and replaced once with a similar CL (n=10). Reprinted from Hsu et al. [237] with permission from Elsevier.

coencapsulation of the drugs in mPEG-PLA micelles, which were directly added to HEMA before CL synthesis (Table 2, entry 24) [242]. *In vitro*, using a Franz diffusion cell, CLs showed a rapid release in the first 6 h followed by slower rate for up to several days. Compared to eye drops, CLs led to lower C_{max} and more sustained levels of drug in tear fluid (Fig. 8 A1 and A2). In this case, the IVIVC was poor because the *in vivo* release rate was lower than predicted from the *in vitro* values (Fig. 8 A3). An impressive decrease in IOP was recorded for CLs compared to eye drops in a glaucoma model (Fig. 8 A4) [242].

Recently, silicone hydrogel CLs soaked in timolol microemulsion (TB-ME-SM) showed two-fold improvement in the loading compared to merely soaking in timolol solution (TB-SM) (Table 2, entry 25) [243]. *In vitro*, TB-ME-SM CLs released timolol more slowly (90% in 48 h) than TB-SM CLs (90% in 12 h) prepared containing similar drug doses (Fig. 8 B1). *In vivo*, TB-SM CL and TB-ME-SM CL had C_{max} at 5 min and provided measurable drug levels in tear fluid for 24 and 72 h, respectively (Fig. 8 B2). If instilled as eye drops, timolol levels in the tear fluid rapidly decayed in the first two hours, although the reduction in IOP was maintained for 6 h. Both TB-SM CL and TB-ME-SM CL caused more intense and prolonged reduction in IOP values (up to 72 h and 96 h, respectively) with a dose equivalent to a single eye drop (Fig. 8 B3).

Delivery of antimicrobial agents using CLs has also been tested. For example, sparfloxacin cannot be directly added to silicone hydrogels (Sp-L method) because it causes phase separation and, thus, a loss in light transmission. This problem was overcome by co-loading of preformed CLs with sparfloxacin and polyvinylpyrrolidone (PVP) (Sp-S method) or applying the drug-PVP combination as a ring to be fixed in the periphery of the CL (Sp-R method) (Table 2, entry 26) [244]. In comparison to Sp-L and Sp-S CLs (which showed a high burst in the *in vitro* release test), Sp-R CLs sustained the release of both sparfloxacin and PVP for 48 h. In tear fluid (rabbit model), the Sp-R CLs released enough drug to achieve the minimum inhibitory concentration (MIC) for *Staphylococcus aureus* for 12 h. Furthermore, these CLs also notably shortened the time to treat the conjunctivitis. The Levy plot failed to correlate the percentage of drug released *in vivo* with that released *in vitro*; once again, the *in vivo* release was faster than predicted. In this case, the authors also suggested that sparfloxacin may be delivered quickly *in vivo* due to binding to lipids present in the tear film [244].

Microemulsions have also been advantageous to increase the loading of ofloxacin in HEMA-based CLs compared to conventional soaking (Table 2, entry 27) [245]. Soaked (Of-SM, 191 μg dose) and emulsion-loaded (Of-ME, 358 μg dose) CLs were compared *in vivo* against eye drops (250 μg dose) in a rabbit model. The C_{max} were 334 ± 104 μg, 660 ± 255 μg and 446 ± 105 μg respectively, and drug levels above the MIC of *S. aureus* were recorded for 24, 48 and 1 h respectively. The authors claimed good IVIVC, with Levy plot correlation coefficients of 0.966 for Of-SM CLs and 0.931 for Of-ME CLs. Importantly, two days wearing of one ofloxacin-loaded lens was shown to be as efficient as repeated eye drop instillation every 4 h for the treatment of conjunctivitis [245].

Gatifloxacin was loaded in CLs using two different strategies: (i) to add functional monomers in the CLs that can attract the drug [246], and (ii) to soak the CLs into drug-micelle solutions [247]. The first strategy (Table 2, entry 28) revealed MAA as the most suitable monomer to enhance the affinity for gatifloxacin (loading from 2 to 12 μg/mgCL). Although *in vivo* release was not investigated, two days of wear showed complete recovery from bacterial keratitis in a rat model [246]. The second strategy (Table 2, entry 29) consisted of a dual approach of adding gatifloxacin in the monomer solution before polymerization (at 0.3 %w/v) and using drug dissolved (at 0.3 %w/v also) in Pluronic micelles as a packaging solution [247]. The drug that had been added directly to the monomers precipitated in the CL, compromising the optical properties. Immersion in the packaging solution allowed drug resolubilization into the micelles and further enhanced drug loading. The resultant CLs (GT-PL-CL; 92 μg dose) showed slower release rates than soaked CLs (SM-CL; 53 μg dose), but both exhibited more than 60% burst release in the first 1 h. Compared to eye drops (150 μg dose) that rapidly disappeared from the ocular surface, SM-CL and GT-PL-CL provided measurable drug levels in tear fluid for 12 and 24 h, respectively [247].

The suitability of CLs as platforms for the sustained release of macromolecules such as HA for amelioration of dry eye syndrome has also been demonstrated. Soaking of CLs in HA solution only allows for surface adsorption and thus leads to complete release in a few hours. In contrast, direct addition of HA to the monomer solution has been shown to render hydrogel CLs that provided therapeutically useful levels of HA both *in vitro* and in tear fluid for 10 days (Table 2, entry 30) [248]. Similarly, HA was added to silicone hydrogel monomers either solely or combined with reduced graphene oxide (rGO) (Table 2, entry 31) or Pluronic F127 (Table 2, entry 32). HA-rGO directly loaded CLs sustained the release for 96 h *in vitro* and for 48 h *in vivo*, and increased rabbit tear fluid volume for 96 h, being more efficient than eye drops or soaked CLs [249]. The combination of HA and Pluronic F127 improved CL wettability and tear production. Direct loading in the silicone monomers rendered CLs that sustained HA release for 48-96 h *in vitro* and 48 h *in vivo*, avoiding the huge burst recorded for CLs soaked in HA [250]. Overall, as for small drug molecules, the achievement and the duration of therapeutic effects observed for HA-eluting CLs were the result of a fine equilibrium between enhanced loading and more controlled release. Thus, prolonged *in vitro* release had a direct correlation on the time the therapeutic outcome could be maintained.

5.3. Comparison of in vitro release profiles and drug accumulation into anterior and posterior segments

Lidofilcon hydrogel CLs were shown to load steroids and provide sustained release for efficient drug penetration into the posterior segment [251]. The CLs were soaked in either prednisolone suspension in saline for injection or beclomethasone dipropionate solution in dimethyl sulfoxide (DMSO):water 16:4 vol/vol mixture (Table 2, entry 33). After washing in saline solution for injection, the release *in vitro* was sustained for 6 h. *In vivo* evaluation consisted of placing drug-loaded CLs on both eyes, which were kept closed with surgical tape for 4 h. Prednisolone was detected in the posterior segment ocular tissue of all rabbits, with concentrations ranging 26–166 ng/g. Prednisolone was found in the vitreous humor of three out of eight eyes and only detected in the plasma of one animal (out of six). Its metabolite prednisone (inactive) was below the quantification limit in all cases. Beclomethasone dipropionate was also detected in the posterior segment tissue, but not in vitreous humour and plasma. Its active metabolite, 17-beclomethasone, was detected in the posterior segment tissue and in most vitreous humor samples. Both prednisolone and beclomethasone dipropionate are small (< 600 g/mol) hydrophobic molecules. If they had penetrated the eye through the cornea and then migrated towards the macula and retina, the parent drugs should also be detected in the vitreous humor at similar levels. Since this was not the case, the drug molecules released from the CLs to the cornea and limbal areas may have entered through a non-corneal route. They could have reached the local vasculature and then been transported toward the posterior segment. The absence of drug in plasma discarded the notion that access to the posterior segment was via systemic circulation [251].

Screening of eleven commercially available CL materials pointed to polymacon (polyHEMA) CLs as the most appropriate ones for loading of pirfenidone, an anti-inflammatory drug that favors the healing of the ocular surface (Table 2, entry 34) [252]. All tested CLs released the drug rapidly *in vitro* (Fig. 9 A), with polymacon having the best release profile (~30 min release duration). In rabbit eyes, the CLs (1147 μg dose) provided relevant pirfenidone levels in tear fluid for 60 min, while eye drops (150 μg dose) disappeared in the first 15 min (Fig. 9 B). Drug-loaded polymacon CLs led to significantly higher drug levels in the cornea, aqueous humor and sclera at all data points assessed (Fig. 9 C, D and F). Importantly, the drug levels in the conjunctiva only showed a minor increase in the first 60 min (Fig. 9 E), which can be correlated

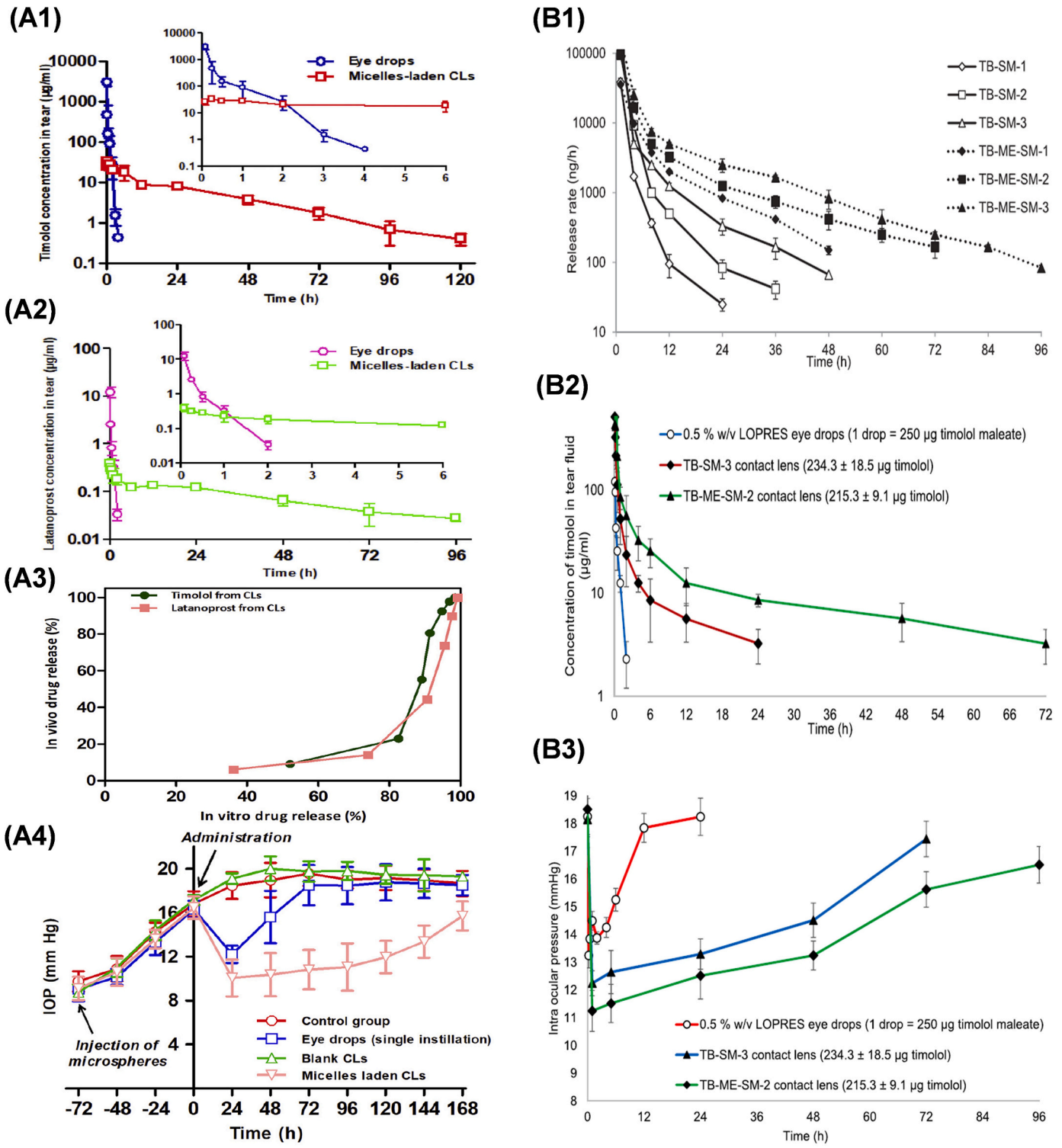

Fig. 8. (A1 and A2) Timolol and latanoprost levels in tear fluid from rabbit eyes after instillation of Xalacom® eye drops (250 µg timolol and 2.5 µg latanoprost) and during wearing of CLs containing both drugs encapsulated in micelles (100 µg timolol and 1 µg latanoprost), (A3) Levy plot for timolol (R^2= 0.7613) and latanoprost (R^2= 0.7119); and (A4) increase in IOP after single injection of polystyrene microspheres three days before treatment and subsequent effect on IOP of the instillation of eye drops or wearing of CLs (drug dose as in former plots; n= 4). Reprinted from Xu et al. [242] with permission from Elsevier. (B1) Timolol release rate in simulated lachrymal fluid from silicone hydrogel CLs loaded by soaking in timolol base solution (TB-SM) or in timolol base microemulsion (TB-ME-SM) (n=3), (B2) timolol levels in tear fluid (rabbit model) (n=6), and (B3) effect of eye drop instillation or CL wearing on IOP values (n=6). Timolol loaded in TB-SM-1, TB-SM-2 and TB-SM-3 was 48.5, 141.3 and 234.3 µg, respectively, and in TB-ME-SM-1, TB-ME-SM-2 and TB-ME-SM-3 was 108.5, 215.3 and 365.8 µg, respectively. Reprinted from Wei et al. [243] with permission by Taylor & Francis Ltd.

(A)

Polymer composition	Drug released(%) 15min	30min
Polymacon	74.5 ± 1.2*	94.1 ± 0.5*
Hilafilcon B	82.1 ± 2.7	97.4 ± 1.3
Omafilcon A	86.2 ± 1.9	98.7 ± 0.5
Nelfilcon A	99.3 ± 0.6*	100.0 ± 0.0
Ocufilcon D	86.8 ± 1.9	99.1 ± 0.5
Etafilcon A	81.0 ± 0.4	97.3 ± 0.4
Iotrafilcon A	91.7 ± 1.2	99.5 ± 0.1
Iotrafilcon B	86.9 ± 0.4	98.4 ± 0.2
Balafilcon A	89.0 ± 1.8	99.0 ± 0.2
Senofilcon A	85.4 ± 0.6	97.6 ± 0.1
Galyfilcon A	92.6 ± 0.8	99.5 ± 0.2

The data is plotted as the mean ± SDs ($n = 3$).
*$p < 0.05$.

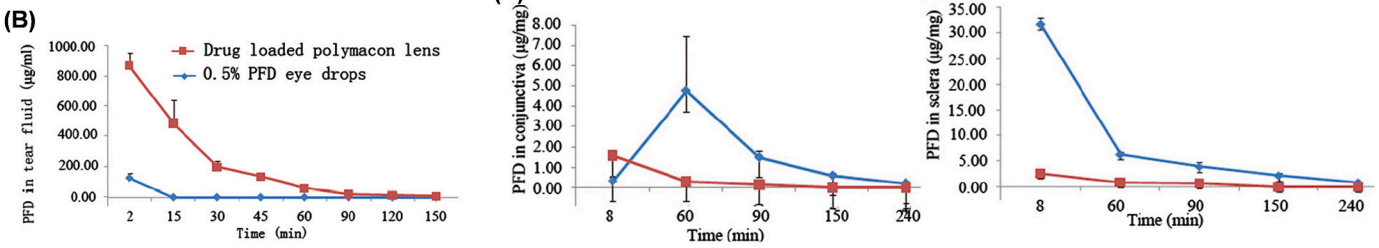

Fig. 9. (A) Percentage of pirfenidone (PFD) released in PBS from commercially available CLs that were loaded by soaking in 2 mL of 0.5 mg/mL drug, (B) levels of PFD in tear fluid (rabbit model) after instillation of one drop of 0.5% PFD eye drop and during wearing of PFD-loaded polymacon CLs; (C-F) PFD levels in different ocular tissues at different times after eye drop instillation and CL wearing. Reprinted from Yang et al. [252] with permission by Taylor & Francis Ltd.

with the preferential release of the drug towards the post-lens lachrymal fluid. Therefore, low levels in the conjunctiva may be the result of rapid clearance, as well as systemic absorption. Simultaneous improvements in pirfenidone loading and controlled release (80-260 min) were observed for silicone hydrogel CLs (Acuvue Oasys®) pre-treated with vitamin E (Table 2, entry 35). In an animal model of alkali burn, pirfenidone-loaded CLs efficiently down-regulated the gene expression of several inflammatory cytokines IL-1β, TNF-α, and TGF-β1 in the cornea [253].

In a subsequent study, CLs showing prolonged release of pirfenidone were designed by embedding a drug insert into two layers of a silicone elastomer (Table 2, entry 36) [254]. The CLs exhibited a very low water content (11%) and 10-times lower dose (15 μg) than the amount instilled using eye drops. *In vitro*, CLs released 52% of the loaded dose in the first hour, followed by ten-times lower release rate in the next 15 hours. *In vivo,* CLs sustained drug levels for 8 h in tear fluid, which led to a higher drug concentration in the aqueous humor after 2 h of wear compared to the eye drop instillation, despite releasing less drug [254].

Pegylated (p-SLNs) and non-pegylated (SLNs) solid lipid nanoparticles have also been tested to enhance the loading of epalrestat (an aldose reductase inhibitor used for the treatment of diabetic neuropathy) for delivery to the retina (Table 2, entry 37). *In vitro* release profiles in simulated tear fluid revealed that CLs directly loaded with epalrestat-encapsulated p-SLNs (DL-EP-p-SLN) had a smaller burst and sustained the release up to 196 h, compared to CLs loaded by soaking (SM-EP-p-SLN), which prolonged the release up to 144 h. DL-EP-p-SLN CLs and SM-EP-p-SLN CLs provided measurable drug levels in tear fluid (rabbit model) for 96 h and 48 h, respectively [255]. Epalrestat accumulation in various ocular tissues after wearing of DL-EP-p-SLN CLs for 24 h were in rank order of lens (7.28 μg/g) > cornea (6.34 μg/g) > aqueous humor (4.84 μg/g) > retina (0.21 μg/g). In contrast, after 24 h of an eye drop instillation, the only measurable levels of epalrestat were detected in the lens (0.87 μg/g) and aqueous humor (0.82 μg/g). These findings support that CLs may facilitate drug penetration to the back of the eye.

Efficient drug delivery to the posterior segment was investigated for the antibiotic ofloxacin loaded in HEMA-based corneal CL, scleral/corneal CL (S/CL) and rings (Table 2, entry 38) [256]. The composition was the same in all cases; the only change referred to the size and shape of the device, which led to different weights: 44 mg CL, 261 mg S/CL, and 183 and 72 mg for ring 1 and 2, respectively. After soaking in the antibiotic solution, the amounts loaded were 282, 1715, 1200 and 565 μg per device, respectively. Drug release was evaluated *in vivo* (rabbit) in terms of the difference between dose and amount of drug remaining in the device after certain wearing periods (Fig. 10 A1). As expected from their higher loading, S/CL and ring 1 released more drug, although the percentage released after 1 h of wear was slightly lower (47.5% and 40.9%, respectively) than that recorded for the CL (59.6%). Preferential biodistribution of ofloxacin to anterior segment tissues was observed for CLs, which provided the highest drug accumulation in the cornea (Fig. 10 A2). S/CL led to high drug levels both in anterior and posterior segment tissues, while the rings facilitated drug accumulation in the posterior segment (Fig. 10 A3). All devices were much more efficient than eye drops in drug biodistribution and provided therapeutically useful drug levels in all tissues, including the retina-choroid after 1 h of wear (0.4 μg/g with CL, and ~4 μg/g with S/CL and rings) [256].

There are only a few studies that report on *in vitro* and *in vivo* release kinetics together with therapeutic outcomes and drug accumulation in ocular tissues [257]. HEMA-based CLs were used to test the potential value of using gold nanoparticles (65 nm) to increase the loading and slow the release of timolol (Table 2, entry 39). Two different approaches were investigated: (i) addition of gold nanoparticles to the monomers before polymerization; and (ii) addition of gold nanoparticles to the timolol solution in which the hydrogels were soaked. These approaches slightly increased the capability of the hydrogels to uptake timolol (284 and 277 μg, respectively) compared to the same hydrogels processed in the absence of gold nanoparticles (253 μg). Regardless of the procedure, all hydrogels released most of the drugs within one hour when tested *in vitro*. Unexpectedly, *in vivo* (rabbit) results showed that timolol levels in tear fluid were quantifiable for 60 h. A significant decrease in IOP values were recorded in the first 24 h of wear. Thus, once again the therapeutic effect appears to be more prolonged than the release profiles recorded *in vitro* under sink conditions. This finding can be related to drug accumulation in various ocular tissues, as observed in Fig. 10 B1 and B2 [257]. Specifically, accumulation of timolol in the ciliary muscle, where most β-receptors are located [258], may explain prolonged IOP decrease. Unfortunately, a similar analysis for the drug instilled using eye drops was not available.

Latanoprost-eluting CLs have been designed by encapsulating a drug-loaded poly(lactic-co-glycolic)acid (PLGA) film in methafilcon (Table 2, entry 40) [259]. Two high molecular weight (118 kDa) PLGA of 65

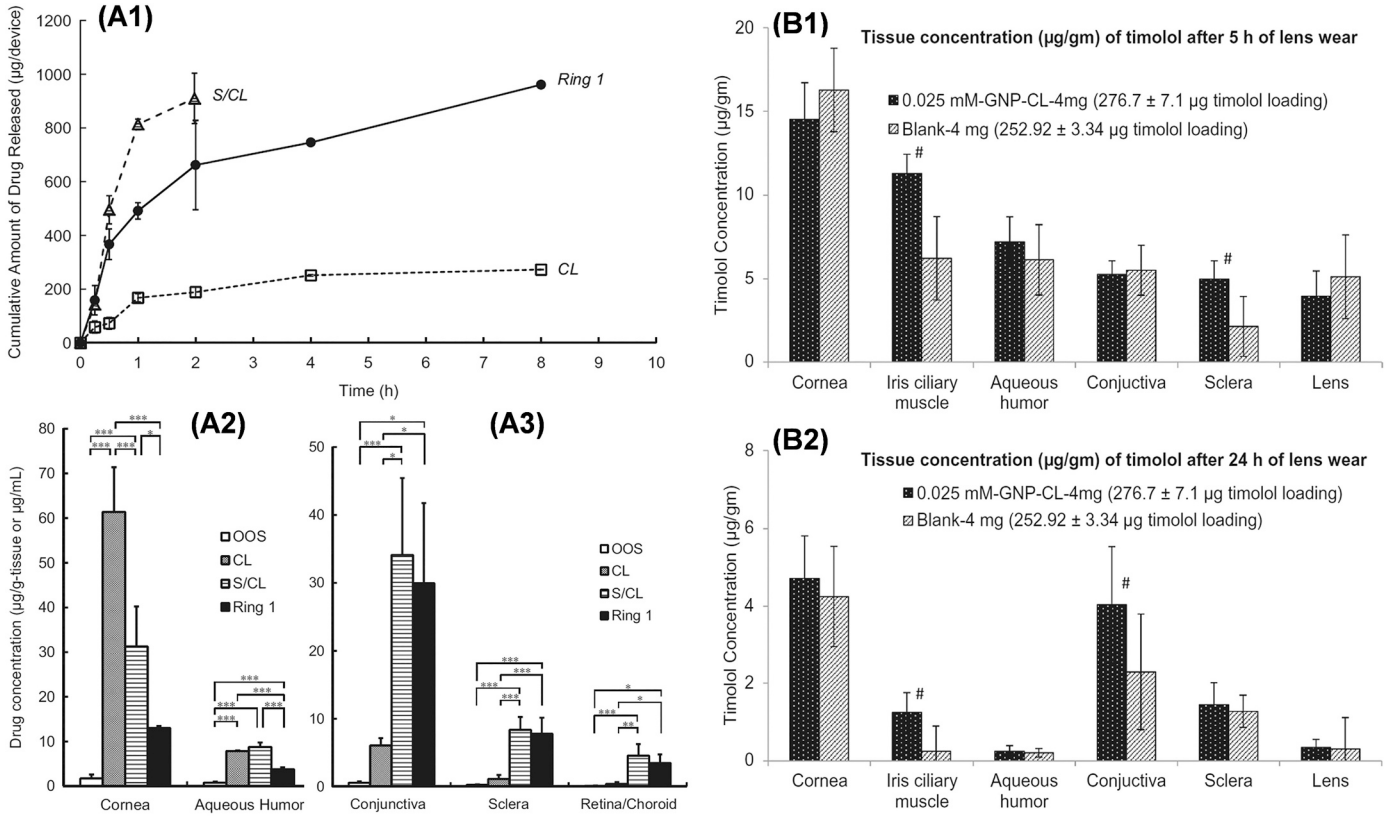

Fig. 10. (A1) Ofloxacin released from HEMA-based corneal CL, scleral/corneal CL (S/CL) and rings once placed in Japanese albino rabbits (nictitating membranes were removed); the S/CL fell out of the eyes after 2 h; and (A2 and A3) ofloxacin levels in ocular tissues after 1 h wearing compared to the levels achieved after one drop instillation of ofloxacin ophthalmic solution (OOS) (n=3; *p<0.05, **p<0.01, ***p<0.005). Reprinted from Shikamura et al. [256] with permission from Taylor & Francis Ltd. (B1 and B2) Evolution of timolol levels in various ocular tissues after wearing of CL with (0.025 mM-GNP-CL-4 mg; 277 µg of timolol) or without (Blank-4 mg; 253 µg of timolol) gold nanoparticles (mean ± SD; n = 3; # p < 0.05). Reprinted from Maulvi et al. [257] with permission from Elsevier.

glycolide:35 L-lactide ratio and 85 glycolide:15 L-lactide ratio were used, and three sets of CLs were prepared containing films of thickness 20, 40 and 45 µm. $CL_{65:35,\ 20}$, $CL_{65:35,\ 40}$ and $CL_{85:15,\ 45}$ contained 89, 178 and 178 µg latanoprost, respectively, and released *in vitro* 90%, 48% and 45% of the drug dose in the first three days. $CL_{65:35,\ 400}$ and $CL_{85:15,\ 45}$ sustained drug release for 20 days more (Fig. 11 A1). *In vivo* (rabbits) concentration of latanoprost was continuously monitored in the aqueous humor for 4 weeks (Fig. 11 A2). Compared to the low C_{max} (54 ng/mL) and the rapid concentration decrease recorded after one drop instillation, $CL_{65:35,\ 20}$, $CL_{65:35,\ 40}$ and $CL_{85:15,\ 45}$ led to C_{max} of 970, 854 and 1473 ng/mL, respectively, and average steady concentration (Css) of 5.6, 39.6 and 21.0 ng/mL. Interestingly, good IVIVC was observed for the percentage of total drug absorbed *in vivo* (percentage of $AUC_{0\text{-}28\ days}$ in aqueous humor) with respect to the percentage of drug released *in vitro*. Moreover, the correlation coefficient became closer to 1 (R^2 =0.98) when $CL_{85:15,\ 45}$ was presoaked for 1 or 3 days in PBS to remove the drug released as a burst before wearing (Fig. 11 A3) [259]. This finding opens the possibility of predicting drug levels in the aqueous humor from the *in vitro* release values. Since latanoprost does not decrease IOP in rabbits, the therapeutic efficacy of similarly designed CLs (PLGA 50:50 and 147 µg drug) was demonstrated *in vivo* in glaucomatous eyes of cynomolgus monkeys [260] (Fig. 11 A4).

Recently, methafilcon CLs encapsulating PLGA 85:15 films loaded with dexamethasone were shown to sustain drug release *in vitro* over 7 days and to provide therapeutic levels in various ocular tissues, including the retina (Table 2, entry 41) (Fig. 11 B1 and B2) [261]. In the aqueous humor (rabbit model) the drug levels were sustained for 7 days, and the CLs effectively prevented suture-induced corneal neovascularization and inflammation (Fig. 11 B3) and also lipopolysaccharide-induced anterior uveitis [262].

Some other *in vivo* studies have been carried out with one optimized formulation and the drug concentration in tissues and the therapeutic response evaluated. Since only one CL type was reported, the effect of a change in the release rate on the *in vivo* levels and therapeutic outcomes cannot be evaluated. Nevertheless, all the studies evidenced that compared to eye drops, CLs favor drug accumulation and prolong the therapeutic levels, which in turn leads to improved therapeutic response with either less dose or less frequent administration. These findings have also been reported for CLs loaded with cyclosporine A impregnated in nanoporous silica by means of supercritical CO_2 (Table 2, entry 42) [263]. *In vitro*, CLs sustained drug release for 8 h, while *in vivo*, high levels of drug were detected for 48 h in cornea and conjunctiva. CLs increased tear volume and stabilized tear film after 1 and 2 weeks of treatment.

6. Conclusions and future perspectives

Rapid release *in vitro* (even in the frame of hours) has resulted in researchers questioning the capability of CLs to really act as drug depots *in vivo*. However, the many examples gathered in previous sections reveal that most *in vitro* tests are not good predictors of *in vivo* performance and indeed CLs that show fast release *in vitro* may lead to sustained levels in tear fluid and remarkably high drug accumulation in key ocular tissues. CLs favor drug accumulation on eye surface tissues, which in turn leads to improved therapeutic response, with either fewer doses or less frequent administration than eye drops. Prolonged supply of drug to the post-lens tear fluid has been demonstrated as a key factor to increase drug ocular bioavailability, consequently leading to favorable drug binding to ocular tissues, drug penetration to the posterior segment, the formation of drug depots ("tissue reservoir effect"), and

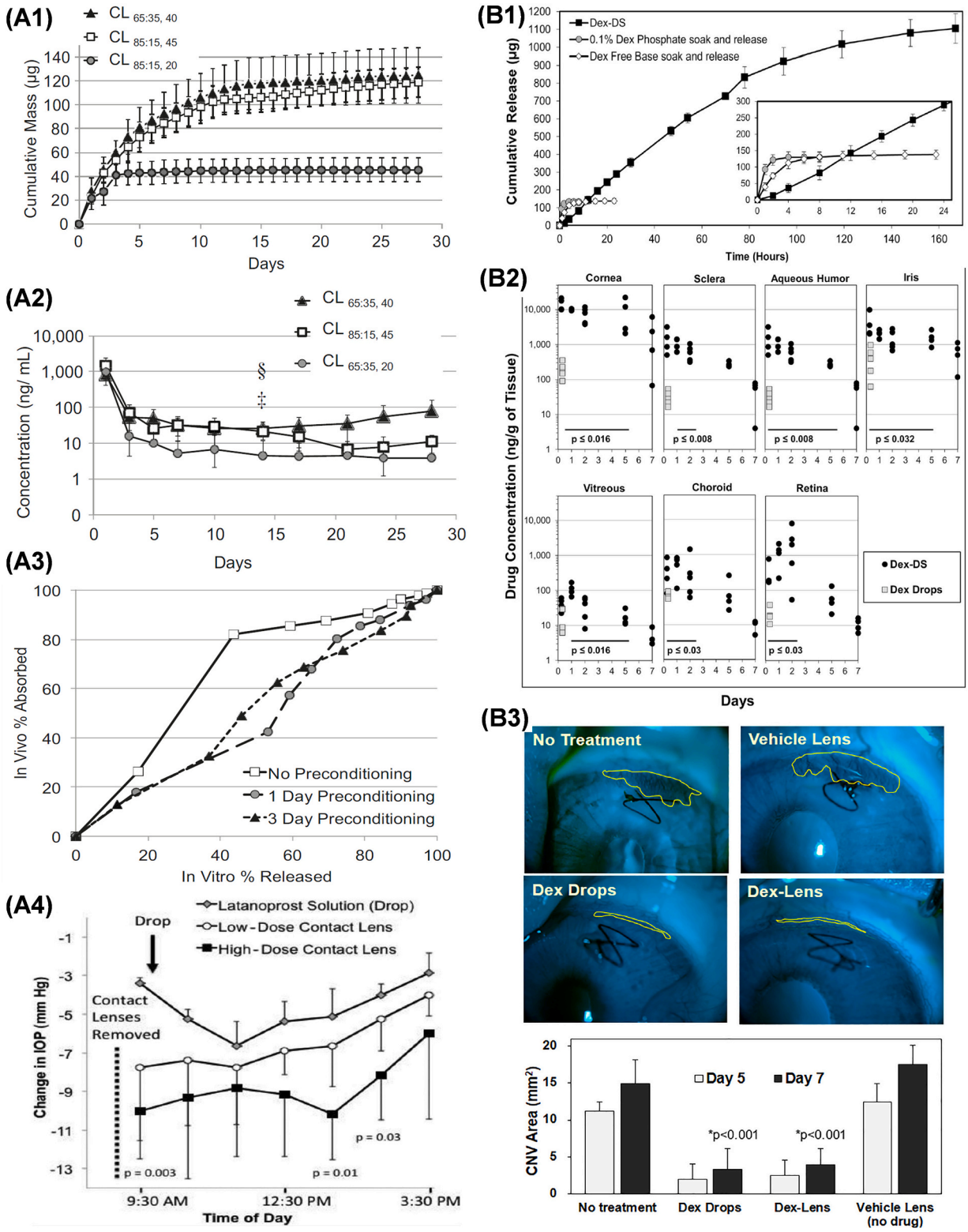

Fig. 11. (A1) Latanoprost release profiles *in vitro* from CL embedding drug-loaded films of PLGA 65:35 of thickness 20 µm ($CL_{65:35,\ 20}$) and 40 µm ($CL_{65:35,\ 40}$) and PLGA 85:15 of thickness 45 µm ($CL_{85:15,\ 45}$); (A2) latanoprost concentration in aqueous humor (rabbits) during CL wearing; and (A3) Levy plots for $CL_{85:15,\ 45}$ without pre-conditioning ($R^2 = 0.875$) and with pre-conditioning for 1 day ($R^2 = 0.979$) or 3 days ($R^2 = 0.982$). Reprinted from Ciolino et al. [259] with permission from Elsevier. (A4) Decrease in IOP recorded in female cynomolgus monkeys (n=4) after the fifth instillation of latanoprost eye drops (two 25 µL-drops of 0.005% drug per day) and after 7 days of continuous wearing of the drug-loaded CLs (97 µg and 147 µg dose), and IOP values recovering after CL removal. Reprinted from Ciolino et al. [260] with permission from The American Academy of Ophthalmology and Elsevier. (B1) Dexamethasone (Dex) release profiles *in vitro* from CLs soaked in either Dex phosphate or base solutions and from CLs embedding drug-loaded films of PLGA 85:15 (Dex-DS); (B2) Dex accumulation in ocular tissues after eye drop instillation and after Dex-DS CLs continuous wearing. Reprinted from Ross et al. [261] with permission from Elsevier. (B3) *In vivo* model of cornea neovascularization (CNV) induced by sutures placed along superior and inferior cornea; the pictures were taken 7 days after suture placement, and bar plots evidence that Dex-loaded CLs decreased the CNV invasion area compared to eyes that received no treatment or only blank CLs. Reprinted from Bengani et al. [262] with permission from Elsevier.

decreased side effects by minimizing drug spillover to the conjunctiva and nasolacrimal duct and systemic circulation.

In most reports on *in vitro* drug release, regardless of whether the test fulfils *sink* conditions, the volume of medium to which the drug-loaded CL is exposed is much larger than the 10 μL of tear fluid available on the ocular surface. A large volume in the *in vitro* release medium may generate a concentration gradient that is much more intense than the one that can be established *in vivo*, which in turn may trigger a faster drug discharge. Small release volume in *in vitro* studies may be not a shortcoming, but composition and dynamics may be more critical. Indeed, some of the best IVIVC have been obtained when the *in vitro* release medium consisted of 2 mL of simulated tear fluid at 34 °C and 100 rpm, and the medium was completely replaced at each sampling time. This was the case for CLs loaded with ketotifen [223], cyclosporine [226], ofloxacin [245] and timolol [257]. Nevertheless, this finding should be interpreted with caution, since the drug was encapsulated in or associated with nanostructures. The situation may be different for drugs directly interacting with the CL. The reasoning behind the use of a 2 mL release medium is that this value approximately matches the daily tear turnover.

Interestingly, CLs that release the drug at slower rate *in vivo* than *in vitro* have also been reported. This is the case for drugs encapsulated in pH- or ionic strength-sensitive coatings, which were tested *in vitro* in 10 mL of simulated tear fluid or PBS at 35 °C and 100 rpm, with replacement of 2 mL at each sampling point [231,232]. Slower release *in vivo* was also recorded for timolol and latanoprost encapsulated in micelles and directly added to the monomers before CL polymerization. The release *in vitro* was evaluated in Franz diffusion cells with 1 mL medium in the donor compartment and 7 mL in the receptor kept at 35 °C and 50 rpm, with 1 mL replacement of the release medium at each sampling point [242].

In addition to volume and dynamics of the release medium, composition is also a key aspect. Biorelevant release medium may require a decrease in polarity of simulated lachrymal fluid (with the addition of organic miscible solvents that resemble lipid components in tear fluid) or an increase in binding substances that could mimic proteins that bind the specific drug. Addition of enzymes typically present in tears may be needed when the drug is linked to the CL or nanoparticles using labile bonds. Such a need was evidenced, for example, in the case of timolol loaded into CLs after being linked to nanoparticles through ester bonds; the *in vitro* release in PBS was sustained for weeks, while the IOP decrease *in vivo* was only maintained for 4 days [239].

Application of 3D printing and microfluidics may enable the design of devices that can tune the composition and flow of the release medium through the drug-loaded CLs in a more biomimetic way. The development of versatile microfluidic devices may help in the progress towards more accurate ways of evaluating *in vitro* drug release from CLs, although strong efforts for validation *in vivo* are still needed. Increasing feasibility of producing a variety of testing devices may lead to more biorelevant testing conditions, but it also has the risk of proliferation of too many models which would not help results comparison.

Currently, improved *in vitro* release tests are demanded as predictive tools of the capability of the CLs to sustain drug release *in vivo*. With the approval of the first drug-loaded CLs, one can envision that in the next years generic drug-releasing CLs may appear and therefore *in vitro* studies that can be used as predictive of bioequivalence will be highly demanded. Therefore, advances in the identification of specific setups for *in vitro* release testing of CLs are becoming an urgent demand. Ideally, experts in the field and regulatory agencies should reach consensus on *in vitro* test conditions and devices. Standardization is very much needed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jconrel.2022.02.014.

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