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Next-generation contact lenses: Towards bioresponsive drug delivery and smart technologies in ocular therapeutics

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ABSTRACT

In contrast to the conventional ocular formulations, contact lenses are well known for their diverse applications ranging from bio-sensing, prevention of myopia, cosmetics, and drug delivery. With a tremendous change in the lifestyle, contact lenses for therapeutic purposes have increased several fold. Contact lenses as medicated lenses suffer from several disadvantages, and to overcome the same numerous approaches have been explored. Researches worldwide have come a long way from cyclodextrin-based and vitamin E-based modified contact lenses to bioinspired approaches to enhance the effectiveness of the drug-eluting contact lenses. The bioinspired approach exploits bioinspired polymeric systems to enhance biocompatibility, specific molecule recognition technique by molecular imprinting, or stimuli-responsive system to improve the biocompatibility, drug loading, and drug delivery efficacy of the drug-eluting contact lenses. Moreover, recent innovations in ocular therapeutics such as nanowafers and microneedle contact lenses, and ocular patches have gained tremendous attention in ocular therapeutics. Another potential application of the contact lenses are smart lenses applied in the biosensing and diagnosis of various ocular disorders. The review summarizes and discusses the widespread therapeutic applications of next-generation contact lenses and various fabrication approaches, including its clinical implications, efforts taken by researchers in exploring the novel materials and diverse forms of the lenses, mechanisms of drug release, clinical trials, and their toxicity and safety concerns.

1. Introduction

The human eye is a very vital and complex sensory organ directly exposed to the environment. The intricate modeling of the ocular globe can be divided into two segments, namely the anterior segment, extending from the cornea to the lens, containing aqueous humor along with ocular tissues like the cornea, conjunctiva, iris, lens, and pupil [1]. The posterior vascular segment extends from the rear side of the lens to the retina and contains vitreous humor. The eye is susceptible to various physical and pathological conditions in both anterior and posterior segments. The prevalent anterior segment diseases are glaucoma, dry eye syndrome (DES), cataracts, eye infections, inflammation, eye tumors (uveal melanoma in the uveal tract, retinoblastoma in the retina, and conjunctival melanoma), and physical eye injury. Simultaneously, conditions such as age-related macular degeneration (AMD), posterior uveitis, retinitis, and diabetic retinopathy (DR) are posterior segment diseases [2].

The potential threat of ocular diseases or conditions with manifestation into blindness or visual impairment raises a global concern. Cataract and uncorrected refractive errors are responsible for nearly 75% of the total issues of blindness worldwide, among which cataract is the leading cause of ocular morbidity [3]. Apart from cataracts, DES and glaucoma are also listed as priority eye diseases by the World Health Organization (WHO), following an approximate prevalence rate of 50% and 3.54%, respectively [4,5]. In recent times, glaucoma is regarded as one of the principal causes of irreversible blindness worldwide, whereas DR accounts for visual impairment. Ocular diseases negatively impact the quality of life and impose an economic burden [6].

Chronic ocular complications such as glaucoma, DES, and infections have effective treatment options such as eye drops and ointments. However, they result in poor management and recovery from the affected conditions due to the eye's substantial anatomical barriers. The conventional therapies require frequent administration at high doses to achieve the therapeutic concentration, reducing their acceptance by the pediatric and elderly patients [7]. Moreover, oily eye drops and

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ointments also cause blurring of vision. Contact lenses (CLs) have shown potential to overcome topical eye drops' insufficient contact time and provide extended drug release. Thus, CLs offer improved bioavailability (BA), reduced side effects, and a well-suited platform for chronic treatment of eye disorders [8].

2. Barriers at the ocular surface and within the eye

Ocular drug delivery encounters discrete barriers ranging from static anatomical barriers, practical physiological barriers, and drug and formulation related barriers. Currently ocular diseases are treated by topical delivery, intravitreal injections, and systemic medications, presenting certain drawbacks and limiting their efficacy and patient compliance [9]. Topically instilled ocular formulations get absorbed mainly through two routes, namely the corneal and scleral routes. The drug absorbs through aqueous humour in the corneal route and reaches the anterior and posterior ocular tissues. The scleral route is molecular weight dependent, and passive diffusion of the drug occurs through the conjunctiva, which enters the posterior segment of the eye [10]. The corneal epithelium hinders hydrophilic drug molecules' permeation, which predominately gets absorbed utilizing the *para*-cellular pathways. Whereas, in the case of lipophilic molecules, the hydrophilic stromal layer hinders the diffusion. The lipophilic drug molecules get absorbed principally by the transcellular routes. The conjunctiva is most permeable to molecules of 5000–10,000 Da, followed by sclera and cornea having the least permeability allowing the passage of molecules $<$ 500 Da [11].

Topical ocular delivery suffers from low ocular BA, typically amounting to $<$5% of the applied dose. The remaining 95% of the treatment gets eliminated by nasolacrimal drainage and systemic absorption through the conjunctival route [12]. The intravitreal injections are employed to bypass the ocular anatomical and physiological barriers and to deliver the drug directly into the vitreous humor of the posterior compartment. Intravitreal injections are reported to present potential systemic and ocular risks and adverse effects such as endophthalmitis, intraocular infection, retinal detachment, intraocular pressure (IOP) elevation, and ocular haemorrhage [13]. Though the risks associated with intravitreal injections are not significant, they are considered responsible for ocular morbidity. For instance, endophthalmitis was reported to occur in 0.04%–1% [14], intraocular inflammation in 1.4–2.9% [13], retinal detachment in ~0.67%, and hemorrhage in 10% of the patients who had undergone treatment with intravitreal injection [15].

The potential role of the non-corneal route in the absorption of drug via bulbar conjunctiva and sclera reaching the eye's posterior segment has been suggested in several reports [10,16,17]. The posterior drug flux can be improved by increasing drug residence time at the ocular surface and providing sustained drug delivery, which can be achieved with CLs. Schultz *et al.* observed the time-dependent increase of drug in the posterior ocular tissues facilitated by a continuous drug availability at the ocular surface [18]. The post-lens tear film (POLTF) aids in slowing down the tear turnover, thereby improving the drug residence time at the cornea and the amount of drug that could penetrate the retina. Nanocarriers or permeation enhancer loaded CLs can further aid in improving the drug influx [16]. Small molecules and lipophilic drugs are easily absorbed through the corneal route. However, conjunctival and scleral routes are the predominant absorption pathways for large and hydrophilic drugs bypassing the anterior segment [10]. However, more research and in-depth understanding is warranted before replacing intravitreal injections by DECLs and enhancing drug absorption following topical delivery.

The inadequacy of systemic administration in achieving therapeutic concentration in the posterior and anterior compartment of the eye is explained by the blood-aqueous barrier (BAB) and blood-retinal barriers (BRB). BAB's tight junction complexes hinder the drug's permeation into the anterior compartment's aqueous humor. In contrast, highly selective and specialized retinal pigment epithelium cells (RPE) restrict the drug's intercellular diffusion in the eye's posterior chamber [19]. Oral delivery, the non-invasive, and patient-friendly administration route is also being explored to treat ocular diseases. However, it requires a high drug dose and a highly bioavailable drug to achieve the therapeutic concentration in the eye. Apart from that, BAB and BRB further restrict the drug's absorption from systemic circulation upon oral delivery. The oral delivery is also limited in ocular treatment owing to safety and toxicity concerns [20].

To overcome the anatomical and physiological barriers, toxicity, and safety concerns, and to achieve the therapeutic concentration in the anterior and posterior segment of the eye, diverse novel techniques are being explored. The use of mucoadhesive polymers, *in situ* gelling systems, ocular inserts, and nanotechnology have been employed to increase the residence time of drugs and hence ocular BA. The *in-situ* gel and mucoadhesive polymers are associated with irritation, blurred vision, and patient noncompliance [21]. Ocular inserts have aided in extended drug release but lead to expulsion, occasional membrane rupture, and burst release [22]. CLs demonstrated superiority over conventional ocular treatment modalities decades ago. CLs are being explored for their diverse vision corrective, drug-eluting, and biosensing capabilities. Also, dual-purpose CLs addressing both the correction of refractive errors and drug-delivery or biosensing are being investigated as per the patient's need.

3. Contact lens - An emerging tool

The CLs are fragile, concave-shaped transparent lenses made of different hydrogel forming polymers. The everyday use of CLs is to correct refractive errors and protect eyes by applying them onto the cornea [23]. United States Food and Drug Administration (US-FDA) and the European Union (EU) have classified CLs under the medical device category prioritizing the patient's safety and efficacy. According to the US-FDA, the daily-wear soft and rigid gas permeable (RGP) lenses have been classified under class II, which exhibits moderate risk. In contrast, extended wear lenses have been listed under class III attributed to their higher risk. The EU has classified short term corrective lenses in class IIa, and long-tern corrective lenses underclass IIb attributed to moderate and high risk, respectively [24].

The applications of CLs and their superiority in the correction of refractive errors such as myopia, hyperopia, presbyopia, and astigmatism are well-established [23]. CLs are preferred over conventional spectacles and refractive surgery. The use of CLs to correct astigmatism has increased, and accounts for $>$12% of the total soft CLs market [25]. The advancement in the fabrication technology offers the CLs in the affordable range. Further, the modern lifestyle has increased the demand for CLs. Apart from vision corrections, the cosmetic CLs with no medical purpose has gained a significant market. The cosmetic CLs has been introduced to protect the eyes from harmful ultraviolet (UV) radiation such as UV-A and UV-B and beautify the eyes [26].

According to global reports, 150 million people use CLs globally [27]. The potential diverse applications and benefits offered by CLs over conventional ocular modalities led to much attention towards further investigation and development of CLs. The advancement in technology aids and fuels the investigation and emergence of CLs as a non-invasive platform technology for ocular applications [28]. The improved vision, quality of life, treatment efficiency, self-reliance, better-perceived appearance, and suitability for sports have further expanded the outreach of the therapeutic modality [29,30]. The CLs are rapidly emerging as an ocular drug delivery device (Table 1) attributed to the *in vivo* and clinical investigations supporting improved ocular BA up to 50% compared to low BA ($<$5%) with conventional formulations [31]. DECLs can deliver a drug to the posterior segment of the eye by increasing the drug concentrations at the ocular surface and providing controlled delivery, which helps to overcome the physiological and anatomical barriers of the eye [18,32].

Table 1
Various types of contact lens in ocular therapeutics.

Drug	Ocular disease	CL type	Monomer	Fabrication technique	Results and Significance	Reference
Brimonidine	Glaucoma	p-HEMA	MAA & MAAM	Molecular imprinting	Improved drug loading and controlled release	[167]
Bimatoprost	Glaucoma	SiHCL	DMA & MAA	Molecular imprinting	Improved drug uptake and sustained drug release	[108]
Olopatadine	Allergic conjunctivitis	SiHCL	DMA	Copolymerization	Retained optical and swelling properties, No protein deposition observed	[107]
Cerium oxide	Ocular surface diseases	pHEMA	NVP & MAA	Copolymerization	The protective effect in the presence of excessive reactive oxygen species	[168]
Timolol	Glaucoma	SiHCL	DMA	Soaking	Prolong IOP reduction for 96 h, Improved drug loading, and drug uptake	[106]
Voriconazole & Diclofenac	*Acanthamoeba* keratitis	SiHCL	–	Soaking	Sustained drug release and improved drug efficacy	[169]
Betaxolol	Glaucoma	SiHCL	NVP	Copolymerization	Minimal drug loss during storage Drug release observed for ten days	[105]
Dexamethasone	Retinal vascular leakage	Soft contact lens	–	–	200 fold increase in retinal drug concentration compared to Dex eye drops	[32]
Loteprednol	Inflammation	pHEMA	NVP	Copolymerization	Drug release extended up to 12 days without any cytotoxicity	[176]
Pirfenidone	Scarring	SCL	–	Soaking	Improved drug retention and concentration in cornea and aqueous tear	[170]
Biosensor	IOP sensor	SCL	–	–	24 h continuous IOP monitoring	[139]
Cysteamine	Corneal Cystinosis	Nanowafers		PDMS molding technique	Improved therapeutic efficacy, safety profile, and extended drug release	[147]
Dexamethasone	Dry eye disease	Nanowafers		PDMS molding technique	Reduced dose and superiority over Dex eye drops	[145]
Olopatadine	Allergic conjunctivitis	p-HEMA	–	Molecular imprinting	Sustained drug release and ocular biocompatibility	[128]
Timolol	Glaucoma	p-HEMA	MAA	Copolymerization	Drug release sustained for 2–4 weeks	[131]

Schultz *et al.* have investigated the potential of hydrogel contact lenses (HCLs) to deliver the steroids, small molecule, and large biomolecules to the posterior segment of the eye. The significant concentration of prednisolone and beclomethasone in the posterior segment and vitreous humor were detected in the rabbit eyes after treating with drug-loaded HCLs [18]. Ross *et al.* have developed dexamethasone eluting CLs (Dex-DS) to treat the inflammation present in the posterior segment and evaluated for safety and efficacy. The Dex-DS efficacy was assessed in a rabbit model of retinal vascular leakage. A significantly higher concentration (200 times) of Dex was observed in the retina followed by Dex-DS application compared to Dex eye drops without any toxicity upon a 4-week repeated dose study. Dex-DS successfully inhibited retinal vascular leakage [32]. Zhu *et al.* have developed PEGylated solid lipid nanoparticles laden CLs to treat cataract and diabetic retinopathy by sustained delivery of epalrestat. The biodistribution studies exhibited a significantly higher concentration of epalrestat upon applying PEGylated solid lipid nanoparticles (SLNs) laden epalrestat CLs in the retina compared to epalrestat eye drops [16]. Apart from improved BA, the DECLs minimize the drug loss, frequency of administration and increase patient compliance.

4. Development of contact lenses

4.1. Key considerations for manufacturing

Considering the eye's sensitive nature, the formulation and application of the ocular drug delivery systems need extra caution to preserve visual acuity and homeostasis. To maintain the comfort and visual acuity and normal physiological functions for the wearers of CLs, appropriate transparency, oxygen permeability, water diffusion, and mechanical stability play an essential role. All these parameters are crucial that decide the biocompatibility of the CLs [33].

The oxygen permeability (Dk) is the lens material's property, representing the ability to permeate oxygen to reach the eyes, and oxygen transmissibility (Dk/t) depends on the CLs, which represents the degree to which oxygen permeates the lens of a given thickness [34]. The higher the Dk/t, better comfort, and prolonged tolerance, while reduced oxygen transmissibility can lead to corneal epithelial acidosis, hypoxia, and discomfort. The studies conducted in the open eye show that the lens transmissibility (Dk/t) in the range of 20–24 Barrer/cm is sufficient to prevent corneal swelling. The oxygen permeability is directly proportional to water content in an HCL, whereas it is inversely proportional in a silicone CLs [35,36]. The water content plays a vital role in maintaining stable tear film, and the hydrophobic nature of the CLs may alter the tear film. The water content of the poly(hydroxyethyl methactrylate) (pHEMA) is directly proportional to the oxygen transmissibility and decrease in the refractive index. It was also observed that high water content attracts the deposition of debris on the CLs. The maximal comfort with minimal physiological alteration and wear tolerance is reported to depend on the water content of the CLs [37,38]. The CLs are placed on the the ocular surface, and lens material characteristics directly influence the surface wettability properties. In the presence of hydrophobic surface properties, the tear film gets disrupted, and it requires hydrophilic properties to maintain the integrity of the tear film. The better surface wettability of the CLs prevent irritation and discomfort due to dryness and improves the compliance and acceptability by the wearer [39].

Apart from Dk/t and wettability, transparency and transmittance of UV–visible light through CLs are an essential parameter to be considered. Transparency plays a critical role in preserving the visual acuity of the eye. Another significant aspect is protecting ocular tissues from carcinogenic radiations by averting the transmittance of harmful UV radiations. The mechanical stability of the CLs are another parameter to be considered. The degree of comfort of wearing CLs dramatically depends on the chemistry and material properties. Mechanical strength influences the durability of the CLs. Appropriate mechanical strength is required to prevent mechanical deformation during storage and blink upon application [40]. The biocompatibility and quality of the HCL also depend on the degree of protein sorption from the tear film. The accumulation of denatured and degraded proteins upon extended wear time leads to dryness and is also associated with immunological and infective reactions. The protein adsorption on the surface of CLs is associated with microbial and fungal infections [41]. The glass transition temperature of the polymeric material determines the thermomechanical characteristics of the CLs. The thermomechanical properties play an essential role in providing comfort to the end-user. Apart from these factors, the

composition of the CLs affects the physiology of the eye, drug loading, and drug release kinetics from DECLs [42].

4.2. Evolution of contact lens materials

The advancement in CLs materials is continuously evolving from introducing a glass scleral lens in the 1930s to date (Fig. 1). The material from the hard CLs, also called a rigid gas permeable (RGP) lens to soft silicone hydrogel contact lens (SiHCL), has come a long way. Currently, the CLs market is dominated by silicone hydrogel (64%), followed by hydrogel (22%.) The use of RGP materials declining over a while contributes only 1% of the total market [43]. The lens material plays a significant role in determining the mechanical properties, wettability, oxygen permeability, water content, and visual acuity, which further decides the comfort and wear time.

Based on the materials, the CLs are classified into two different types: the rigid or hard CLs and the soft CLs. The rigid contact lens (RCLs) are prepared using different polymers such as PMMA (polymethyl methacrylate), CAB (cellulose acetate butyrate), SMA (siloxy methacrylate), and FSA (fluro-siloxy methacrylate). The glass material was replaced by the first RCL prepared using PMMA by Mulle and Ohring in 1936 [8]. The PMMA lenses improved optical clarity, ocular biocompatibility, and mechanical durability but suffered from negligible oxygen permeability and water content. The intermolecular forces and low free volume present between PMMA polymeric chains render them immobile and prevent the permeation of oxygen and water [44]. In the 1980s gas permeable lens, SMA, and FSA combined with MMA (methyl methacrylate) emerged and prevailed over PMMA due to their superior oxygen permeability and rigidity. The application of RCLs are continually declining due to inherent inflexibility, protein adsorption, abrasive nature, and shorter wear time (<1 day) [8].

Despite better durability, lightweight, high optical resolution, and decent wettability, RCLs have disadvantages such as lower oxygen permeability, poor tolerability, and low adaptability, making them less acceptable. To overcome these drawbacks, the hydrogel-based soft contact lens were developed. The soft contact lenses (SCLs) are a cross-linked network of hydrogels composed of hydrophilic monomers. HCLs offer improved wettability, oxygen permeability, and adaptability and comfort over RCLs. The SCLs have dominated the contact lens market, reaching a point of >85%. The SCL has proven safety, comfort, and improved ocular tissue compatibility compared to the RCL. The increased oxygen permeability, water content, visual acuity, and mechanical properties of the HCLs have increased the acceptance by the patients. The different polymers used for the preparation of SCL are p-HEMA, MAA, polydimethylsiloxane (PDMS), dimethyl methacrylate (DMA), and n-vinyl pyrrolidone (NVP) [45].

Fig. 1. Evolution of contact lenses (CLs) from the first introduction as scleral CLs made of glass to the introduction of customized silicone-hydrogel contact lenses (SiHCLs).

The HEMA-based and SiHCLs are copolymerized with the hydrophilic monomer to increase the water content, oxygen transmissibility, and wettability. The conventional HCL has water content below 45%, which affects the oxygen transmissibility, and is associated with dryness and discomfort. Various hydrophilic monomer, such as NVP and MAA, are used to increase the water content of the CLs [46,47]. But the potential drawback of a hydrophilic monomer is the protein adsorption due to increased hydrophilicity and electrochemical charges [48]. Modern HEMA-based HCLs have evolved with diverse techniques of chemical modifications such as grafting with silver and copper nanoparticles (antimicrobial) and cationic or anionic surfactants to improve the lens functionality [49]. Various commercial HCL and SiHCL, the FDA classification, and their material properties have been provided in Table 2.

HEMA-based SCL's major drawback is short wear time attributed to the inadequate oxygen permeability [50]. SiHCLs comprise polymers with Si-O bonds in their backbones, such as silicone, siloxanes, fluorosiloxanes, and their derivatives copolymerized with a hydrophilic monomer such as HEMA, DMA, and NVP. The widespread use of SiHCLs are associated with their highest oxygen permeability (>100 Dk) among various materials. The prevailing concerns related to SiHCLs applications are precorneal deposits or lipid plugs (known as mucin balls), wettability issues due to the hydrophobic nature of SiHCLs, and ocular surface incompatibility [51]. To overcome these, SiHCLs are grafted or encapsulated with hydrophilic antifouling materials using chemical modifications to enhance wettability and antifouling behavior. Plasma treatment as a post-fabrication technique is also helpful in improving lens wettability [44].

4.3. Fabrication strategies for drug-eluting contact lenses

In general, manufacturing techniques for commercial CLs are lathe cut method, spin coating method, and injection molding method at the large-scale productions [8]. The characteristics and purpose of the prepared CLs mainly depend on the fabrication technique. The lathe cut technique is commonly used for the preparation of all types of CLs. Still, injection molding technology is taking over the market due to efficiency and low-cost processing. The trend of disposable CLs has further increased the dominance of the injection moulding technique. Apart from the industrial setup, laboratory investigations also rely on the injection moulding technique due to simple and easy operation without using large equipment and tools as required in other methods. The injection molding technique involves implementing UV or thermal polymerization for the fabrication of the CLs. The polymerization technique further affects the characteristics of the CLs. For instance, thermal polymerization produces rigid and fragile lenses, whereas UV polymerization leads to a more flexible and high-water containing lenses.

The DECLs employ a commercially available CLs instead of exclusive preparation due to equipment requirements and cost constraints. The current research is directed towards the materials and fabrication technique of CLs to achieve efficient lenses with pertinent visual performance drug loading and release kinetics. The reported strategies for the fabrication of DECLs are soaking in concentrated drug solution, cyclodextrin (CD)-based fabrication, and molecular imprinted CLs [42].

Table 2
Commercial hydrogel and silicone hydrogel Contact lens and contact lens material properties.

Commercial name	Polymer Material	Monomers	Water Content (%)	Oxygen transmissibility (Dk/t)	FDA Group	Manufacturer
Hydrogel contact lens						
Alden HP	Hioxifilcon B	pHEMA/GMA	49	22	I	Alden Optical
ACUVUE Moist	Etafilcon A	pHEMA/MA	58	17	IV	Johnson & Johnson
Biotrue	Nesofilcon A	pHEMA/NVP	78		II	Bausch & Lomb
Biomedics 1-day	Ocufilcon B	pHEMA/MA	52	16.8	IV	Cooper Vision
Clear38LE	Polymacon	pHEMA/NVP/CMA	38	7.5	I	Clearlab
Dailies	Nelfilcon A	PVA/FMA/HPMC/PEG	69	26		Alcon
Easy day	Ocufilcon	pHEMA/MA	55	24	IV	Cooper Vision
Focus Monthly	Vilfilcon A	pHEMA/MA/NVP	55	16	IV	CIBA Vision
NewVue	Vifilcon A	HEMA/PVP/MA	55	16	IV	CIBA Vision
Optima FW	Polymacon	HEMA	38	24	I	Bausch & Lomb
Proclear Multifocal	Omafilcon B	pHEMA/PC	62	21.3	II	Cooper Vision
Proclear 1-day	Omafilcon A	pHEMA/PC	59	28	II	Cooper Vision
SofLens	Hilafilcon B	pHEMA/NVP	70	22	II	Bausch & Lomb
Sauflon 55	Methafilcon A	pHEMA/MA	55	18	IV	Bausch & Lomb
Silicone hydrogel contact lens						
ACUVUE OASYS	Senofilcon A	mPDMS/pHEMA/DMA/siloxane macromer/ PVP/TEGDMA	38	121		Johnson & Johnson
ACUVUE TruEye	Narafilcon A	MS/DMA/pHEMA/TEDGMA/PVP	46	118	–	Johnson & Johnson
ACUVUE Advance	Galyfilcon A	mPDMS/DMA/pHEMA/EGDMA/siloxane macromer/PVP	47	86	I	Johnson & Johnson
Air Optix Aqua	Lotrafilcon B	DMA/TRIS/Siloxane macromer	33	110	I	CIBA Vision
Bioinfinity	Comfilcon A	–	48	160	I	Cooper Vision
Focus Night & Day	Lotrafilcon A	DMA/TRIS/Siloxane macromer	24	140	I	CIBA Vision
Clariti 1-day	Somofilcon A	–	56	86	–	Cooper Vision
PureVision	Balafilcon A	Siloxane macromer/NVP	36	99	III	Bausch & Lomb

FDA classification: FDA Group I: Nonionic (<1%) and low water content (<50%), Group II: Nonionic (<1%) and high water content (>50%), Group III: Ionic (>1%) and low water content (<50%), Group IV: Ionic (>1%) and high water content (>50%). pHEMA: poly-2- hydroxyethyl methacrylate, GMA: glycerol methacrylate, NVP: N-vinyl pyrrolidone, CMA: cyclohexyl methacrylate, FMA: N-formylmethyl acrylamide, HPMC: hydroxypropyl methylcellulose, PEG: polyethylene glycol, PC: 2-methacryloyloxyethyl phosphorylcholine, mPDMS: monofunctional polydimethylsiloxane, DMA: N, N-dimethyl acrylamide, PVP: polyvinyl pyrrolidone, TEGDMA: ethylene glycol dimethacrylate, EGDMA: tetra ethylene glycol dimethacrylate, TRIS: trimethylsiloxy silane.

4.3.1. *Soaking technique*

In the soaking technique, the lens is soaked in a concentrated aqueous drug solution, wherein the drug loading is achieved by the drug's physical adsorption (Fig. 2A). The concentration gradient leads to the non-covalent adsorption of a drug on the polymeric matrix, followed by drug release based on molecular diffusion. The drug loading and release kinetics are significantly influenced by drug concentration in soaking solutions, the molecular weight of the material, and the water content [174]. The soaking technique is the most cost-effective and straightforward technique for drug loading, but it suffers from disadvantages such as lower drug loading, non-reproducibility, and burst release. To overcome the burst release, vitamin E (Vit E) as a diffusion barrier is employed (Fig. 2B). Vit E is a potent antioxidant, biocompatible, and offers potential therapeutic benefits. Vit E increases the diffusion path length of a drug and imparts sustained and controlled drug release kinetics while maintaining efficient visual acuity and drug loading without any interference [52–54].

4.3.2. *Molecular imprinting techniques*

The molecular imprinting technique is based on the bioinspired or bio-mimicking principle (Fig. 3). The high-affinity cavity in a polymer matrix is generated by employing a drug template or mimicking receptor structure for the drug with high selectivity and specificity [55]. Molecular imprinting technique enhances the molecular recognition characteristics and hence improvement in drug loading. Further, molecular imprinting technology has the potential to sustain the drug release for a more extended period. The molecular imprinting technique is discussed in-depth under the section '*Bioinspired Contact Lenses*.'

4.3.3. *Implantation and layered coating techniques*

Desai *et al.* have developed drug implant-laden CLs to prevent the burst release from the therapeutic CLs [33]. Bimatoprost and timolol loaded implants were fabricated and cast on the base monomer solution to prepare drug implant loaded CLs. The center cavity was left blank to avoid visual disturbances (Fig. 4). Multiple implants of bimatoprost/timolol loaded SiHCLs showed minimal burst release and sustained drug release for 72 h compared to conventional soaking methods for drug loading into the CLs. The *in vivo* pharmacodynamics study of CLs showed the reduction of IOP for 120 h, without any ocular irritation, conjunctival swelling, and chemosis. The technique was seen to bypass the side effects of the initial burst release of a drug upon application.

Ongkasine *et al.* have reported methotrexate loaded implantable intraocular lens (IOL) to treat posterior capsule opacification. The IOL exhibited a significant effect on the reduction of fibrosis by inhibiting epithelial-mesenchymal transformation [56]. The implantation technique reduces patients' risk in compliance and critical and lengthy surgical treatments in such cases. Another drug loading technique is layered coating to prevent the protein adsorption and sustain the drug release by preventing the initial burst release (Fig. 5). Silva *et al.* have investigated diclofenac loaded SCLs by applying layer by layer coating of ionic polysaccharides such as chitosan, sodium alginate, and sodium hyaluronate. The coating sustained the drug release for a more extended period and prevented initial burst release [57].

4.3.4. *3D printing techniques*

3D printing has revolutionized the medical and surgical disciplines worldwide. Various studies have been reported employing 3D printing technology to manufacture eyewear and medical devices [58–60] and more recently the generation of 3D human corneal model [61]. 3D

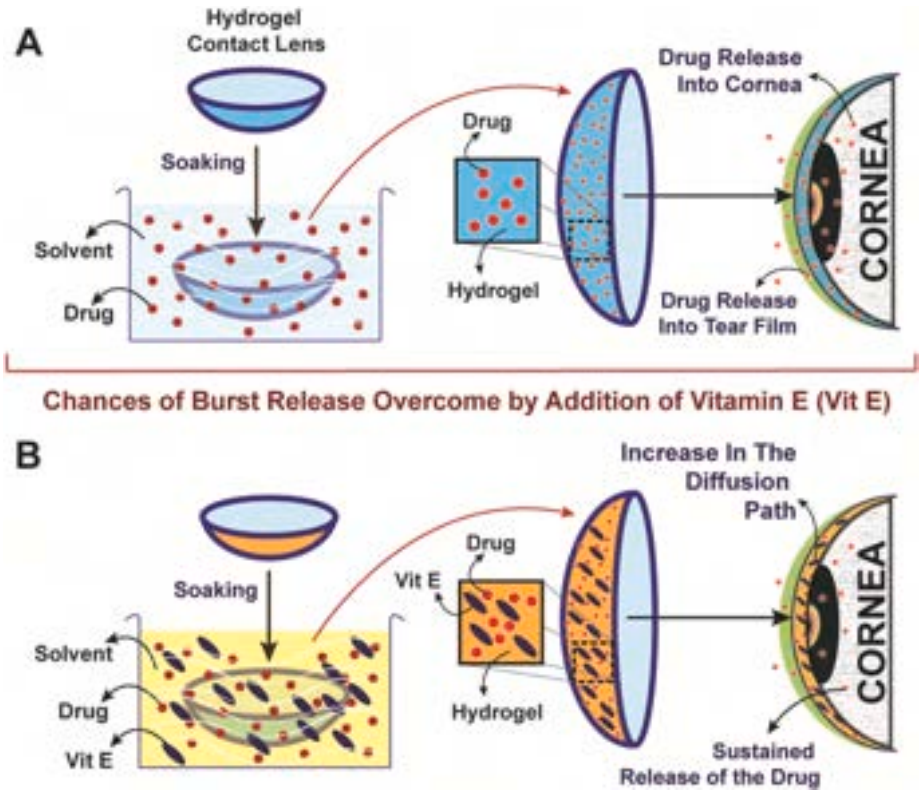

Fig. 2. Soaking technique for the loading of drugs onto the hydrogel contact lens (A) and the prevention of burst release with the addition of Vitamin E (B).

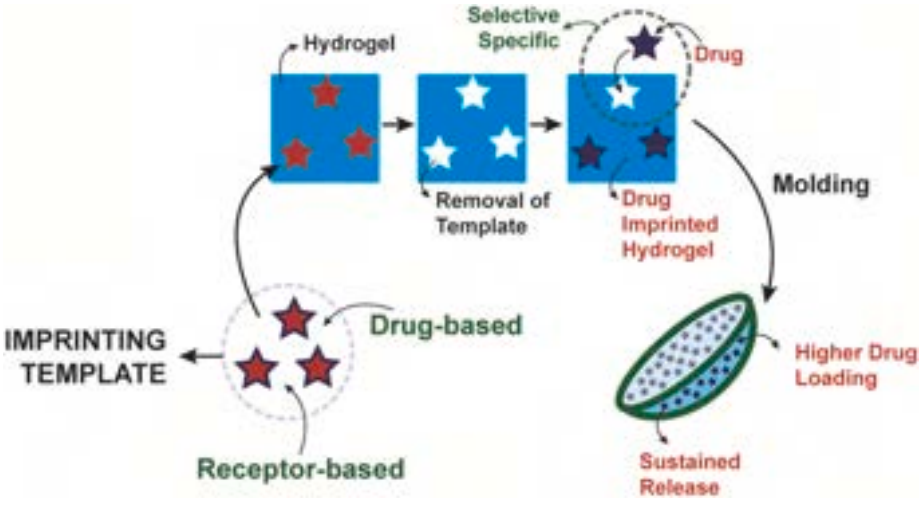

Fig. 3. Molecular imprinting technology for specific and selective drug loading onto the hydrogel contact lens using drug-based or receptor-based imprinting template.

printing technology can be a potential alternative to the personalized medication of the DECLs. 3D printing can be employed to fabricate the desired modified CLs to achieve more flexibility and customized lenses for efficient design, drug delivery, and patient compliance [59].

4.4. Interaction at the ocular surface and release kinetics

The cornea and sclera of the eye are directly exposed to the environment and are covered by 7–10 μm thick pre-corneal tear film, which accounts for approximately volume of 6–7 μL [62]. The tear film functions as a protective and nutritional medium, and preserving the homeostasis is necessary to balance ocular health and vision acuity. The tear film comprises an anterior 0.015–0.16 μm thick lipid layer followed by a 4 μm thick aqueous layer and posterior mucin layer in contact with the epithelial surface [63,64]. The lipid layer's essential functions include stabilizing tear film and preventing evaporation of the aqueous layer. In contrast, the aqueous layer lubricates the ocular surface for physiological functions and aids in smooth light refraction. The mucin layer assists in water re-spreading by keeping the ocular surface wet [65]. The tear film contains various proteins, salts, accessory secretions, lipids, and mucins, which help maintain the ocular surface and tear film's homeostasis [64,66].

The interaction of CLs at the ocular surface establishes the drug release, drug availability at the corneal surface, sink condition, and

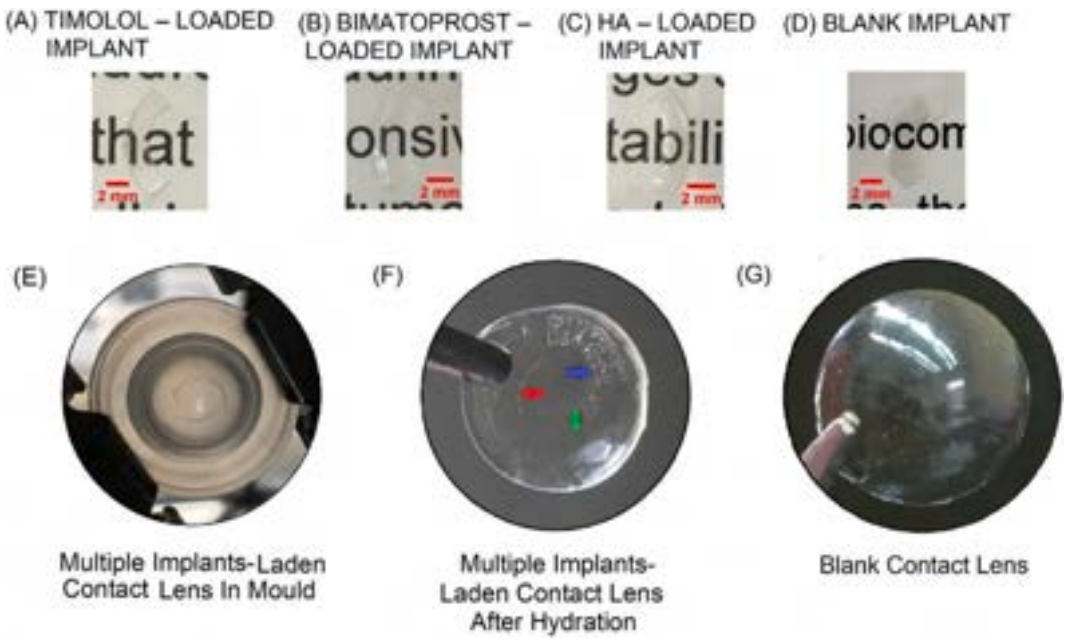

Fig. 4. Timolol loaded implant (A), bimatoprost loaded implant (B), and hyaluronic acid (HA) loaded implant (C) along with blank implant (D). Multiple implants loaded contact lens before the hydration (E) and after hydration (F) and blank contact lens (G) can be seen. The 6 mm center aperture in (E) and (F) can be seen for optical clarity. (Reproduced from Desai *et al.* [33] with permission from Elsevier).

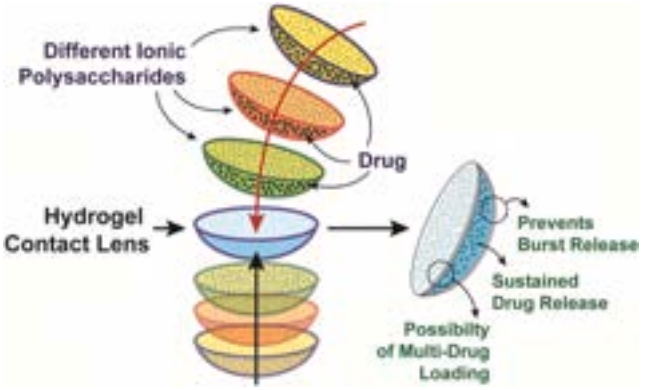

Fig. 5. Loading of the drug on hydrogel contact lens by layer-y-layer coating using ionic polysaccharides, allowing for higher drug loading, sustained release, and effectively preventing the burst release.

corneal permeation. The CLs divide the pre-corneal tear film into pre-lens tear film (PLTF) and post-lens tear film (POLTF), as presented in Fig. 6**.** The PLTF is directly exposed to the outer surroundings, whereas POLTF forms between the posterior lens and cornea. Both PLTF and POLTF play a significant role in balancing ocular health and vision acuity as the irregular or rough surface of the PLTF may affect the quality of vision. In contrast, the thickness of the POLTF determines the oxygen transmission and hence the ocular comfort [67]. The role of PLTF is to stabilize the lipid layer for wearing comfort and quality of vision and facilitate rehydration of the lens surface in addition to preventing dehydration. The POLTF helps epithelial nutrition, epithelial hydration, lubrication for lens movement and comfort, and promotes epithelial exfoliation [68].

Golding *et al.* also observed that increased blinking rate leads to a decrease in POLTF and lowers the lens movement. The thickness of the CLs decreases over the period as part of the dehydration process observed in the case of HCLs. The high water content - CLs dehydrates rapidly compared to the low water content irrespective of the CLs thickness [69]. The POLTF aids in removing cellular and inflammatory debris and depletion in the same makes ocular surface prone to inflammation or infections and arcuate staining.

The release kinetics from the CLs is influenced by PLTF and POLTF, as both play a significant role in maintaining the drug release, drug diffusion, and sink condition. The mass transfer process is also called 'diffusional transport processes' from CLs to the PLTF or POLTF, dependent on the polymer swelling and drug-polymer interactions. The CLs releases the drug into the PLTF and POLTF upon application, in which the blinking phenomenon limits drug diffusion in PLTF. The rapid breaking of PLTF during the blinking process increases the film's

Fig. 6. The ocular surface and the tear film where (A) the layers of the typical tear film, namely the outer lipid layer, the intermediate aqueous layer, and the inner mucus layer in contact with the cornea; and (B) the placement of the contact lens within the aqueous portion of the tear film thereby dividing the tear film into two sections namely the pre-lens tear film (PLTF) and post-lens tear film (POLTF).

dehydration and reduces the drug flux. The increased ocular BA offered by CLs are attributed to the poor mixing of POLTF and outer tear fluid and hence longer residence time of the drug into the eye. The drug's partition between the polymeric membrane and tear film is defined by solubility, affinity, and interaction of the drug with both the medium [70].

The drug uptake and release kinetics depend on the various parameters such as the drug's solubility, the water content, lens properties, and drug loading techniques. The excellent drug uptake during drug loading was observed for the lipophilic compound, whereas the highly hydrophilic drug nature reduces the drug uptake [71]. Similarly, CLs with high water content increases the drug loading compared to the SiHCLs. The high drug loading in the high-water content CLs also releases the drug rapidly compared to the SiHCLs [72]. The release kinetics from the CLs reported the initial burst release followed by sustained release. The cross-linked hydrogel structure of the CLs entraps the drug into the gel-like structure, and the physical adsorption of a drug on the surface is the reported phenomena for the drug loading. Furthermore, the drug loading is also limited to equilibrium, restricting the drug release [70]. Various drug loading techniques have been employed to increase the drug release and overcome the burst release kinetics observed, such as molecular imprinting, drug copolymerization, and vit E loaded CLs, and dispersion of drug-loaded nanoparticles [73–75].

To study the drug release kinetics from the CLs, the parameters employed in *in vitro* studies are inconsistent. They require *in vivo* experimental data to mimic the complicated ocular physiology, which is not explored well. The average tear turnover rate in healthy eyes increases from 1.51 ± 0.58 μL/min to 2.82 ± 1.45 μL/min while wearing the CLs [76]. The small sink conditions employed to carry out release studies without external mixing and no solvent exchange further limit the mass transfer process. The application of the Higuchi equation to define release kinetics in a non-perfect sink condition may result in erroneous results. Li *et al.* attempted to model the dispersive properties of POLTF based on lid movement-driven dispersion and mass transfer in POLTF. Still, the model only accounted for the specific blink movement [77]. Li *et al.* later proposed the first-ever model to account for the release kinetics from the DECLs by overcoming the Creech model's limitations. The clinical results suggested that the drug delivery by CLs is approximately 33 times more significant than the conventional eye drops, which agrees with the model developed by Li *et al.* based on the Fickian diffusion in CLs mediated drug delivery [78].

5. Next generation contact lenses

With the advancement in materials and polymers, it is now possible to improve functionality of CLs, thereby prompting their implications for the clinical management of ocular complications. The applications of CLs are not limited to correct visual acuity and cosmetic purposes but expand into the segment of ocular drug delivery and bio-sensing.

5.1. Drug-eluting contact lenses (DECLs)

5.1.1. Unmodified DECLs

DECLs are therapeutic CLs prepared by loading the drug in a commercially available CLs or by CLs exclusively prepared for ocular drug delivery. The DECLs have the potential to overcome the several limitations associated with conventional eye drops, such as non-specific absorption, short residence time, continuous dilution, and precorneal drug loss, which leads to multiple administration and inefficient drug delivery management [9]. The DECLs offer effective and non-invasive extended ocular delivery by enhancing a drug's retention time at an ocular surface up to 30 min compared to 5 min residence time of eye drops [79]. The application of CLs as an alternative approach to ocular drug delivery has potential advantages in ocular BA, dosing regimen, and patient compliance. Otto Wichterle first mentioned using a contact lens for ocular drug delivery and his Czech colleagues in their patents published in 1965, followed by the first report of 1% homatropine soaked CLs by Sedlacek [80].

The unmodified DECLs are medicated CLs prepared by presoaking the marketed CLs in a drug solution to achieve the drug loading. In the earlier days, the drug-soaked CLs were investigated as an alternative to conventional eye drops. The drug-soaked CLs showed improved ocular BA compared to conventional eye drops with a lower dose. In 1955, Foss experimented with 10% acetazolamide by topical and sub-conjunctival route with an insignificant decrease in intraocular pressure (IOP) [81]. In 1985, Friedman *et al.* observed that the 2.5% acetazolamide and methazolamide soaked CLs aided in a significant reduction in IOP (>5 mmHg) attributed to the increased retention and absorption of the drugs [82]. Busin *et al.* reported the sustained release of gentamicin from the presoaked CLs. Gentamicin is an antibiotic and requires multiple instillations to maintain effective concentrations. Using the presoaked CLs, gentamicin delivery was extended to 3 days while maintaining minimum inhibitory concentrations [83]. The extended delivery of 0.5% of gentamicin can be explained by the ability of CLs to act as a drug reservoir and increase the drug availability at the precorneal site for ocular absorption [80].

5.1.2. Modified DECLs

The mere drug loading by soaking into drug solution is accompanied by unspecific absorption of the drug into a polymeric hydrogel network responsible for reduced drug loading, initial burst release, and uncontrolled drug delivery. The initial burst release is associated with the drug molecules loosely adsorbed on a surface, leading to unwanted side effects and drug loss. Drug loading and drug-releasing are two critical parameters for designing DECLs and dependent on many factors such as material of the lens, drug nature, method of preparation, and drug loading techniques. Besides side effects, ocular infections such as microbial or fungal keratitis require the maintainence the inhibitory concentrations for effective treatment; failing the same or incomplete treatment is associated with microbial resistance and the recurrence of infections [73]. The leading cause of glaucoma induced irreversible blindness requires sustained drug delivery therapy for an extended period to avert the irreversible vision loss.

Ocular conditions such as ocular infections, cystinosis, and glaucoma require frequent installations and extended treatment duration, leading to poor patient compliance. To overcome frequent administration, the Vit E modified drug-eluting HCLs has been reported as a potential alternative. The reported studies suggest that sustained drug release up to two weeks can be achieved with HCLs. To overcome low drug release kinetics, Peng *et al.* proposed the Vit E modified SiHCLs. Vit E is safe, biocompatible, and has demonstrated therapeutic benefits in various ocular conditions such as keratocyte apoptosis and cataract [50]. Vit E acts as a diffusion barrier by increasing the diffusion path length and hence decreases the drug transport rate into the tear film from the contact lens polymer network [73]. Peng *et al.* also explored the effect of Vit E on the drug loading and drug release dynamics along with oxygen permeability, ion permeability, transmittance, and UV protection. The study reports that Vit E can increase drug loading and sustains the drug release for a month. The hydrophilic drugs in Vit E modified SiHCLs need to diffuse around the Vit E barrier, whereas hydrophobic drug molecules diffuse through the Vit E aggregates. The Vit E aggregates act as a barrier by generating long, tortuous path length for a drug molecule to diffuse out from the tear film's polymer matrix. The ion permeability reduces significantly, whereas an insignificant change in oxygen permeability by Vit E loading can be explained by the fact that ion permeability takes place from hydrophilic channels, and oxygen permeability takes place from the hydrophobic channel. The hydrophobic nature of Vit E leads to aggregation in the hydrophilic region of the polymer matrix, which hampers the ion transport [50,92]. The Vit E loaded lens effectively prevents the UVB radiations and protects any harmful effect on the cornea.

Several groups have reported the extended drug release from the Vit

E modified lens [93,94] (Table 3). Peng *et al.* reported cyclosporine A release from Vit E-SiHCLs for approximately a month, whereas Kim *et al.* reported dexamethasone release for more than one week [92]. Hsu *et al.* explored the Vit E modified SiHCLs for dual drug therapy to combine timolol maleate and dorzolamide hydrochloride for glaucoma therapy. It was observed that 3–4 times lower drug payload significantly reduced the IOP compared to conventional eye drops. Moreover, the drug release extended for two days, and it was able to maintain the IOP reduction for a week after the lens's removal [95]. The fatty acid-based micro-emulsion and other lipidic systems were well explored to achieve longer precorneal retention and sustain the drug release from the CLs [16,96,97]. Torres-Luna *et al.* explored the impact of the unsaturated fatty acid on CLs for extended drug delivery. The electrostatic interaction between cationic drugs was exploited for extended drug delivery [98].

Ciolino *et al.* have demonstrated the *in vivo* efficacy of latanoprost eluting CLs to treat glaucoma in rabbits. Latanoprost-PLGA encapsulated HCL was prepared by UV photopolymerization. The central aperture (3 mm) was incised from the latanoprost-PLGA film for clear vision (Fig. 7). A significant correlation was observed between *in vitro* drug release and *in vivo* drug absorption. The latanoprost concentration in aqueous humor was comparable to the topical delivery for a month without any ocular irritation or conjunctival redness, suggesting a potential alternative for glaucoma treatment [99]. Furthermore, the efficacy of the developed latanoprost eluting CLs were evaluated in glaucomatous monkeys attributed to their similarity with the glaucomatous human eye. A significant reduction in IOP was observed with latanoprost DECLs compared to the latanoprost solution, which exhibited variation in IOP reduction [100].

Maulvi and the group have contributed extensively to overcome the concerns regarding DECLs, such as initial burst release, optical transparency after drug loading, swelling, and sterilization issues [33,101–103]. The incorporation of Pluronic® F-68 improved gatifloxacin's solubility and addressed issues such as optical transmittance and swelling. Pluronic® F-68 prevents the precipitation of gatifloxacin by forming *in situ* micelles. The gatifloxacin-pluronic-loaded CLs showed desired optical transmittance, swelling, and drug loading [103,102]. The drug leaching from the CLs in the packaging solution and during sterilization is the major challenge in the development of DECLs. The pH triggered the release of cyclosporine A from Eudragit S100 nanoparticles, demonstrated sustained drug release, and minimized drug leaching during sterilization and storage [101].

Table 3
Vitamin E modified Silicone hydrogel contact lens.

Drug	Ocular disease	Results and Significance	References
Cyclosporine	Dry eye syndrome	Extended drug release up to 1 month	[171]
Ciprofloxacin	Bacterial infection	Improved loading capacity and extended drug release for 30–33 days	[73]
Timolol, dexamethasone, and fluconazole	–	Protection from UV radiation, enhanced drug loading, and increase in drug release duration	[50]
Cysteamine	Cystinosis	Improved drug release kinetics, drug stability, and dosing frequency	[94]
Betamethasone	Inflammation	Extended drug release and UV protection	[172]
Dexamethasone	Inflammation	9–16 fold increase in release duration compared to CLs without Vit E	[92]
Timolol & Dorzolamide	Glaucoma	Decrease drug dose whereas Increased drug loading and wear duration	[95]
Levofloxacin & Chlorhexidine	Bacterial & Fungal infection	2.5–10 fold increase in drug loading and drug release extended up to 130–170 h	[173]
Bimatoprost & Latanoprost	Glaucoma	Drug delivery for > 10 days and improved ocular BA > 50%	[54]
Cysteamine	Cystinosis	Extended drug delivery for seven days without exhibiting any adverse effect	[53]
NSAIDs	Inflammation	Sustained drug release for an extended period	[52]

5.1.3. Cyclodextrin based DECLs

Cyclodextrins (CD) are truncated shaped oligosaccharides with an internal hydrophobic cavity and external hydrophilic surface. The application of CD to enhance a lipophilic drug's aqueous solubility by forming non-covalent supramolecular complexes is widely explored. The use of CD in the preparation of the CLs is reported in the literature. The utility of CD in drug delivery is well known, and its safety is well established [84]. The incorporation of CD derivatives in the fabrication of DECLs assist in improving mechanical and swelling properties without compromising its transparency, oxygen diffusivity, and cytocompatibility [85]. The drug-CD complex's direct loading by soaking technique in DECLs have shown burst release with rapid dissociation of the drug-CD complex in the physiological fluid. The various strategies using CD are copolymerization of acrylic/vinyl CD derivatives or grafting of CD, or direct cross-linking of CD during the preparation of pHEMA lenses or SiHCLs (Fig. 8). Various reports suggest that the copolymerization of CD with HEMA lenses or SiHCLs increases the drug loading and longer residence time in the ocular milieu.

The grafting of the CD on the preformed hydrogel network instead of direct participation in the formation of lens structure prevents the interference of CD on optical transparency, swelling degree, oxygen permeability, and drug release kinetics. The grafting or copolymerization of CD hampers the drug-CD complex's rapid dissociation and hence sustains the drug release [86]. It was observed that low drug loading associated with soaking and imprinted molecular techniques can be overcome by cross-linking with poly-(CD). The preformed poly-(CD) cross-linked with citric acid was used as a carrier for ethoxzolamide, further loaded onto the HEMA lens. A forty-fold increase in affinity leading to a 5–8 fold increase in drug loading along with sustained drug release up to 6 days was observed [87]. The copolymerization of CD adjuvant affects the degree of elasticity and swelling properties of DECLs. To overcome the participation of CD and interference, Dos Santos *et al.* proposed a novel strategy of post functionalization of preformed gel. It was observed that the technique could retain the original features of hydrogel and improve diclofenac loading by 1300% and a 15-fold increase in drug affinity. CD significantly hindered the drug leakage during storage and sustained the diclofenac release for two weeks [88]. In another study with miconazole, α-CD and γ-CD increased the drug affinity up to 20-fold and 10-fold, respectively, while maintaining controlled drug release for 6 days. It was also observed that pendant β-CD and γ-CD have the least affinity for protein adsorption than the highest with pendant α-CD [89]. Several groups observed similar results of increased drug affinity, ultimately leading to an increased drug loading with sustained and controlled drug release up to 2 weeks [85,90,91]. CD has a significant influence on protein deposition, and it was observed that α-CD exhibited high protein deposition, whereas γ-CD resulted in low protein deposition. It was observed that the high affinity of CD towards the polymer network produced high drug loading [104]. The cross-linking of CD to form a hydrogel CLs was obtained by employing ethylene diglycidyl ether as a cross-linker. It was reported that this novel strategy aid in enhancing drug loading and sustaining the release for a more extended period [87].

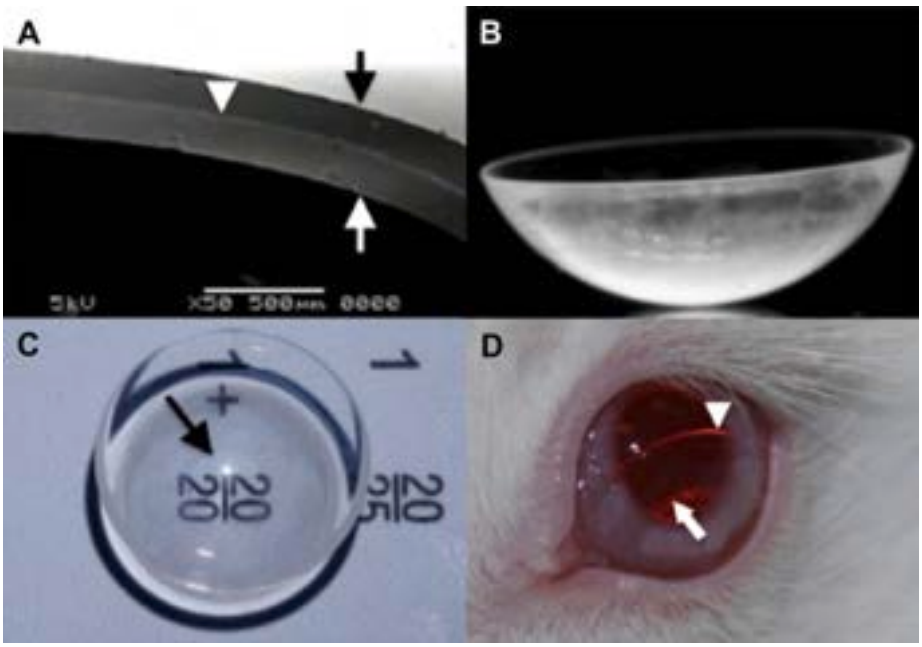

Fig. 7. Latanoprost eluting contact lens with clear central aperture (C) surrounded by a translucent ring of drug-polymer film. The SEM image of the contact lens (A and B) showing the drug-polymer film (White arrowhead) between the inner and outer hydrogel surface (Black arrowhead). The formulated lens applied onto the rabbit's eye (D) (Reproduced from Ciolino *et al.* [99] with permission from Elsevier).

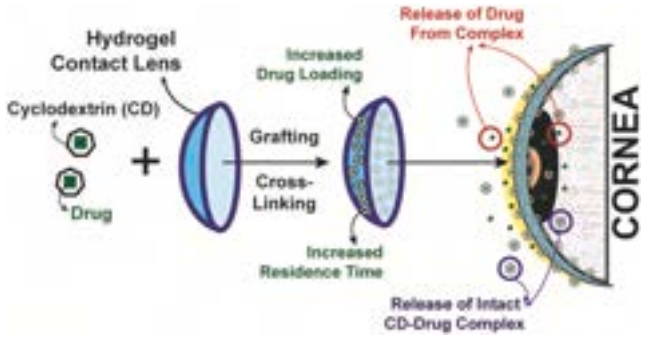

Fig. 8. Loading of drugs into the hydrogel contact lens by cross-linking or grafting with cyclodextrins.

5.1.4. Micro and nanoparticles loaded DECLs

Several approaches have been explored to increase drug loading and achieve controlled release [105–108]. Colloidal nanoparticles are well reported in ocular drug delivery to enhance the retention of drugs or protect the drug from the physiological environment. Colloidal nanoparticles laden HCLs have been explored to further increase the diffusion time of drugs from the nanoparticle matrix to the polymer matrix to ocular fluid. The strategy of incorporation of colloidal nanoparticles in the CLs also hinders the drug leaching during sterilization and storage [101]. Several groups have reported various systems such as microemulsion and polymeric nanoparticles laden CLs in p-HEMA lenses or silicone-based lenses [49,109,110] Kapoor *et al.* compared the drug release of cyclosporine-A from the pure p-HEMA versus surfactant and microemulsion laded p-HEMA. They observed that drug release from later is much longer than the pure p-HEMA lenses [111]. Nasr *et al.* reported CLs loaded with loteprednol emulsion loaded polycaprolactone nanoparticles to overcome low drug loading, homogeneity, and rapid drug release associated with soaking or copolymerization techniques. The nanoparticles were stable in the polymer matrix and released the drug for 12 h [176]. The drug release kinetics of prednisolone and timolol were also extended by incorporating polymeric nanoparticles in the HCL [74,113]. Incorporating a drug into the nanoparticles rather than direct loading of the drug minimizes the initial burst release observed with conventional methods. The low retention of liposome eye drops on the ocular surface can be improved by incorporating the liposomes in p-HEMA lenses or SiHCLs [109].

The critical properties of CLs, such as oxygen permeability, swelling, and optical transparency, change during storage of CLs in packaging solution leading to failure in clinical settings, which needs to be addressed. Xu *et al.* studied the travoprost microemulsion loaded packaging solution and its effect on the critical parameters along with drug uptake and release kinetics. The study suggested improved drug loading and physical properties of the CLs and sustained drug release [97]. The use of PEGylated solid lipid nanoparticles (SLNs) is another strategy proposed by Zhang *et al.* to develop the DECLs without compromising the critical physical properties [96]. Zhu *et al.* reported a similar study to maintain the physical properties by fabricating epalrestat PEGylated SLNs loaded CLs. The sustained drug release was observed, and the effective drug reached the posterior region suggesting the potential for posterior drug delivery applications [16].

5.1.5. Antimicrobial DECLs

The microbial colonization on the CLs is well known for its adverse effects on microbial and fungal keratitis. Kharaghani *et al.* developed an antibacterial CLs by incorporating silver and copper nanoparticles in the PVA CLs. They reported that silver nanoparticle loaded lenses were antimicrobial but showed high toxicity, whereas copper nanoparticle loaded lenses showed minimum toxicity. This can be a potential approach that can control microbial colonization during lens wear, and adverse events such as microbial and fungal infection can be prevented [114]. Salvagni *et al.* have explored the application of antimicrobial peptides onto SCLs to restrict microbial adhesion. The short and ultrashort antimicrobial peptides anchored SCLs exhibited significant microbial colonization inhibition without exerting any cytotoxic effect upon application [115]. Wang *et al.* have developed antimicrobial CLs for corneal infection by reversible grafting of antibiotics. Gentamicin sulfate was coated as a multilayer film on the CLs, which exhibited responsive drug release in the presence of corneal infection [116].

5.2. Bioinspired contact lenses

The bioinspired or biomimetic approach combines technology with the biological sciences, which are inspired or mimic the biological molecules or the cellular and subcellular biological functions for biomedical applications. The bioinspired approach plays a potential role in achieving the drug delivery system's safety and efficacy requirements. It imparts bio-inertness and facilitates the targeted delivery of a drug. The bioinspired approach in CLs can implicate bioinspired polymer systems to enhance biocompatibility, specific molecule recognition to increase the drug loading and efficacy, or stimuli-responsive system [117,118].

The bioinspired polymer system can overcome the non-specific protein adsorption involved in p-HEMA lenses and SiHCLs. Protein adsorption can lead to biofilm formation, a cascade of inflammatory reactions, and the deterioration of the lens. Moreover, protein adsorption reduces visual acuity, comfort, and wear time. The modified phosphatidylcholine, 2-methacryloyloxyethyl phosphorylcholine (MPC), was synthesized by Ishihara *et al.,* conferring antifouling property, wettability and lubricity of the polymeric surface [119]. The intramolecular salt formation (electro-neutrality) in phospholipid polymers further hinders the protein adsorption from biological media and imparts stability to the polymers. Cooper Vision introduced the Omafilcon-A lens [175], fabricated by copolymerization of MPC and p-HEMA. The bioinspired surface impaired the protein and lipid adsorption and bacterial adhesion and biofilm formation on the CLs. The copolymerization of MPC with p-HEMA could resist CLs-related infections and provided comfort for extended wear time. The Omafilcon-A and Hioxifilcon-G72-HW CLs fabricated from bioinspired polymers with up to 72% water content improved the CLs-induced dry eye syndrome [121].

In another bioinspired approach, pockets or cavities were generated by a molecularly imprinted strategy in a loosely cross-linked hydrogel network (Fig. 9). The generated pockets act as receptors such as proteins, enzymes, and antibodies towards which molecules have specific recognition affinity. The alternate strategy involves functional monomer's inclusion during polymerization, which specifically interacts with the drug molecule. This specific drug molecule interaction with generated pockets is responsible for increased drug loading and sustaining the drug release. The molecular imprinting approach has great potential to overcome the issue of low drug loading. The molecular imprinting technique is a chemically irreversible approach based on hydrogel's selectivity and affinity towards the drug molecule. The approach involves immobilization of drug molecules with labile bonds, colloidal structures, or copolymerization with functional groups having an affinity towards drug molecules [79,122–124]. The highly selective cavity is generated into the hydrogel polymer network by utilizing a drug template followed by drug removal and drug reloading by the soaking method.

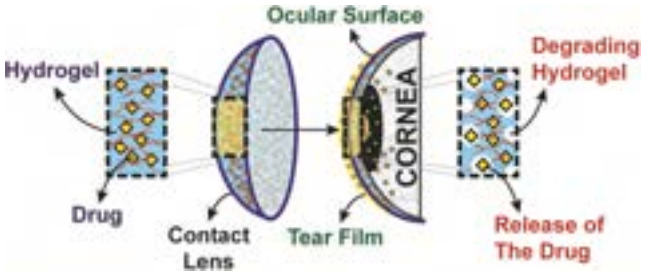

Fig. 9. Representation of the hydrogel contact lens; where (A) shows the interconnected network of hydrogels/polymers entrapping the drug molecules; and (B) the release of the drug by diffusion onto the ocular surface due to the interaction of the aqueous layer of the tear film and may or may not be accompanied by the subsequent degradation of the system.

The low drug uptake in presoaked CLs and burst release is the major drawbacks behind the unavailability of DECLs into the market. The functional monomers and cross-linking agents play a pivotal role in the molecularly imprinted CLs. Excess of both can affect the drug release kinetics by increasing the CLs stiffness and retention of the drug molecule. The highly cross-linked polymers increase the rigidity and low drug loading compared to a weakly cross-linked polymer. Hiratani *et al.* observed that weakly cross-linked imprinted hydrogels adsorb 2–3 times more drug compared to non-imprinted hydrogels [125]. This can be explained by a random distribution of monomer in the polymer matrix and prevention of monomer and drug interaction by cross-linker.

In contrast, in imprinted hydrogels, the adsorption cavities created enhances the drug adsorption [55]. The functional group and template ratio influence cavities' affinity and drug release kinetics in imprinted hydrogel CLs. The drug release kinetics can be controlled by adjusting the functional monomer and template ratio based on the required period of drug delivery [125]. The imprinted hydrogel lenses have been reported to increase the drug adsorption by 9–20-fold compared to the non-imprinted hydrogel lenses [75].

Riberio *et al.* developed acetazolamide and ethoxzolamide eluting bioinspired CLs by generating an artificial domain in the hydrogel polymer network that mimics the carbonic anhydrase receptor [126,127]. A receptor-based biomimetic approach developed olopatadine eluting CLs. The fabrication of molecularly imprinted CLs was carried out by incorporating functional group monomers, which mimic the chemical group and natural H1-receptors to improve the drug loading by increasing the olopatadine affinity for the polymer network [128]. In another study, Ali *et al.* reported controlled release hyaluronic acid (HA) HCLs by molecular imprinting technology for dry eye syndrome. The HA had the highest affinity for CD44 glycoprotein in the human body. The analogous functional monomers are integrated to increase the non-covalent interaction and HA's affinity towards the hydrogel network [129]. Apart from the receptor-based bioinspired CLs, stimuli-responsive hydrogels and HCLs have been reported for ocular therapeutics [130,131]. The temperature-sensitive CLs have been proposed by Jung *et al.* for the ocular delivery of timolol. The DECLs suffer from drug loss during the packaging and storage before application. To overcome this, timolol was encapsulated into the typical cross-linkers such as propoxylated glyceryl triacrylate (PGT) and ethylene glycol dimethacrylate (EGDMA), which were further polymerized with HEMA monomer to fabricate p-HEMA CLs. The extended drug release from nanoparticle loaded p-HEMA was observed for one month compared to 1–2 h of drug release from pure p-HEMA gel [131]. Wang *et al.* devised thermally responsive drug loading and releasing CLs as the platform technology to deliver biologically active peptides in ocular therapeutics [132].

5.3. Smart contact lenses: As bio-sensors and diagnostic devices

The understanding between material science and eyes has come a long way, and now CLs are not just a device to improve vision. The advancement in the field of CLs is exploring material science as an alternative non-invasive tool to understand ocular health and sense the ailments using the ocular tears. The tear film is composed of three different layers, i.e., the lipid layer, followed by an aqueous layer followed by the mucus layer, and contains various proteins and lipids. The different tear proteins are lactoferrin, lysozyme, lipocalin, albumin, secretory immune-globulin, and lipophillin. In contrast, the lipid layer consists of triglycerides, cholesterol, polar lipids, hydrocarbons, and free fatty acids, and each protein and lipid is associated with a different function [133,134]. Experiments are currently ongoing to identify and quantify the biomarkers present in tear film related to the specific ocular disease conditions. The ocular disease conditions can alter the tear film's composition, which can be detected by the biosensor. The domain has been hampered by complex composition, lack of sensitive analytical tools, and elaborate sample preparation before analysis. The bio-sensing

approach can revolutionize ocular therapeutics and ocular disease management at a personalized level.

Continuous glucose monitoring is an integral part of diabetes mellitus management. The non-invasive glucose monitoring sensors, which measures the glucose level of aqueous humor, have been developed to overcome the surgical implantation. The various reported sensors are visible or near-infrared spectroscopy-based techniques, photoacoustic probes, surface plasmon resonance, iontophoretic extraction, and measurement through skin and Raman spectroscopy. The major drawback of these sensors is the need for frequent calibration against direct blood glucose measurement [135]. It is reported that tear glucose in diabetic patients is five times higher than non-diabetic patients, and the correlation between blood glucose and tear glucose level is well established. CLs are being explored as an alternative for tear glucose monitoring based on the spectral determination, fluorescence-based approach, electrochemical determination, and glucose-sensitive hydrogels-based strategy. Clinical trials were carried out with a fluorescent CLs in monitoring glucose levels in type II diabetic patients. The tear glucose was measured for 3 h, without any sign of discomfort, abrasion, or damage. It is a non-invasive potential alternative for home glucose monitoring [136].

Still, long term studies for comfort, adverse effects associated with CLs wear, and toxicity need to be studied for in-depth understanding. Badugu *et al.* proposed the glucose-sensitive SiHCLs. By fabricating glucose-sensitive fluorophores (Glu-SFs) Quin and Quin-C18 embedded CLs. Quin-C18 binds firmly with hydrophobic channels of CLs attributed to C18 alkyl hydrophobic chain, and boronic acid moiety binds towards hydrophilic channels. If the short lifetime and sensitivity of Quin-C18 are effectively taken care of, then Glu-SFs embedded SiHCLs have a promising future as a continuous glucose sensor for diabetes management [137]. Recently, a multifunctional p-HEMA smart CLs have been reported for diabetic diagnosis and therapy by Keum *et al.*[138] The developed smart CLs offered electrically controlled drug delivery with continuous real-time glucose monitoring in the range of 0–50 mg/dL. The amperometric biosensor embedded in the CLs detected the presence of glucose in tears accompanied by on-demand drug delivery for the treatment of diabetic retinopathy (Fig. 10**).** The non-invasive smart CLs were remotely monitored and controlled by wireless power and remote communication systems. The optical image of heat measurement using the thermal infrared camera on New Zealand white rabbits and histological analysis confirmed the safety of the developed smart CLs. The developed wireless CLs paves smart wearable devices to achieve real-time biosensing and on-demand drug delivery for various ocular diseases.

In the progression and management of glaucoma, IOP variability plays a significant role. Frequent monitoring can overcome the challenge associated with diagnosis at the early no symptoms stage and management. The conventional IOP sensors are associated with drawbacks such as surgical implantation and measurement during undisturbed sleep, difficult and inaccurate measurements. Leonardi *et al.* developed SENSIMED Triggerfish® (Fig. 11**)** and a disposable CLs-based marketed sensor for continuous IOP measurement based on its relationship with the circumferential changes in corneal curvature [139]. The 24 h IOP sensor can change the glaucoma paradigm by early diagnosis, individualized and improved treatment adherence, and progression prevention [140]. The clinical interpretation of arbitrary data to mmHg and cost are the significant obstruction associated with the SENSIMED Triggerfish® IOP sensor.

Maeng *et al.* recently developed continuous and qualitative IOP monitoring smart CLs. The photonic crystal pressure sensor-based opal nanostructures were embedded in the PDMS hydrogel matrix. The morphological changes during the IOP cause the shift in the reflected wavelength, which can be measured and analyzed by the simple application program. Apart from applying CLs in glucose and IOP sensors, various biomarkers have been identified for ocular diseases such as dry eye disease, corneal wound healing, and blepharitis, which soon can be determined by exploiting sensor-based CLs [141].

5.4. Recent innovations in contact lenses

5.4.1. Nanowafer contact lens

Nanowafers are an aqueous-based transparent and circular disc-shaped biodegradable spherical film containing an array of drug-loaded nano-reservoirs fabricated using dissolvable polymers PVA, PVP, HPMC, and CMC (Fig. 12). The drug release kinetics profile of nanowafers are well controlled and can sustain the drug release for an

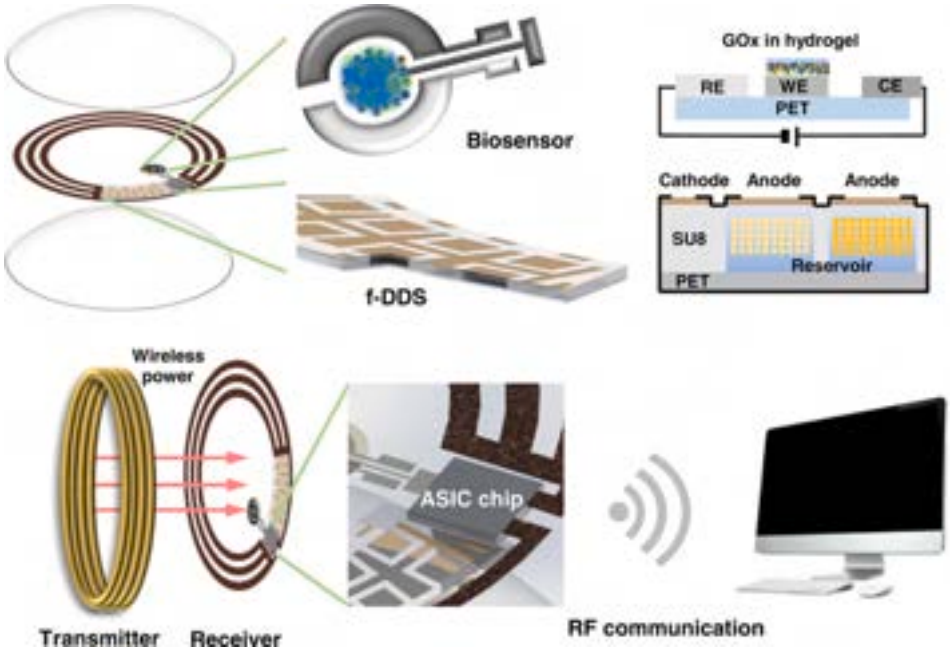

Fig. 10. Schematic illustration of smart contact lenses developed for diabetic diagnosis and on-demand drug delivery for treatment of diabetic retinopathy. The contact lens is embedded with a glucose sensor, an on-demand drug delivery system, a power transmission system, and a remote communication system. (Reproduced from Keum *et al.* [138] with permission from Science, AAAS).

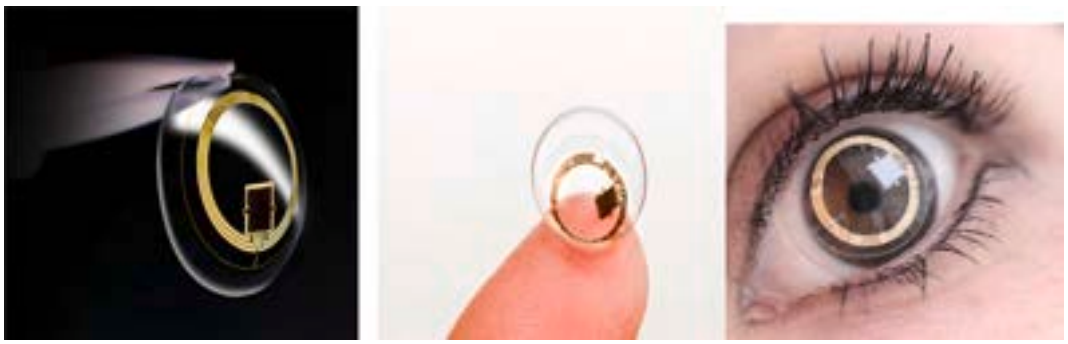

Fig. 11. Photographs of SENSIMED Triggerfish contact lens with the embedded biosensor. (Reproduced with permission from Sensimed AG, Lausanne, Switzerland).

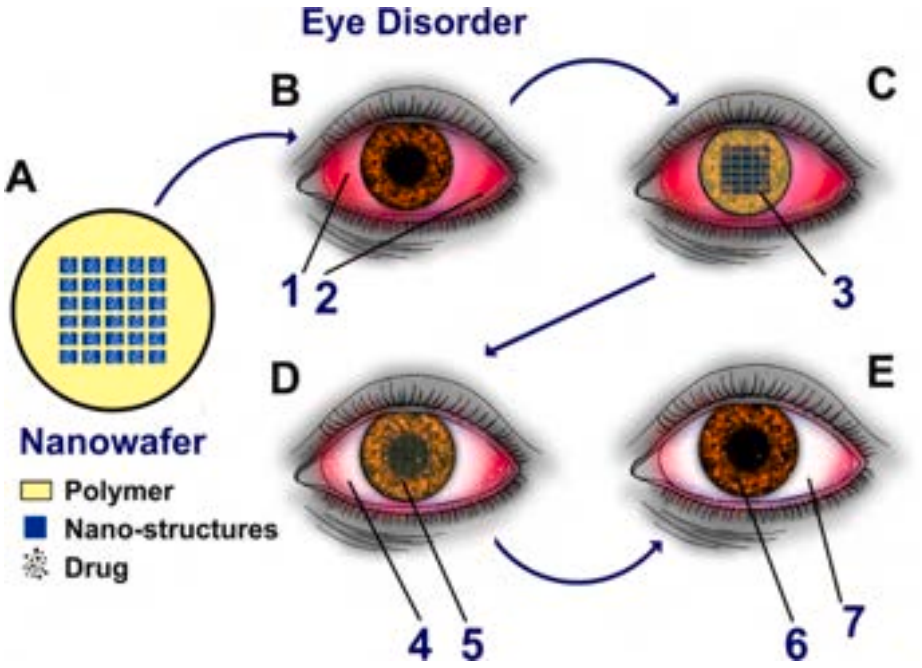

Fig. 12. Representation of nanowafers, a type of next-generation contact lenses; where (A) shows the well-defined nanostructured patterns on the nanowafers serving as cavities to hold the drug molecules; (B – E) shows the application of nanowafers in the treatment of ocular surface disorders, (B) the representation of the human eye during disease showing (1) redness and inflammation, and (2) secretions; (C) the application of drug-loaded nanowafers (3); (D) the management of the disease (4) due to the disintegration of the nano wafer slowly releasing the drug (5) at the site of action; and (E) the complete dissolution and removal of the nano wafer (6) thereby returning the eye to its normal conditions (7).

extended period. The nanowafers can withstand the eye's natural defense mechanisms, including blinking and tear film turnover and increasing drug availability at the corneal surface, hence drug absorption and BA [142]. The potential advantage of nanowafers over CLs is the storage condition and dissolvable biodegradable polymer, which circumvents the wear-related adverse effects associated with CLs. Apart from that, nanowafers can be used as a carrier for the protein and peptide ocular drug delivery [143].

The management of dry eye syndrome still faces challenges regarding convenient dosing and effective drug concentration in the eye. The developed dexamethasone loaded sodium carboxymethyl cellulose (NaCMC) and sodium methylcellulose nanowafers for the treatment of dry eye syndrome showed sustained drug release for up to 24 h. It was observed that in five days of treatment, dexamethasone eye drops were given twice a day. In contrast, dexamethasone nanowafers were applied on the first and third day of the five-day treatment, and the efficacy was comparable. Dexamethasone nanowafers reduced the dosing frequency, improved convenience, and treatment compliance [144,145]. Ocular infections, which require the installation of eye drops every hour, result in patient noncompliance. Maintaining the adequate minimum inhibitory concentration of drug in ocular tissues is another challenge faced by eye drops. Yaun *et al.* demonstrated the effectiveness of axitinib-loaded nanowafers in treating corneal neovascularization in the murine model. The developed axitinib nanowafers were nontoxic, and reduced the dose and dosing frequency to treat the corneal neovascularization [146]. Cysteamine loaded polyvinyl alcohol (PVA) nanowafers developed for corneal cystinosis showed translational potential compared to cysteamine eye drops. Cytotoxicity studies with human corneal cell lines revealed negligible cytotoxic effects. It was also observed that nanowafers hinder the oxidation of cysteamine to its therapeutically inactive form and improve its stability and shelf life [147].

Tummala *et al.* have developed PVA hydrogels reinforced nanocellulose based PVA CLs for ocular therapy. The PVA-based CLs offer high water content, is affordable, and biocompatible. The low mechanical strength issues associated with PVA CLs can be overcome by employing a reinforcing agent such as cellulose (Fig. 13**).** The PVA CLs retained >90% of water with excellent optical clarity [148].

5.4.2. Microneedle contact lenses

Microneedle based ocular drug delivery is an attractive strategy well reported in the literature as it enables penetration to ocular barriers with minimal invasiveness and acts as a reservoir for controlled drug release [149,150]. Dissolving microneedle CLs like patch has gained focus recently and is being explored for its application in diagnosis and effective treatment of ocular conditions (Fig. 14). Roy *et al.* investigated microneedle ocular patch mimicking CLs design to improve the ocular BA and patient compliance. Significant improvement in the amount of drug in the cornea and aqueous humor was observed in contrast to

Fig. 13. PVA contact lens fabricated with 10% PVA and 1% nanocellulose (A and B) composite hydrogel. (Reproduced from Tummala *et al.*[148] with permission from ACS Publications).

topical eye drops [151]. Similar dissolving microneedles were investigated for the ocular delivery of macromolecule by employing low molecular weight fluorescein sodium (FS, 376.27 Da) or a model macromolecule, i.e., fluorescein isothiocyanate (FITC) labeled dextran of 70 kDa or 150 kDa [152]. Amer *et al.* reported self-adhesive microneedles with interlocking features for self-adhesion, preventing detachment after absorbing ocular fluids and providing sustained ocular delivery [153]. A self-implantable ocular patch was devised in a recent study containing a layered micro drug reservoir for controlled delivery of the anti-VEGF agents to treat corneal neovascularization [149]. Dissolving microneedle CLs like patches are a promising alternative for non-invasive ocular therapy for delivering small molecules to macromolecules and attain controlled drug release in both the anterior and posterior chamber of the eye.

5.5. Personalized and self-medication

With the progress in technology and lifestyle, people are more concerned about the quality of life and medical treatment. Point of care (POC) technologies are becoming more insistent in preventive and

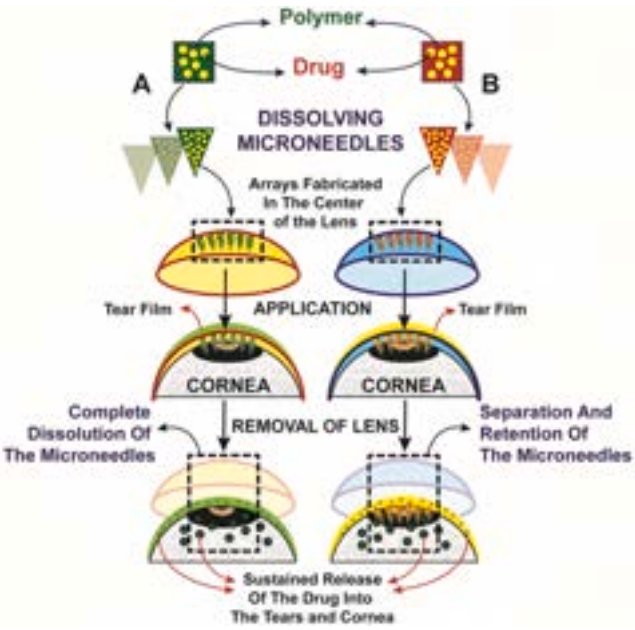

Fig. 14. Ocular drug delivery using dissolving microneedle-based contact lenses. Delivery represented as (A) wherein the microneedles remain attached to the lens base, requiring the lens to be in place on the cornea until the complete release of the drug, and (B) wherein the microneedles rapidly separate from the lens base, and the sustained release of the drug is dependent on the dissolution profile of the hydrogel polymer used.

personalized medical care in modern days. Personalized medicine offers high flexibility, convenience, specificity, and the ability for long term monitoring. The wearable devices have gained more attention in this field attributed to their rapid screening, minimal sampling with reduced cost, rapid detection, and disease monitoring. The ongoing research focuses on lightweight, and miniature wearable CLs integrated with high-bandwidth wireless communications and sensors, measuring the IOP, glucose, and other biomarkers on the specific ocular disease present in ocular fluid for early detection of the disease. The number of patents related to CLs as a biosensor and integration of CLs with new drug delivery increases. The various patents covering the diverse application area from drug delivery to bio-sensing are provided in Table 4.

Along with the biosensor CLs, DECLs can also be personalized based on the type of disease and pharmacological needs. The drug/combination products that act as a single entity to be used as a vision corrector and ocular drug delivery system can be fabricated based on their needs. The drug loading and drug release kinetics can be tailored based on the required dose and conducive for the pathology and CLs wearer. A more focused and detailed knowledge is required before the clinical implication of the same.

6. Translational to the clinics

6.1. Possible limitations of contact lenses

The concept of CLs as an ocular drug delivery device was proposed more than 50 years ago. CLs have proven its efficacy over conventional ophthalmic formulations and diagnostics over the period. The *in vitro* and *in vivo* data supports the superior BA offered by CLs and aids in decreasing dose and dosing regimen. Still, to date, no DECLs are approved by regulatory bodies that raising the concern for thier traslation into the clinics. The translation of DECLs to the clinics is hampered by various factors such as toxicity and safety concerns, reduced drug loading, and release kinetics. The tailoring of the drug loading and release based on the required pharmacological effect is the next big step required for clinical implementation. Apart from sterilization

Table 4
Patents covering vast application areas of contact lens.

Sl. No.	Patent No	Year	Title	Scope
1	US8349352B2	2007	Therapeutic contact lenses with anti-fungal delivery	Molecular imprinted approach to fabricate drug-eluting contact lens. Use of recognitive polymeric hydrogel by using bio-template for antimicrobial or fungal ocular drug delivery
2	US8388995B1	2009	Controlled and extended delivery of hyaluronic acid and comfort molecules by a contact lens platform	The patent covers molecularly imprinted contact lenses for extended-release of ketotifen fumarate, fluconazole, diclofenac sodium, hyaluronic acid, and hydroxypropyl methylcellulose
3	US8273366B2	2004	Ophthalmic drug delivery system	The patent covers the loading of nanoparticle dispersion into contact lens for ocular drug delivery
4	US8623400B2	2011	Drug-carrying contact lens and method for fabricating the same	The patent covers the biocompatible hybrid nanocarriers loaded contact lens and method for the fabrication of the same. The invention also includes the heat and light-sensitive drug molecules drug encapsulation in hybrid nanocarriers incorporation into contact lens for ocular drug delivery
5	US8764185B1	2013	Devices and methods for a contact lens with an inward-facing light source	The patent covers the contact lens as the biosensor to identify and measure biomolecules in a tear film such as glucose by combination with electronics technology
6	WO2011053633A1	2011	Fast-response photochromic nanostructured contact lenses	Incorporation of photochromic agents in a contact lens to protect eyes from harmful lights
7	WO2010022056A1	2008	Microbial cellulose contact lens	Contact lens fabrication from *Gluconacetobacter xylinus* cellulose material and the use of the same for corrective and non-corrective vision
8	US20140377327A1	2014	Extended-release drug-delivery contact lenses and methods of making	Fabrication of prolonged drug-releasing contact lens by electrospinning technology with improved oxygen permeability
9	WO2009094466A3	2008	Contact lenses for extended-release of bioactive agents containing diffusion attenuators	Silicone hydrogel contact lens comprising diffusion barrier such as vitamin E to extend the drug release for a more extended period
10	US8414926B1	2007	Nanoparticles with covalently bound surfactant for drug delivery	The patent covers the encapsulation of surfactant-free nanoparticles in a contact lens for ocular drug delivery in human and non-human subjects by covalent bonding to the polymer moiety
11	EP2978453A4	2014	Drug delivery from contact lenses with a fluidic module	Use of fluidic module in a contact lens to prevent drug release during storage conditions and to release the drug in response to the pressure of the eyelid
12	US8469934B2	2011	Pulsatile *peri*-corneal drug delivery device	The patent covers the contact lens, which releases the drug in a pulsatile manner for an extended period. Separate and distinct units are distributed in the annular reservoir and dispose of the drug as multiple different discrete units
13	WO2014116421A1	2014	Reader Communication with Contact Lens Sensors and Displays	Continuous Glucose sensing contact lens
14	US8446341	2009	Contact Lens with Integrated Light-Emitting Component	Continuous glucose monitoring
15	US7137952B2	2001	The intraocular pressure recording system	Non-invasive approach for IOP measurement for continuous monitoring for a more extended period by semi-rigid contact lens device

complications, packaging, shelf life, lens insertion, and removal are still surrounding the translation to clinics and hurdles to regulatory approval. Sterilization and packaging limit the potential of DECLs and combination products, which serve both the purpose of refractive error correction and drug-eluting device. Further, the use of preservatives to avert the contamination poses challenges to drug loading and drug release kinetics. In chronic ocular diseases, which have a high prevalence in the geriatric population, the lens application and removal can be a serious issue due to deteriorating muscle skill, which needs to be addressed. Although DECLs have failed to reach the clinic, CLs as biosensors has gained momentum. The first disposable continuous 24 h IOP sensor SENSIMED Triggerfish®, is currently available in the market, and the glucose-measuring CLs are under clinical trials.

6.2. Toxicity and safety concerns

Although generally well-tolerated, the CLs have several foreseeable impacts on the tear turnover physiology, oxygen transmissibility, corneal metabolism, corneal epithelium, and endothelium sensitivity and architecture. These physiological, anatomical, and generation of biologically active surface diversification can lead to various reversible and irreversible CLs-related ocular diseases. The wear is susceptible to physiological stress, exposure to bacteria through contaminated lens solution, patient compliance and hygiene, reduced bacterial clearance, and increased bacterial colonization. Dart et al. have contributed clinically to CLs-based disorders better to understand their pathogenesis and management [154].

The incompatibility between the CLs and the ocular surface can lead to intermittent or continual adverse ocular sensation with or without disturbing visual acuity. The CLs-induced discomfort incidence is 23–94%, with RGP lenes being more compared to SCLs. This discomfort is associated with the decrease in wear time to temporary or permanent discontinuation of CLs. The CLs-induced discomfort is the primary reason behind high dropout rates of wearers [155]. The extended wear of CLs potentially affect the ocular surface by altering physiologic conditions. The acidic shift in pH, increased osmolarity, hypoxia, and mechanical pressure on ocular physiology can culminate into edema, distortion, thinning, and rare deep stromal opacities.

The principal concern about lens wear is increased susceptibility to corneal infection, including microbial keratitis associated with *Pseudomonas aeruginosa*. The complex and multifactorial pathogenesis of microbial keratitis is also responsible for vision loss. The lens wear provides a favorable environment for microbe growth and virulence by conferring protection from standard defense mechanisms such as blinking shear forces. Further, the biofilm development on the CLs surface upregulates the resistance to antimicrobials and immune effectors. The possibility of lens associated biofilm with cell adaptions leading to change in gene expressions or development of mutations favorable for bacterial virulence capacity in ocular milieu and resistance to antimicrobials is reported [156].

Corneal neovascularization (CNV) is a physiological effect imparted by the CLs wear due to reduced oxygen transmissibility responsible for reduced oxygen availability in the avascular cornea. It is reported that 10–30% of total CNV is associated with wear. The SCLs are more prone to CNV compared to a RGP lens attributed to its smaller diameter covering the central portion of the cornea. The theory proposed for CLs mediated CNV is a vascular response to CLs-induced corneal neurology changes. The closed eye represents the condition of subclinical inflammation with a considerable increase in polymorphonuclear leukocyte recruitment and upregulation of angiogenic factors, which is balanced by angiostatic factors in normal conditions. Extended CLs wear can alter these balanced states and play a crucial role in the development of CNV. The new generation of CLs, such as SiHCLs, has high oxygen transmissibility, which reduces hypoxia and the chances of developing CNV [157,158].

CLs associated papillary conjunctivitis is an immunologically mediated disease resulting from an allergic response due to ocular deposits. The tear film proteins tend to deposit on the CLs, such as lysozyme. It is observed that US-FDA types II and IV, which have water content, have substantial protein adsorption compared to low water CLs, including US-FDA types I and III. Apart from high water content, the ionically charged lens is more prone to ocular deposits. Hence, the US-FDA type IV, including ionic and high-water CLs, has the highest protein depositions. The protein deposition on the CLs surface initiates the cascade of inflammatory reactions responsible for CLs-induced inflammation and infections [159]. Another adverse effect closely associated with wear of CLs is dry eye, called a CLs-induced dry eye (CLIDE). The reports suggest that approximately 50% of lens wearers complain of dry eyes. The CLs divides the tear film into two separate films, including PLTF and POLTF. The thin anterior PLTF is exposed to enhanced tear evaporation and dewetting of the film. The dry eye disease associated with CLs is typically evaporative dry eye disease. The CLIDE is associated with the ocular surface desiccation and alteration in the tear film, which hampers the visual acuity and progresses into discomfort and decreased wear time or discontinuation and bacterial binding and infection. The possible explanation for evaporation and dewetting of the CLs surface is a high tendency of polar head groups of lipidic tear film towards high water CLs, exposing nonpolar groups away from the lens surface [160].

Although CLs have superiority over conventional ocular devices or formulations with excellent optical transparency, it has its own set of side effects associated with biological incompatibility, which needs to be taken care of to maintain the ocular physiological conditions milieu. The CLs-related unfavorable effects are correlated with the lens material, lens fitting, design, patient compliance, hygiene, care solutions, and failure to culminate into ocular diseases. The safety and adverse effects associated with the use of the same raise the concern. They need to be addressed to promote the coexistence of CLs on the ocular surface without any detrimental effect on ocular health and to improve the quality of life.

6.3. Clinical trials

Several clinical trials exploring the clinical effectiveness of DECLs are reported. The high drug penetration was observed for carbenicillin, gentamicin, and chloramphenicol with the Sauflon® CLs, which contains higher water content, during a study carried out on 173 patients with uncomplicated cataract by Jain *et al.* [161]. In another study, carried out on 466 patients waiting for senile cataract surgery. The comparative study was carried out by subconjunctival and SCLs mediated delivery of carbenicillin gentamicin and chloramphenicol. It was observed that SCLs mediated delivery exhibited significantly higher drug penetration than subconjunctival therapy [162]. Kalayci *et al.* observed similar results upon applying ciprofloxacin presoaked SCLs to the patients with senile cataracts. A higher drug penetration and retention up to 12 h were observed [163]. The above clinical studies suggested the effectiveness of unmodified CLs in ocular delivery by overcoming the patient incompliance attributed to multiple administration.

Clinical feasibility and effectiveness of medicated CLs were also assessed for glaucoma therapy. Schultz *et al.* assessed the clinical feasibility of timolol maleate or brimonidine tartrate presoaked CLs on 3 glaucoma patients. The study suggested long-term IOP control with a low dose of timolol maleate or brimonidine tartrate [164]. Pall *et al.* reported CLs mediated ketotifen fumarate delivery for ocular allergy on 244 patients. It was observed that the CLs mediated ketotifen fumarate achieved a clinically and statistically significant reduction in ocular itching [165]. Currently, an ongoing clinical trial is exploring the effectiveness of CLs loaded dorzolamide-timolol combination therapy for glaucoma [166].

7. Conclusion and prospects

The *in vivo* results and clinical investigations suggest that the contact lenses are a promising technique for anterior and posterior drug delivery. CLs have demonstrated improved ocular BA with increased drug residence time by overcoming the respective physiological and anatomical barriers. DECLs are an emerging tool to address the unmet clinical needs in ocular therapeutics. The tailoring of drug loading and drug release kinetics based on disease and pathology depending on the patient's age group can revolutionize ocular therapeutics and personalized medications. The next generation and bioinspired approach can assist in tackling these challenges and further optimization of the design. The amalgamation of vision corrector CLs and DECLs or bio-sensing CLs in the single entity can reshape the ocular therapeutics and create new horizons in CLs application.

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