Contact lens technology

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Contact Lens Technology: From Fundamentals to Applications

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Contact lenses are ocular prosthetic devices used by over 150 million people worldwide. Primary applications of contact lenses include vision correction, therapeutics, and cosmetics. Contact lens materials have significantly evolved over time to minimize adverse effects associated with contact lens wearing, to maintain a regular corneal metabolism, and to preserve tear film stability. This article encompasses contact lens technology, including materials, chemical and physical properties, manufacturing processes, microbial contamination, and ocular complications. The function and the composition of the tear fluid are discussed to assess its potential as a diagnostic media. The regulatory standards of contact lens devices with regard to biocompatibility and contact lens market are presented. Future prospects in contact lens technology are evaluated, with particular interest given to theranostic applications for in situ continuous monitoring the ocular physiology.

1. Introduction

The human eye is one of the most complex organs of the animal kingdom, and its retina one of the most complex tissues. The human eye can be capable of detecting a single photon.[1] However, eye dysfunctions affect a significant percentage of the modern population. According to the World Health Organization, 1.3 billion people worldwide experience visual deficiency. Among them, 189 million people have mild distance vision impairment[2], 217 million have moderate to severe distance vision impairment[2], 826 million people live with a near vision impairment[3], and 36 million people are blind.[3] The majority of vision impaired individuals are over the age of 50 years, and the leading causes include uncorrected refractive errors, cataracts, glaucoma, and diabetic retinopathy. Approximately the 80% of all vision impairment is considered avoidable.[2, 3] Eye surgery technologies to restore vision have gained popularity in the last three decades, particularly Laser Assisted In-Situ Keratomileusis (LASIK), to re-shape the cornea and restore its ability to properly focus light on the retina. However, post-LASIK ocular complications have been extensively reported[4-7], and the most common methods currently used for vision correction remain spectacles and contact lenses.

Contact lenses are optical devices regulated by the US Food and Drug Administration (FDA).[8] Approximately 140 million people worldwide and 40.9 million people in the US use contact lenses to correct refractive errors in myopia, hyperopia, and astigmatism cases.[9] The contact lens global market is predicted to reach over 19 billion US dollars by 2024.[10] Therapeutic contact lenses are used to treat eye dysfunctions, particularly corneal irregularities, and for post-refractive surgery rehabilitation. Cosmetic contact lenses, such as colored lenses and limbal-ring lenses, are also popular, especially in Asian countries, and they are now classified as medical devices in the UK, US, China, Singapore, Malaysia and Korea.[11-14] Contact lenses were used as smart delivery systems to achieve extended drug releasing times, and as wearable bio-sensing platforms.[12, 15-19] On the other hand, contact

lens wear was found to induce adverse effects[20], the most frequent being discomfort[21, 22], microbial keratitis[23, 24], allergies[25, 26] and corneal complications.[27]

1.1 History of contact lenses

Leonardo da Vinci introduced the concept of contact lenses in 1508[8], followed by René Descartes in 1636. However, both Da Vinci's and Descartes' ideas were impracticable.[28] The first pair of contact lenses was manufactured by Thomas Young in 1801.[29] John Herschel conceived the possibility to obtain molds of the cornea by impression on a transparent material.[30] In 1888, Adolf Fick successfully constructed and fitted scleral lenses for the first time. They were made of heavy blown glass, with diameters ranging from 18 to 21 mm. Fick's lenses were fitted on rabbits and on human volunteers using a dextrose solution, and they allowed a maximum wearing time of two hours.[31] The development of Plexiglas in the '30s allowed to manufacture plastic contact lenses. Contact lenses made of fully plastic materials were produced by István Györffy in 1939.[28] Polymethyl methacrylate (PMMA) corneal lenses gained popularity in the 1960s.[28] Upon realizing that the low oxygen permeability of PMMA was the cause of several adverse effects, from the 70s Rigid Gas Permeable (RGP) materials were introduced. In 1965, Bausch & Lomb started to manufacture contact lenses with hydrogels in the US[28], previously invented by Wichterle and Lím in 1959.[32] The first hydrogel contact lenses appeared in the 1960s, and in 1971 the Soflens material received the first FDA approval. In 1972, disposable soft contact lenses were produced. The first silicone hydrogel contact lenses were successfully manufactured in 1998. Silicone hydrogels combined high oxygen permeability and wearing comfort. Diverse commercial materials with similar properties followed shortly after. Nowadays, silicone hydrogels and RGP materials lead the market of soft and rigid lenses, respectively. A timeline on the history of contact lenses is illustrated in **Figure 1**.

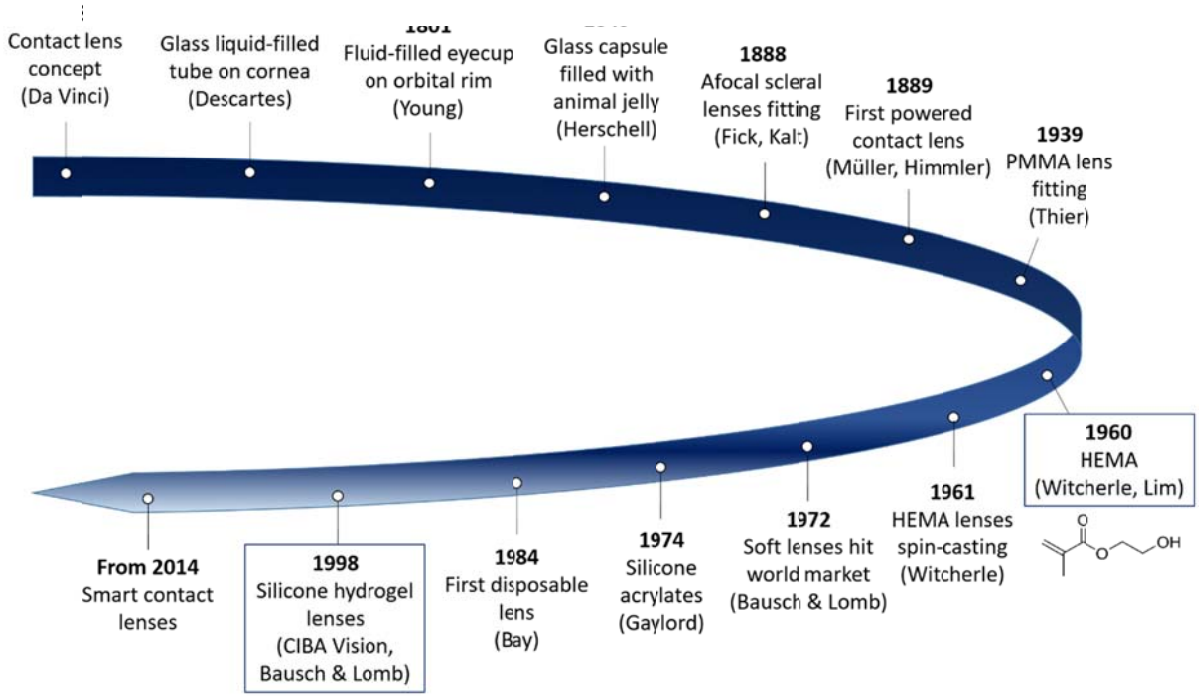

Figure 1. Timeline of contact lens evolution. The highlighted inventions of HEMA in 1960 and silicone hydrogel contact lenses in 1998 are defined as the most ground-breaking developments in contact lens history.[28]

2. Physiology of the human eye

The first reported eye-like structure dates back to 521 million years ago, during the Cambrian explosion, in which earth has seen the first optical devices in animals in the form of eyes with lenses, followed by the first reflector around 13 years later.[33, 34] In the same period, a variety of life forms started differentiating from the worm-like animals that inhabited earth until then to most of the phyla known today, and visual systems quickly became a dominant arm in the survival game. Optical structures found in animals were identified as multilayer reflectors, diffraction gratings, liquid crystals, light scattering structures, and natural photonic crystals.[35-37] Despite soft tissues rarely fossilize whilst maintaining the full original

information, different eye structures were found in fossils[38, 39], adding pieces to the evolution of the human eye puzzle.[39]

The human eye can be divided into two main chambers, namely the anterior and the posterior segments.[40] The anterior chamber hosts cornea, iris and lens. Vitreous, retina, choroid, optic nerve and sclera are located in the posterior chamber. The cornea acts as a protection for the front-eye side, and it focuses light into the retina. The sclera is the outer white shell, connected to the cornea via the limbus. The iris is a pigmented circular structure surrounding the pupil, that is capable to adjust its dilation together with the sphincter muscles to regulate the amount of light entering the eye. The ciliary body produces the aqueous humor, located between lens and cornea, with immunological and nourishment functions, which drains from the posterior to the anterior chamber via the pupil, maintaining an intraocular pressure (IoP) of 12 to 22 mmHg in healthy conditions.[40] The most relevant eye structures in the framework of this review are cornea and sclera. All contact lenses are used in direct contact to the cornea and/or the sclera. The human vision process starts in the eye, where the optical input is received. Light enters the eye through cornea, pupil and lens. Photons reaching the inner retina are converted into electrical signals by rods and cones, photoreceptive cells that respond to different intensities and wavelengths of light. Intrinsically photosensitive retinal ganglion cells project to the lateral geniculate nucleus, where the electrical signals travel to three sites of the visual cortex. The visual centre of the eye, i.e. the line of sight, is not centred within the pupil, it can rather be found dislodged towards the left hand side.[40]

2.1. The tear fluid

Tears are bio-fluids that may reflect ocular and systemic physiological health.[41-45] The tear fluid nourishes the ocular surface tissues, and flushes away the waste products of corneal metabolism. Tears can be divided in three main layers: the outer lipid layer, secreted by the

Meibomian glands, the aqueous layer, secreted by the lacrimal glands, and the mucin layer, produced by the conjunctival globet cells.[40] The tear fluid is often referred to as the proximal fluid, which is the outer layer of the lacrimal function unit (LFU). Tear fluid can be collected with minimally-invasive procedures **(Figure 2a)**.[46] This is an advantage over body fluids such as plasma, serum and blood that need a specialized operator, and cerebrospinal fluid or biopsy that require hospitalization.[8] Shirmer's test is the gold standard for tear fluid collection. However, the collected fluid may be contaminated by proteins from epithelial cells. The Schirmer's test consists on placing a paper strip, known as Schirmer's strip, inside the lower eyelid for 5 minutes. The strip is further stored at -70 to -80 °C to deactivate enzymes and hydrolases found in tears. The sample may be frozen either before or after extraction, both methods showing advantages and drawbacks.[47, 48] Alternatively, tear samples may be collected with capillary tubes, made either of glass or plastics, that can be inserted horizontally in the lower eyelid.[46] The physical properties of the pre-ocular tear film are summarized in **Figure 2b**. The tear fluid composition can be analyzed with different techniques. The best methods for mass screening of tear proteins are considered to be SELDI-TOF-MS and LC-MALDI.[44, 45, 49] The most sensitive technique to study lipodome in tears is LC-MS[47], to address the limitations of NMR and GC-MS. Low-weight substances are studied by MALDI-TOF-MS and LC-MS/MS techniques.[50]

The tear fluid is composed of a mixture of lipids, electrolytes, proteins, peptides, glucose, amino-acids, and O-linked carbohydrates with a protein core.[47-49] The typical protein concentration in tears is 5-7 μg μL^{-1}, given by over 1500 different proteins, the 90% of which include lysozyme, lipocalin, lacritin, lactoferrin.[50, 51] The most complete human tears lipidome has individuated over than 600 lipid species.[48, 52] Tear lipids are involved in anti-inflammatory processes, they maintain tear film stability, they reduce the surface free energy, act as a barrier to the aqueous layer, and control water evaporation from the ocular surface.[52]

Very low concentrations of hydrophilic metabolites were also found in the tear fluid[48, 49], as well as vitamin A, E and of the B family (B1, B2, B3).[53-55] Different expressions of micro RNAs and mucins (MUC1, MUC5AC, MUC4, MUC16) have also been targeted as potential biomarkers to be found in tears.[47] The composition of the human pre-ocular tear film is summarized in **Table 1**. Multiple studies are currently working towards the identification of biomarkers in the tear fluid.[48] Potential tear fluid biomarkers associated with ocular and systemic disorders are summarized in **Table 2**.

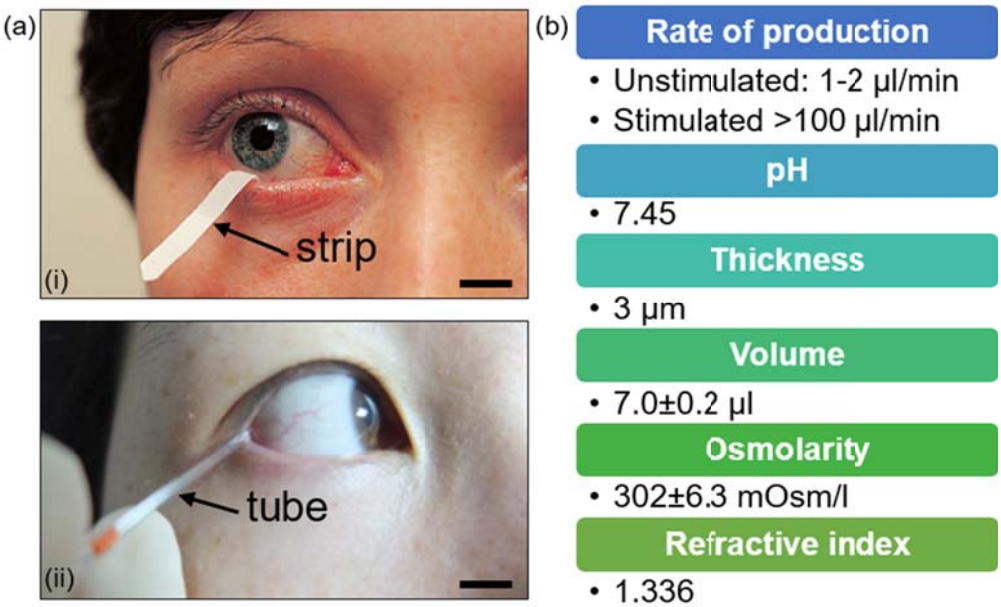

Figure 2. The tear fluid. (a) Tears collection methods. (i) Shirmer's test. Reproduced with permission.[56] Copyrights 2016, Springer Nature. Scale bar: 1.5 cm. (ii) Capillary tube. Reproduced with permission.[57] Copyrights 2017, Elsevier. Scale bar: 1.5 cm. (b) Physical properties of the pre-ocular tear film.

Table 1. Composition of the pre-ocular tear film.

Components	Concentration	Ref.
Electrolytes		

Na^+	135 mEq L^{-1}	[49, 58]
Cl^-	131 mEq L^{-1}	[60]
K^-	36 mEq L^{-1}	[60]
HCO^{3-}	26 mEq L^{-1}	[49, 60]
Ca^{2+}	0.46 mEq L^{-1}	[60]
Mg^{2+}	0.36 mEq L^{-1}	[60]
Proteins	*5-7 µg µL^{-1}*	[51]
Lysozyme	2.07 g L^{-1}	[60]
Secretory IgA	3.69 g L^{-1}	[60]
Lactoferrin	1.65 g L^{-1}	[49, 60]
Lipocalin	1.55 g L^{-1}	[60]
Albumin	0.04 g L^{-1}	[49, 60]
IgG	0.004 g L^{-1}	[60]
Aquaporin 5	31.1±23.9 µg L^{-1}	[49]
EGF	5.09±3.74 µg L^{-1}	[49]
Lipids		
Wax esters	41%, 44%	[49, 59]
Cholesteryl esters	27.3%	[61]
Polar lipids	14.8%	[60]
Hydrocarbons	7.5%, 2%	[60]
Diesters	7.7%	[60]
Triacylglycerides	3.7%, 5%	[49, 61]
Fatty acids	2.0%	[60]
Free steroids	1.6%	[49, 61]

Table 2. Tear fluid biomarkers.

Complication	Biomarkers	Ref.
Dry Eye Disease (DED)	*Proteins*	[50, 60, 61]
	Lysozyme, S100 A9/calgranulin B, Mammaglobin B, lactoferrin, LPRR3-4, Calgranulin A/S100 A8, S100 A4, lipophilin A, S100 A11, Transferrin, lactotransferrin.	
	Mucin	[62]
	(MUC)5AC	
	Neuromediators	[50, 63]
	NGF, CGRP, NPY	
	Serotonin	
	Cytokines/chemokines	[50, 65]

	Interleukins, CXCL11/I-TAC, RANTES/CCL5, EGF, TNF-α, INF-γ, MMP-9.	
	Lipids	[50, 65]
	Lysophospholipids, HEL, HNE, MDA	
	Metabolites	[50, 65]
	Cholesterol, creatine, acetylcholine, arginine, glucose, phenylalanine	
Ocular allergies	*Cytokines/Chemochines*	[50]
	Interleukins, eotaxin-1/CCL11, eotaxin-2/CCL24, RANTES/CCL5, TNF-α, IFN-γ.	
	Proteins	[50]
	Histamine, MMP-1, TIMP-2, Haemopexin, Transferrin, mammaglobin B, IgE.	
	Neuromediators	[50]
Keratoconus	GCDFP-15/PIP, RANTES/CCL5, MMP-13, MMP-9, IL-6, IFN-γ, Prolidase, galectin-1, galectin-3	[50, 64-66]
Ocular GVHD	Cytokines/chemokines	[50, 65]
Trachoma	Immunoglobulins, EGF, TGF-β1, TNF-α	[50, 65]
Graves' orbitopathy	Interleukins, TNF-α, RANTES/CCL5	[50]
Aniridia	Zinc-α2-glycoprotein, lactoferrin, VEGF, Ap4A, Ap5A	[50]
Glaucoma	Immunoglobulins, lysozyme C, protein S100, lactotransferrin, cystatin S, MUC5AC.	[50]
Diabetic retinopathy	NGF, LCN-1, lactotransferrin, lysozyme C, lacritin, lipophilin A, TNF-α	[67-74]
Systemic sclerosis	CFD, EGF, MCP-1, MMP-9, VDBP	[75-77]
Cystic fibrosis	IL-8, IFN-γ, MIP-1α, MIP-1β	[78, 79]
Breast cancer	Lacryglobin, cystatin SA, malate dehydrogenase, immunoglobulins, protein S100-A4, keratin II, pericentrin.	[48, 80-83]
Multiple sclerosis	IgG	[84-86]
Alzheimer's disease	Lipocalin-1, dermcidin, lysozyme-C, lacritin	[86, 87]
Parkinson's disease	α-Antichymotrypsin, TNF-α	[88-90]

2.2. The eye microbiota

The ocular surface is exposed to the external environment, hence to different types of microbes. Bacteria are naturally present in the ocular environment and they act as a protection against colonization of pathogens in the eye. Three main types of bacteria populate the ocular environment in healthy conditions and they are coagulase negative *Staphylococci, Corynebacterium sp. And Propionibacterium sp.*, also known as skin-like bacteria[91].

Coagulase-negative staphylococci are the most represented bacteria in the conjunctiva, lids and tears (over 50%).[92-95] Other bacteria isolated from the ocular surface in a lower percentage include *Propionibacterium sp.* and *Diphteroid* bacteria, the most common of which is *Corynebacterium sp.*[91] The broth used to culture bacteria may induce the growth of preferential strains.[96] Thioglycolate broth grows coagulase-negative *Staphylococci*, whereas blood agar plates increases the growth rate of *Corynebacterium sp.*[96] Other factors can affect the resulting dominant strain, such as growth in aerobic or anaerobic conditions[96], culturing the conjunctiva before or after sleep[97], and the use of eye drops.[98] By using sequencing methods, other bacteria have been found to compose the eye microbiota, and they are extensively described elsewhere.[99]

3. Polymers in contact lenses

Contact lenses interact with the ocular surface via the tear film, the corneal epithelium, and the conjunctival epithelium. A contact lens must allow sufficient oxygen flow to maintain aerobic metabolism, corneal homeostasis, and tear film stability. Contact lenses can be grouped in three main categories based on their composition: soft, rigid, and hybrid contact lenses.

3.1. Rigid lenses

Rigid lenses were the first to be introduced in the form of glass lenses.[28] Rigid contact lenses are used to address astigmatism and corneal irregularities with a variety of designs, including front-toric, back-toric, and bi-toric.[100-102] The first rigid lens was made of glass, further replaced by poly methyl methacrylate (PMMA). PMMA was obtained by polymerization of methyl methacrylate (MMA) **(Figure 3a)**. PMMA in turn exhibited substantial limitations in terms of corneal respiration, which increased the risk of undergoing ocular complications.[28]

Several flexible thermoplastics were proposed to replace PMMA, including poly (4-methyl-1-pentene) **(Figure 3b)**, and cellulose acetate butyrate (CAB) **(Figure 3c)**.[103] Both exhibited an oxygen permeability 20 times higher than that of PMMA, and they could be fabricated by molding techniques. However, they lacked of dimensional stability.[103] The oxygen permeability of silicone rubber may be up to 1000 times higher than that of PMMA, due to its silicon-oxygen atoms backbone **(Figure 3d)**, but its low hydrophilicity never made it suitable to be used in contact lenses.[103]

The development of RGP materials started with the introduction of silicone acrylates, which combined the oxygen permeability of silicone with the accessible manufacture of PMMA. Examples were siloxy-methacrylate monomer **(Figure 3e)**, tris (trimethyl-siloxy)–methacryloxy-propylsilane (TRIS) **(Figure 3f)**, and the incorporation of fluoroalkyl methacrylates to enhance oxygen permeability.[103] Siloxy-methacrylate-based materials with enhanced wettability laid the foundations to the development of Boston RPG materials. Among them, the additional use of methacrylic acid, and the incorporation of an itaconate ester on the traditional TRIS structure **(Figure 3g)**.[103] Menicon is credited with introducing the first contact lenses with hyperoxygen transmissibility (*Dk*=175), composed of tris (trimethylsiloxy) silyl styrene and fluoromethacrylate **(Figure 3h, i)**. As of 2019, Menicon Z contact lenses are the only rigid lenses that received FDA approval for 30 days of continuous wear. Current RGP lenses on the market and their composition are summarized in **Table 3**. **Table 4** presents a comparison between commercial Boston RGP materials.[104] Rigid lenses were initially fabricated as corneal lenses or scleral lenses, with diameters ranging from 7.0 to 12.0 mm, and above 18.0 mm, respectively. Over the past decade, therapeutics drove the market towards manufacturing rigid lenses with intermediate dimensions. Nowadays, rigid lenses are used in the form of corneo-scleral lenses, with diameters ranging from 12.0 to 15.0 mm, and miniscleral lenses, with diameters of 15.0 to 18.0 mm.

3.2. Soft lenses

Soft lenses are made of hydrogels, i.e. water-containing polymers, which allow better comfort and higher flexibility than rigid lenses. Soft lenses are 2-3 mm larger than the cornea, with a diameter of 14.5 mm. They are produced solely in the form of corneal lenses, and they lay on the cornea. Soft lens materials may be hydrogels (low-*Dk* materials) or silicone hydrogels (high-*Dk* materials).[105] Hydrogel lenses were firstly produced by polymerization of HEMA **(Figure 3j),** leading to a water content of the 40%.[32]

Manufacturer	Commercial name	Polymer	Dk
Bausch & Lomb	Boston II, IV	Silicone acrylate	12, 19
	Boston Equalens, II	Fluorosilicone acrylate	47, 85
	Boston ES, EO, XO, XO_2	Fluorosilicone acrylate	18, 58, 100, 141
GT laboratories	Fluorex 300, 500, 700	Fluorosilicate acrylic	30, 50, 70
InnoVision	Accu-Con, $HydrO_2$	Fluorosilicone acrylate	25, 50
Lagado Corporation	SA 18, 32	Silicone acrylate	18, 32
	FLOSI, ONSI-56	Fluorosilicone acrylate	26, 56
	TYRO-97	Fluorosilicone acrylate	97
The LifeStyle	SGP, SGP II	Siloxane acrylate	22, 43.5
Company	SGP 3	Fluorosiloxane acrylate	43.5
Menicon	Menicon Z	Fluorosiloxanyl stirene	163
Stellar	OP-2, OP-3, OP-6	Fluorosilicone acrylate	15, 30, 60

Table 3. Selected rigid contact lenses on the market [105-108].

Table 4. Comparison between Boston RGP materials.[104]

Property	Boston Material			
	ES	EO	XO	XO_2
Refractive index	1.441	1.429	1.415	1.424
Oxygen permeability (Dk)	18	58	100	141

Oxygen transmissibility (Dk/t)	15	48	67	94
Silicone content (%)	5-7	5-6	8-9	12-13
Wetting angle (°)	52	49	49	38
Dynamic contact angle (advancing/receiving) (°)	52/50	62/60	59/58	50/40

However, hydrogel materials transport oxygen via the water channels, which limits their water content. This limitation was addressed with the introduction of HEMA copolymers, including *N*-vinyl pyrrolidone (NVP) (**Figure 3k**), and the copolymerization of MAA and NVP. However, the addition of MAA also resulted in an ultra-sensitivity to changes in tonicity, pH, and heat. A material with high wettability was produced utilizing Glyceryl methacrylate (GMA) **(Figure 3l)** with HEMA. The resulting bio-inspired material mimicked the hydrophilicity of mucins, and it was insensitive to pH variations. Commercial contact lenses based on this technology are the hioxifilcon A (Clear 1 Day lenses by Clearlab), and Proclear lens (Coopervision). Disposable soft lenses were also produced using poly vinyl alcohol (PVA) **(Figure 3m)**.[105] FDA classifies soft lenses in four groups, based on their equilibrium water content (EWC) and ionic content (IC). Selected commercial hydrogel lenses are listed in **Table 5**. Silicone hydrogels were firstly introduced in 1998.[105] First generation silicone hydrogel lenses include balafilcon A, and lotrafilicon A. Reduction of surface hydrophobicity was achieved using gas surface plasma treatments. However, limitations in wettability were reported. Further generations of silicone hydrogel lenses exhibited increased water content and lower modulus, resulting in a lower incidence of papillary conjunctivitis associated to contact lens wear.[105] The use of internal wetting agents eliminated the need of surface treatments.[109] Selected silicone hydrogel contact lenses on the market are grouped in **Table 6**.

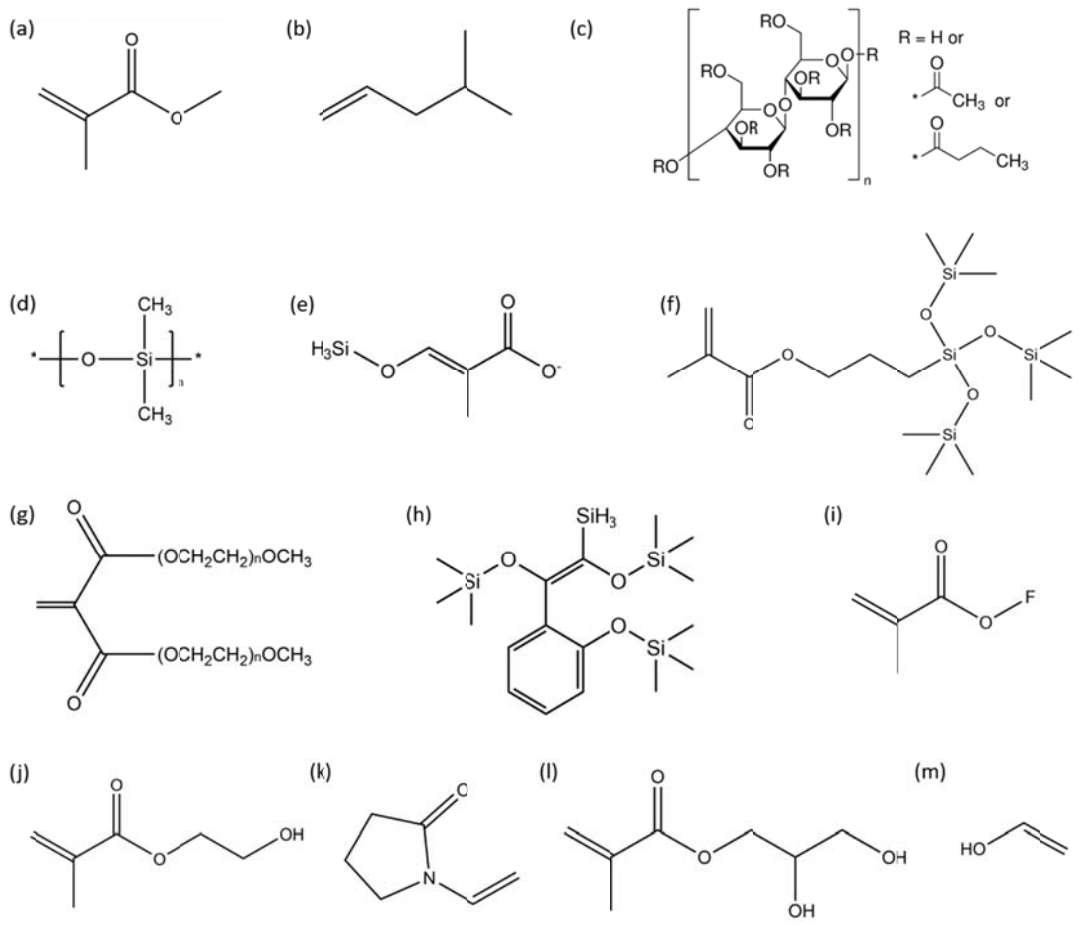

Figure 3. Contact lens polymers. (a-j) Chemical structures of rigid lens polymers. (a) Methyl methacrylate. (b) 4-methyl-1-pentene. (c) Cellulose acetate butyrate (CAB). (d) Silicone rubber. (e) Siloxy methacrylate. (f) Tris(trimethyl-siloxy)-methacryloxy-propylsilane. (g) Itaconate ester (h) Tris(trimethylsiloxy) silyl styrene. (i) Fluoro methacrylate. (j-m) Chemical structures of soft lens polymers. (l) Hydroxyethyl methacrylate. (m) N-Vinyl pyrrolidone. (o) Glyceryl methacrylate. (p) Vinyl alcohol.

Table 5. Selected commercial hydrogel contact lenses [105, 106, 108-110]

Commercial name	Supplier	Polymer Type	EWC (%)	USAN name
FDA Group I				
Durawave	UltraVision CLPL	HEMA, GMA	49	Hioxifilcon B

Menicon soft	Menicon	HEMA, VA, PMA	30	Mafilcon A
SOfLens 38	Bausch & Lomb	HEMA	38	Polymacon
FDA Group II				
Biotrue one day	Bausch & Lomb	HEMA, VP	78	Nesofilcon A
Dailies AquaComfort plus	Alcon	PVA	69	Nefilcon A
SofLens daily disposable	Bausch & Lomb	HEMA, VP	59	Hilafilcon B
FDA Group III				
Accusoft	Ophthalmos	HEMA, PVP, MAA	47	Droxifilcon A
Comfort Flex	Capital Contact Lens	HEMA, BMA, MAA	43	Deltafilcon A
Soft Mate II	CIBA Vision	HEMA, DAA, MAA	45	Bufilcon A
FDA Group IV				
1-day Acuvue moist	Johnson & Johnson	HEMA, MAA	58	Etafilcon A
Frequency 55	Coopervision	HEMA, MAA	55	MethafilconA
Permalens	CIBA Vision	HEMA, VP, MAA	71	Perfilcon A

Table 6. Selected commercial silicone hydrogel soft contact lenses [105, 106, 108, 111].

Name (USAN name)	**Supplier**	**EWC (%)**	**Oxygen permeability (Barrers)**	**Surface treatment**	**Polymers**
Pure Vision (Balafilcon A)	Bausch & Lomb	36	91	Oxygen plasma	NVP, TPVC, NCVE, PBVC
Dailies Total 1 (Delefilcon A)	Alcon	33 core >80 surface	140	Water surface gradient	DMA, TRIS-Am, siloxane, polyamidoamine and poly(acrylamide-acrylic acid) copolymers
Biofinity (Comfilcon A)	Coopervision	48	128	N/A	NVP, VMA, IBM, TAIC, M3U, FM0411M, HOB
Acuvue Oasys (Senofilcon A)	Johnson & Johnson	38	103	N/A	MPDMS, DMA, HEMA, siloxane macromer, TEGDMA, PVP
Premi O (Asmofilcon A)	Menicon	40	172	Plasma treatment	SIMA, SIA, DMA, pyrolidone derivative
Clarity 1 day (Somofilcon A)	Sauflon	56	60	N/A	Alkyl methacrylates, siloxane monomers, NVP

3.2. Hybrid lenses

Hybrid contact lenses have a central optical zone made of RGP material, surrounded by a peripheral fitting zone made of a silicone hydrogel. They have a diameter of 14.5 mm and they combine the wearing comfort of soft lenses with the clearer optics of RGP lenses.[112] As of 2019, only a few companies provide hybrid lenses and they did not gain high popularity. Advantages and disadvantages of hybrid lenses over other designs are highlighted in **Table 7**.

Table 7. Advantages and disadvantages of hybrid contact lenses compared to other designs.

	Hybrid/GP	**Hybrid/Soft**	**Hybrid/Scleral**
Advantages	More comfortable. Quicker adaptation. Easier to center. More stable vision. Vaulting. Firm positioning. Lower negative power. Unilateral wear.	Higher visual quality. Astigmatism correction without stabilization. Better for high order aberrations. Better for presbyopia correction in astigmatic patients.	Soft skirt conforms to scleral shape. Less chance of seal-off. Lower clearance. Higher oxygen permeability. Reduced fogging.
Disadvantages	More difficult to apply and remove. Longer time to settle. More frequent replacement.	Higher costs. Difficult to fit. More difficult to apply and remove.	Longer time to settle. More difficult to fit in irregular corneas. More frequent replacement

4. Properties of contact lens materials

Ideal properties for a contact lens material are durability, stability, clarity of vision, and the ability to preserve corneal metabolism by allowing a sufficient oxygen flow to the cornea[112, 113]. Properties of contact lenses may be grouped in mechanical, optical, and chemical. Contact lenses are also defined and designed considering a range of geometrical properties.[110, 114-117]

4.1. Chemical properties

Chemical properties with highest significance with regards to contact lens polymers are wettability, water content, oxygen permeability, and swell factor. The surface properties of a polymer determines the way it will interact with the tear fluid.[118] In vivo wettability is evaluated by tear film break-up time and interferometry tests, and it reflects the ability of the contact lens to keep a stable tear film within the ocular surface. In vitro wettability is assessed by evaluating the contact angle at the solid-liquid-air interface, and measuring the hysteresis, i.e. the difference between advanced and receding contact angle. **Figure 4a** displays a contact angle measurement on a hydrophobic contact lens surface.

The equilibrium water content (EWC) of a hydrogel lens is described by[105]:

$$EWC = \frac{weight\ of\ water\ in\ polymer}{total\ weight\ of\ hydrated\ polymer} * 100 \quad \text{(Eq. 1)}$$

The EWC of a hydrogel is influenced by environmental conditions, pH, tonicity, and temperature. The International Organization for Standardization (ISO) defines the regulatory standards for EWC measurements in contact lens hydrogels. Both thermogravimetry and back-calculation by refractive index measurements are considered valid techniques for EWC assessment.[111]

The oxygen permeability is indicated as *Dk*, where *D* is the diffusivity and *k* is the solubility of the material.[103, 105] Hydrogels transport oxygen via the water channels and their oxygen permeability is closely related to temperature and EWC, according to the following equation [105]:

$$Dk = 1.67e^{0.0397EWC} \quad \text{(Eq. 2)}$$

The amount of oxygen transported from the anterior to the posterior surface $O_{2,\ A \rightarrow P}$ of a lens can be calculated dividing the oxygen permeability *Dk* by the lens thickness *t*[105]:

$$O_{2,\mathrm{A}\rightarrow\mathrm{P}} = \frac{Dk}{t}$$ (Eq. 3)

Oxygen permeability and EWC are closely dependent on each other. **Figure 4b** presents the variation of Dk as a function of EWC in silicone hydrogels and hydrogels.

Another important parameter of a contact lens is the swell factor, which is a measure of the dimensional stability of a hydrogel lens[105]. The swell factor is influenced by temperature, pH and tonicity, and it is described by the following relationship [105, 108]:

$$SF = \frac{wet\ dimension}{dry\ dimension}$$ (Eq. 4)

Hydrogels swell anisotropically. Their radial swell factor can be obtained by [105]:

$$SF_{rad} = 2 * \frac{SF_{dia}}{SF_{ax}}$$ (Eq. 5)

Where SF_{rad} is the radial swell factor, SF_{dia} is the diametral swell factor and SF_{ax} is the axial swell factor.

4.2. Mechanical properties

The mechanical properties of contact lenses determine their comfort, visual performance, fitting methods, and durability. Soft lenses are obtained with wettable polymers, which properties change with water content.[103, 105] Mechanical testing involves applying a stress (compression, tensile or shear) and observing the resulting strain. Contact lens polymers are mechanically characterized by their stress–strain curve, and their Young's modulus is defined by the formula $E = \sigma * \varepsilon^{-1}$, where σ is the applied stress, and ε is the corresponding strain.[120] The modulus of rigid lens materials amounts to 10 GPa[103], whereas hydrated soft lenses have modulus of 0.2 to 1.5 MPa.[105] The increased content of siloxy-methacrylates in RGP materials confers them a higher oxygen permeability, but it reduces their dimensional

stability.[103] Another parameter to be evaluated in contact lenses is the friction exerted between eyelid and contact lens. The coefficient of friction (CoF) of a contact lens is defined as the ratio of the sliding force to the normal force that keeps the two surfaces together. There is no standard reference value due to the difficulties in replicating an eye environment, and the optimization of this parameter is currently under investigation.[103, 105]

4.3. Optical properties

Optical properties of contact lenses play a crucial role in providing a good visual performance. The most important optical parameters of a contact lens are optical transparency and refractive index of the polymer. Hydrogels have a light transmission >90%.[105] Sometimes micro-phase separation of water occurs, negatively affecting hydrogels transparency by creating zones with different refractive indexes. Ideally, the refractive index of a contact lens matches the one of the cornea (1.37).[103] The refractive index is measured using an Abbé refractometer[111]. Fluorosilicone acrylate lenses have a refractive index of 1.42-1.46, and silicone acrylates have a refractive index above 1.460.[103] The refractive index of PMMA is 1.49.[105] Commercial contact lenses with higher refractive indexes (1.51-1.54) include Optimum HR (Contamac) and Paragon HDS HI (Paragon Vision Science), and they are advantageous in aspheric multifocal designs [109].

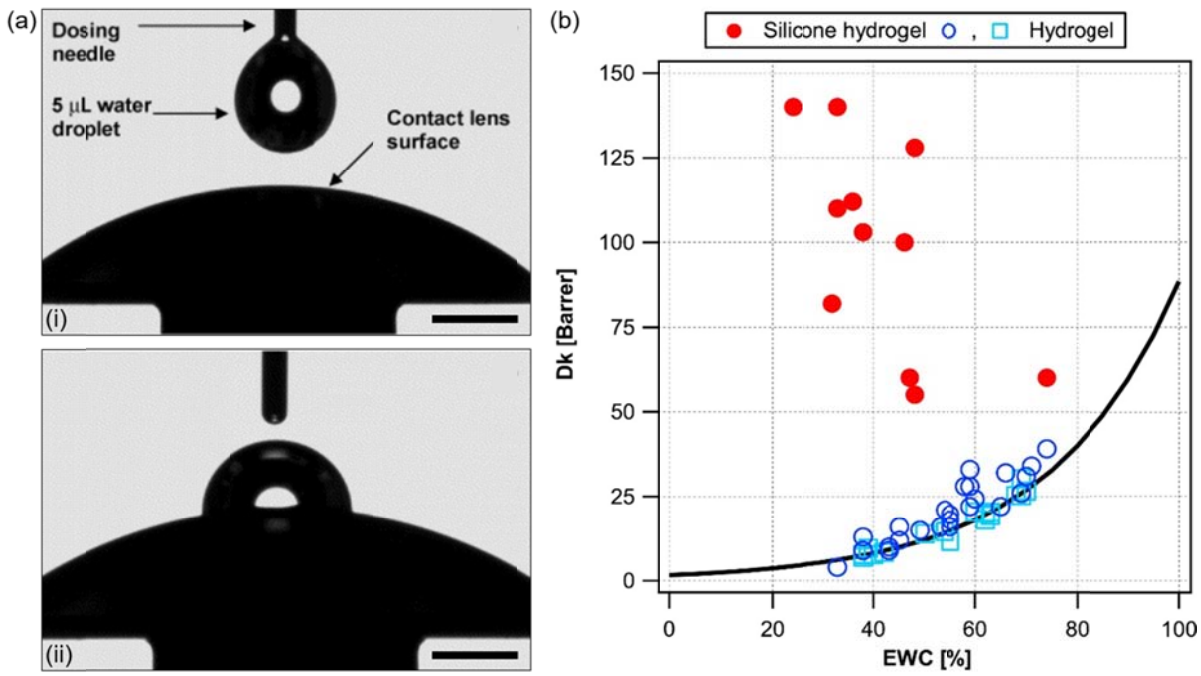

Figure 4. Properties of contact lens materials. (a) Wettability evaluated by contact angle measurement. Reproduced with permission.[119] Copyright 2014, Elsevier. Scale bars: 2.0 mm. (b) Equilibrium Water content and oxygen permeability. Reproduced with permission.[120] Copyrights 2017, Elsevier.

5. Contact lens manufacture

Contact lenses are manufactured by shaping a plastic material into specific curvatures, namely the central anterior curve (CAC) and the central posterior curve (CPC). Contact lenses may be manufactured by either molding or lathe cutting. Molding is an additive process that consists on curing a solution inside a lens-shaped mold, and it is used for mass-production in general prescriptions. Lathe cutting is a subtractive process where a blank of material is modelled to the desired shape for individual prescriptions.[106, 121]

5.1. Molding

The molding process is primarily dedicated to soft lenses fabrication. It can be done by spin-casting, compression, or injection.[106] The first soft lenses were obtained by spin casting. Compression molding was used in the past for PMMA lenses fabrication, but it has now fallen out of fashion.[121] Nowadays, individually packaged, disposable soft contact lenses are mass-produced by spin casting and injection molding. The spin casting process is illustrated in **Figure 5a**. The contact lens solution is spun at a controlled speed inside a mold, resulting in the liquid being uniformly spread all over the mold, under UV curing. The resulting lens is peeled off, edged and hydrated. Lenses are then autoclaved and packaged. The injection molding process **(Figure 5b)** is equivalent to spin casting, but the lens is shaped by using a two-pieces mold. In injection molding, the molten plastic is injected into the mold under pressure and cured under UV irradiation. The lens is peeled off, cooled, and finished on a lathe. Contact lenses are finally softened by hydration prior to undergoing quality assurance tests.

5.2 Lathe cutting

Lathe cutting is primarily adopted in customized rigid lenses production, but soft lenses can be also fabricated by lathe cutting in a similar manner. The fabrication of rigid lenses by lathe cutting is illustrated in **Figure 5c**. In a first step, back and front surfaces are etched and polished. The blank is centrally mounted on a micro-lathe where the diameter is reduced to 0.10-0.15 mm above the final diameter of the lens. The back-optic zone radius (BOZR) is cut using a diamond tool and further polished using a double rotation technique. Subsequently, fine diamond-coated tools are used to generate secondary and peripheral curves. BOZD and peripheral diameters are measured using a band measuring magnifier. Peripheral curves are left unpolished until the very last stage of production, to avoid damaging the blank. The blank is removed from the button, it is cleaned and mounted by its back surface on a chuck, where

the front optic radius is cut with a diamond tool. At this stage, the lenticulation of positive powered lenses takes place. In positive lenses, the lenticulation is polished before the front optic, whereas in negative lenses the optics is polished before the lenticulation to control power adjustments more accurately. The hard lens is ready for the next steps, whereas the soft lens needs to be hydrated and cleaned. Subsequently, edge and peripheral curves are shaped and polished. The dry lens is mounted on a hot chuck with the concave surface facing up, and centred on a rotating vertical spindle. A razor blade is used to reduce the diameter and to shape the lens, from the back surface to the lower front surface. Peripheral curves are polished and blended, and the edges of the lens are then polished. The lens is removed from the chuck, rinsed, dried, and inspected. The lens is now fully fabricated. When dealing with soft lenses, any error will be increased by a multiple of the linear expansion ratio when the lens will be hydrated, thus special measures to avoid hydrate before completion need to be taken. The polish material used has to be water-free. The dehydrated lens has to be cleaned in an ultrasonic bath of solvent prior to hydration, and the lens needs to be sterilized in an autoclaving process. After the front and back surfaces are shaped with automated cutting tools, the lens is hydrated. Hybrid lenses are obtained in a similar fashion to lathe cutting of soft contact lenses, but the blanks feature a GP center bonded to the surrounding non-hydrated soft material. Peculiar shapes, such as toric and bifocals, are addressed with similar machinery after preparation of a suitable blank.

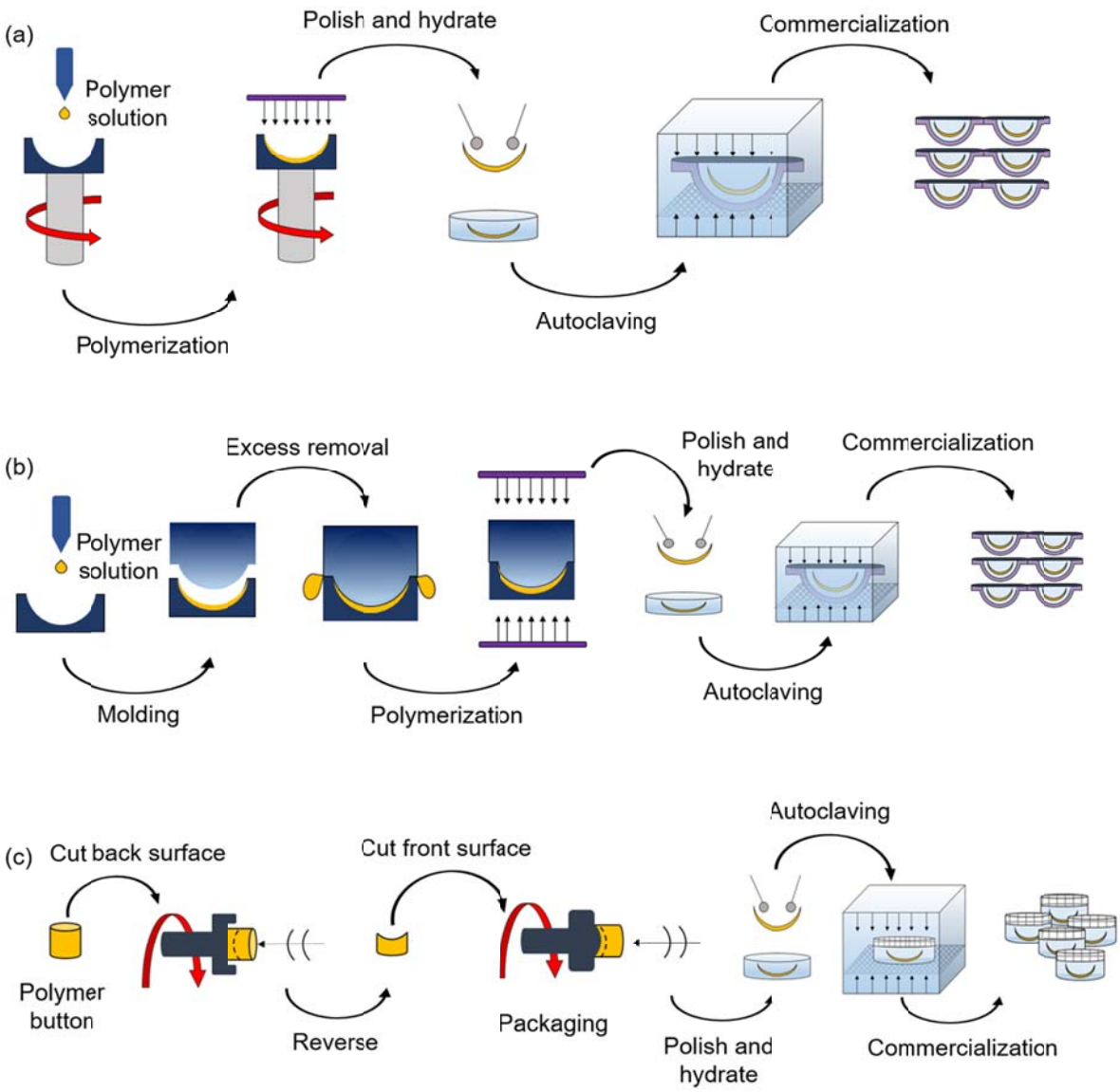

Figure 5. Contact lens manufacture. (a) Mass production of soft contact lenses by spin-casting. The mold is mounted on a spinning cylinder, where the contact lens solution is poured. The solution is further polymerized via UV light exposure, resulting in a lens-shaped piece. The lens is peeled off and refined, and the edges are polished. The contact lens is hydrated in a saline solution, inspected, packaged in a blister, sealed, and autoclaved. Contact lenses are ready to be dispatched. (b) Production of individually packaged contact lenses via injection molding process. The contact lens solution is poured on the concave piece of the mold, and the complementary convex mold is pressed over the concave mold until reaching

full contact. The excess polymer is squeezed out, followed by polymerization under UV light. The resulting contact lens is peeled off, the edges are polished, and the lens is hydrated in a saline solution. The lens is placed in a sealed blister, and autoclaved. Contact lenses are ready to be dispatched. (c) Contact lens manufacture by lathe cutting. A button-shaped dry polymer is inserted in a spinning chuck, where back and front surface are cut using a diamond tool. The lens is removed from the lathe, inspected, edge-polished, and hydrated in a saline solution. The lens is transferred into a glass vial containing a saline water solution, sealed, and autoclaved. Contact lenses are ready to be individually dispatched inside the same glass vials, right after autoclaving.

5.3. Quality control and packaging

Finished lenses undergo quality assurance tests prior to be introduced in the market.[106, 121] Diameter and curvature are measured with automated tools. After inspection and measurement, the lens is sterilized. **Figure 6a** displays the measurement of the contact lens diameter using s v-gauge. Commercial contact lenses are packaged in glass or plastic vials containing a saline solution. When defects are found in the lens during quality control, the lens cannot be commercialized. Examples of defects include the presence of excess material, notches, tears (intended as the name of a particular type of defects), edge roughness, splits, blemishes, and the more evident lens breakage into multiple pieces **(Figure 6b-e)**. Defects may also be intentionally produced within a contact lens, for customized applications. An example is the notching of scleral lenses, which consists on etching an additional part of the lens in a specific area, to avoid physical contact between the lens and the injured scleral area of the patient's eye. Lab-made contact lenses for diverse research purposes have been fabricated with multiple customized methods, mostly inspired to spin-casting and injection molding techniques. Hydrogel contact lenses were recently fabricated using eyeball molds

immersed in a petri dish containing a hydrogel, followed by polymerization and cutting.[122] In the majority of cases, injection molding is used to fabricate contact lenses based on novel solutions incorporating sensing properties.[123-125]

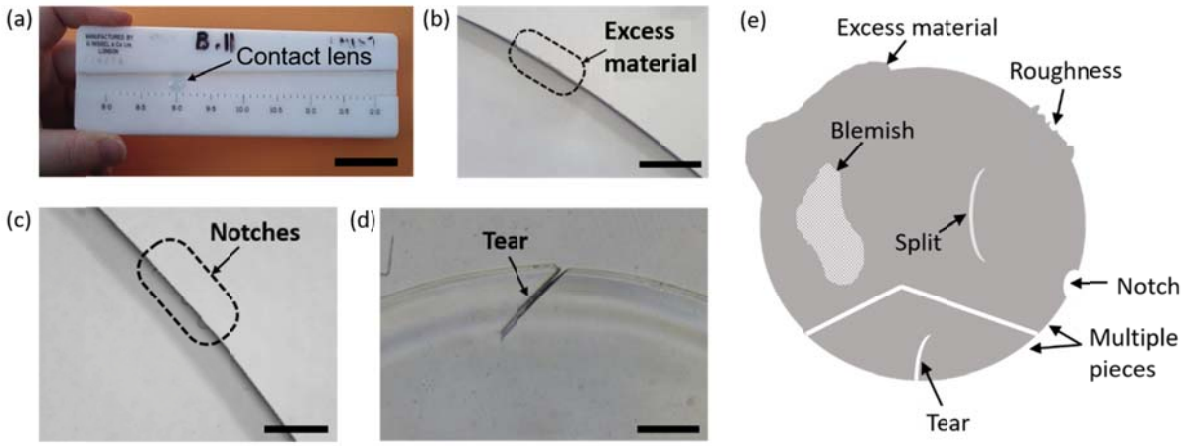

Figure 6. Contact lens inspection and measurement prior to dispatch. (a) Measuring the diameter of a contact lens using a v-gauge. Reproduced with permission.[111] Copyright 2018, Elsevier. Scale bar: 4 cm. (b-e) Contact lens defects. (b) Excess material. Scale bar: 2.0 mm. Reproduced with permission.[109] Copyright 2018, Elsevier. (c) Notches. Scale bar: 2.0 mm. Reproduced with permission.[109] Copyright 2018, Elsevier. (d) Tear. Scale bar: 3.0 mm. Reproduced with permission.[109] Copyright 2018, Elsevier. (e) Illustration of the most common defects found in contact lenses.

6. Applications

The intended use of contact lenses drives their design and materials. Contact lenses are classified in corneal, mini-scleral, and scleral, according to their diameter (**Figure 7**). Contact lenses are also classified in corneal, mini-scleral, and scleral based on the ocular structure they lay on. Hence, rigid lenses may be corneal, mini-scleral, and scleral. Note that mini-scleral rigid lenses are sometimes called scleral lenses. Soft and hybrid lenses only exist with a diameter of 13.0 to 14.5 mm, and they are referred to as corneal lenses because they are mechanically hold by the cornea. Primary applications of contact lenses are the correction of

refractive errors, prosthetics, and therapeutics. Novel contact lenses are being used as sensing platforms and as vehicles for drug delivery, exploring the potential of contact lenses as theranostic devices. The versatility and the popularity of contact lenses make them suitable to be used as smart platforms in personalized medicine.[8, 15] The functionalization of contact lenses for ocular drug delivery allows to achieve slow releasing times.[126, 127] Integrating sensors within contact lenses has a broad range of applications, including continuous health monitoring[8, 12], wearable displays[128], and minimally-invasive screening methods[16, 19]. Contact lenses produced with new technologies may also improve the performances in existing applications. Switchable liquid crystal contact lenses were developed as an alternative to bifocal contact lenses for presbyopia correction.[129] Photochromic contact lenses were developed to adapt the wearer's vision at different sunlight levels[130], and to block UV light[131]. Contact lenses for color vision deficiency were obtained by submerging contact lenses in a color filtering dye.[132]

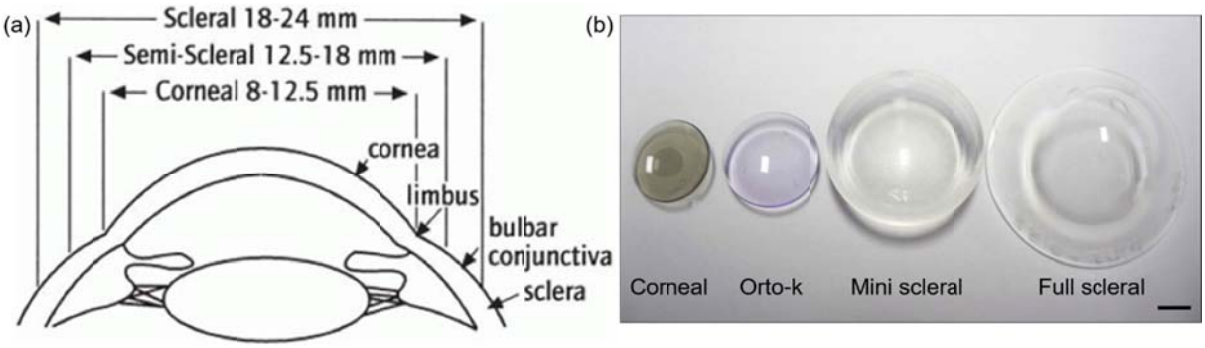

Figure 7. Classification of contact lenses based on their geometry. (a) Diagram displaying the difference between scleral, semi-scleral, and corneal lenses. (b) Photograph of corneal, orto-k, mini-scleral, and full scleral lenses. Scale bar: 4.0 mm. Reproduced with permission.[133] Copyright 2017, Elsevier.

6.1. Refractive disorders

Eye disorders of refractive nature consist on the inability to focus light on a single focal point on the retina, leading to poor visual performances. All refractive errors result from a re-shape of the eyeball, which can occur as a consequence of genetic predisposition, environmental factors, and visually intensive occupations. Refractive errors are one of the most common causes of blindness, along with cataracts, macular degeneration, and vitamine A deficiency. An eye free from refractive errors is defined as emmetropic. An eye that needs accommodation to properly focus light on the retina is called ametropic. In optometry, an object is defined as distant when it is located beyond 6.0 meters from the eye. Considering the limitations of the human visual system, 6.0 meters is considered as the threshold beyond which the light impinges on the eye in the form of parallel rays. On the contrary, an object is defined as near when it is located at a maximum distance of 6.0 meters from the eye. The most common forms of ametropias are myopia or near-sightedness, hyperopia or far-sightedness, and astigmatism [2, 3, 6]. The myopic eye features an elongated eyeball that focuses light anteriorly to the retina, leading to blurred vision of distance objects. Myopia is the most common among refractive disorders, whereas hyperopia primarily affects children and elder individuals. The eyeball of a hyperopic eye is shortened, and it focuses light beyond the retina, leading to a blurred vision of near objects. The cornea of the astigmatic eye features an irregular shape that focuses light in multiple focal points, resulting in a stretched vision. The astigmatic eye features a higher optical power across one meridian. The corneal shape is approximated to a cylinder having an axis defined by the angle between the high performance meridian and the horizontal. This results in a vision quality dependent on the spatial orientation. Another leading refractive disorder is presbyopia, induced by a functional loss of ciliary muscles in the elder eye, which causes the inability to sufficiently shape the lens to adjust the focal power needed to properly focus the light entering the eye on the retina. This results in a hyperopia-like visual deficiency, with near distance objects appearing

blurred. Presbyopia affects most people over the age of 35.[2, 3] Refractive errors are corrected with eyeglasses, contact lenses, or LASER surgery, and they are diagnosed by eye examination comprising an objective refraction test using a retinoscope and a test by elimination, known as subjective refraction. The latest consists on applying glass or plastic lenses with different optical powers to the exterior of the eye, until the one that produces an optimal vision is identified.

Contact lenses can provide a wider field of vision than spectacles, and they are convenient in a series of circumstances where eyeglasses wear is not recommended. Examples include sport activities, humid environments, and situations where a wide field of vision is necessary (e.g. driving). However, spectacles are an external, non-invasive method to correct eye refractive errors, and they are preferred in some cases. LASER refractive surgery permanently changes the shape of the cornea to restore visual capabilities. **Figure 8** presents the most common eye refractive errors and their correction via convex or concave lenses. Nearsightedness and farsightedness correction are addressed using concave and convex lenses respectively, to diverge/converge light rays prior to reaching the cornea. Presbyopia can be corrected with bifocal or progressive lenses. Astigmatism is addressed with cylindrical lenses, to induce refraction of light in a preferential meridian.

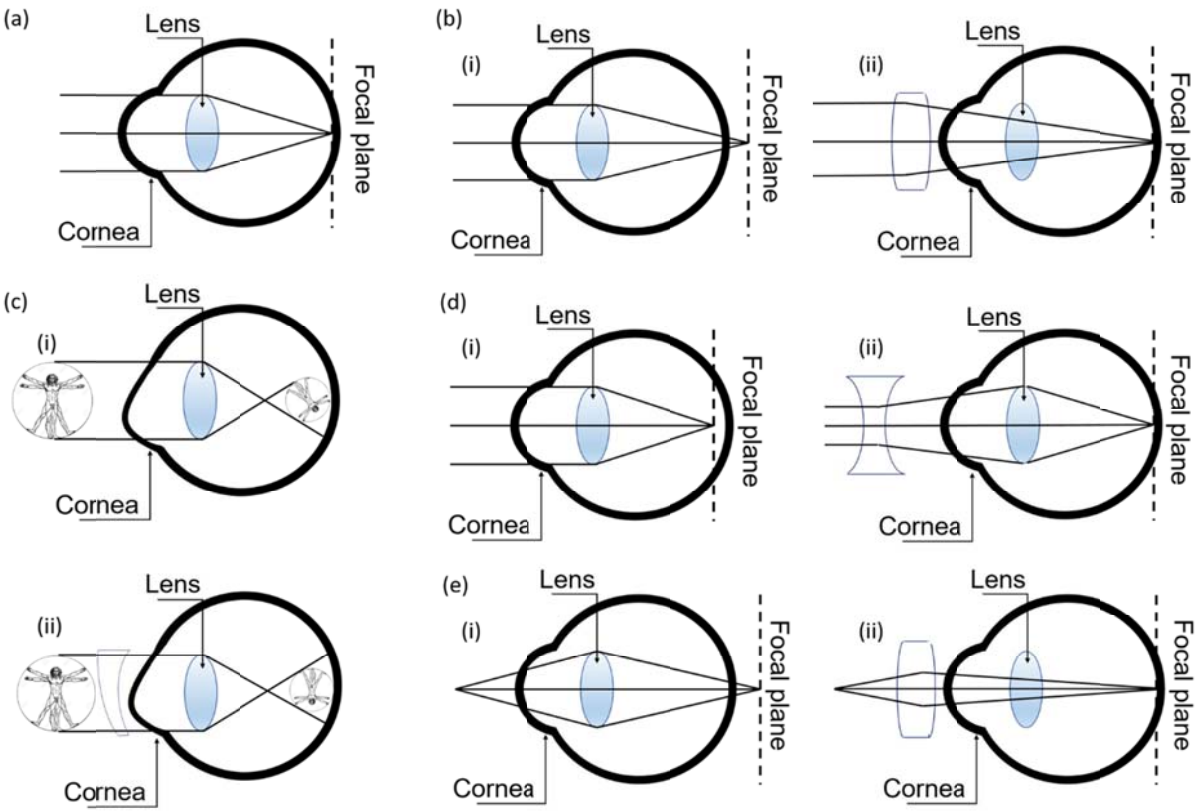

Figure 8. The most frequent refractive errors in the human visual system. (a) Normal vision or emmetropia: light focuses on the retina in a single focal point. (b) Hyperopia or far-sightedness: the focal point is posterior to the retina. (c) Astigmatism: light focuses on multiple focal points, resulting in blurred vision. (d) Myopia or near-sightedness: light focuses on a focal point anterior to the retina. (e) Presbyopia: the lens hardens with age losing the ability to modulate its shape.

6.2 Prosthetics

An important slice of contact lenses market is reserved to tinted contact lenses with prosthetic purposes. Prosthetic lenses are used to aid the management of aniridia, ocular albinism, leukoma, diplopia, and iris atrophies.[40, 41] Prosthetic lenses are produced in different designs, including pupil and iris occlusion, clear iris, and clear pupil. Diameters can be varied according to the prescription. Soft tinted lenses may be produced with pupil and iris occlusion, and iris pigment on the frontside. Patients who have permanent dilated pupils may

use front-painted, iris-occluded lenses. Patients who have dark iris color may choose a black iris occlusion lens. Pupil-occluded lens feature a black central area to reproduce the shape and color of a regular pupil, and they block the vision.[134, 135] They may be used to hide a white pupil, for vision occlusion, or for the correction of aesthetic defects in a blind eye. Prosthetic contact lenses may be soft or rigid. The most diffused types of prosthetic lenses are translucent tinted lenses, computer-generated printed lenses, and hand painted lenses. Translucent tinted lenses feature a homogeneously colored iris and they offer a low degree of customization. Pigments are not dense enough to provide a good contrast in patients with light colored iris. Computer-generated lenses can be designed in specific colors and diameters.[136] Pupil and iris occlusion can be achieved, as well as dark or light back iris occlusion. Limitations are the predefined colors and geometrical parameters. Hand painted lenses have the highest degree of customization, and they can be produced in any diameter. Prosthetic contact lenses may be grouped based on their applications, with regards to the eye-site, as presented in **Table 8**.

Table 8. Applications of prosthetic contact lenses based on defective eye site [136].

Cornea	Iris	Lens	Globe	Other
Leukoma	Heterochromia	Leukoria	Phthisis bulbi	Photophobia
Band keratopathy	Aniridia		Buphthalmos	Rod cone dystrophy
Advanced Arcus	Polycoria			Color deficiency
Scarring	Coloboma			Strabismus
Keratopathy	Albinism			Migraines
Microcornea				

6.3. Therapeutics

Therapeutic contact lenses are primarily used to provide relief of discomfort, vision aid in eyes with irregular corneas, and to heal injured ocular tissues. Therapeutic contact lenses as drug delivery vehicles are individually addressed in the next subsections. Soft contact lenses are used to aid the management of post-refractive surgery in eyes that under epithelial removal, and in corneal degenerations. The high oxygen permeability of silicone hydrogels allows to minimize the induced hypoxic stress. Silicone hydrogel lenses are largely used in post- photorefractive keratectomy (PRK) and laser-assisted subepithelial keratomileusis (LASEK), and they reported better results when compared to hydrogels. Rigid lenses are used as therapeutic devices to correct corneal abnormalities and eye disorders related to deficiencies of the tear film. The most common corneal abnormalities are keratoconus, keratoglobus, and cornea plana. **Figure 9a** presents the different shapes of a normal cornea, a keratoconic cornea, a keratoglobic cornea, and a planar cornea. In the last decade, successful results in correcting corneal ecstasia with soft contact lenses has been achieved, but scleral lenses remain the gold standard.[137] Contact lens wear is reported to be the best existing solution to corneal aberrations, as an alternative to both surgical treatments and implantation of intrastromal corneal rings. Aqueous leakage post-surgery or trauma can be sealed with a hydrogel or silicone hydrogel contact lens **(Figure 9b)**.[137] Scleral lenses are also used for the correction of advanced Sjogren's syndrome **(Figure 9c)**, associated to a dysfunction of the Meibomian glands in tear film secretion, or to a high evaporation rate of the tear film. The lens ensures the formation of a fluid reservoir over the eye, by covering the surface and limiting tear evaporation. Rigid lenses can be used to protect the cornea undergoing re-epithalization following a chemical burn **(Figure 9d)** and to address Steven Johnson syndrome **(Figure 9e)**. Rigid corneal lenses are used to protect the cornea from abnormal lashes and keratinized lid margins. Rigid scleral lenses can fit any eye shape, they provide

complete protection of cornea and bulbar conjunctiva, and overnight wear can be targeted using RGP materials.[137]

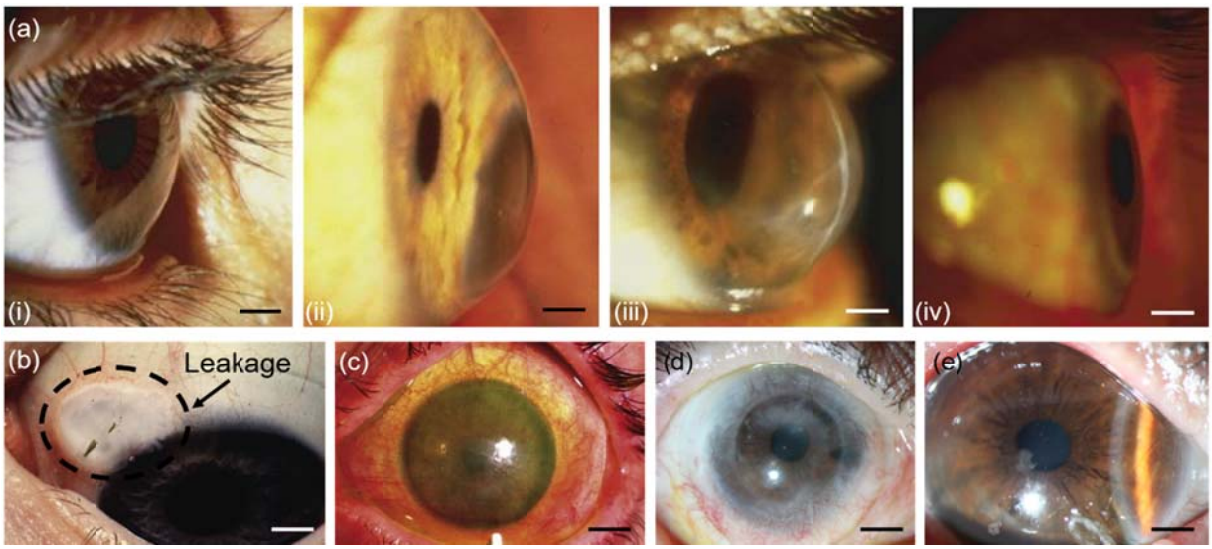

Figure 9. Eye disorders and therapeutic contact lenses. (a) Corneal shapes. (i) Normal cornea, (ii) keratoconus, (iii) keratoglobus, (iv) cornea plana. Scale bars: 2.0 mm. Reproduced with permission.[138] Copyright 2018, Elsevier. (b) Post-surgery aqueous leakage sealed with a soft contact lens. Scale bar: 3.0 mm. Reproduced with permission.[136] Copyright 2018, Elsevier. (c) A rigid contact lens fitted on an eye affected by Sjogren's syndrome. Scale bar: 4.0 mm. Reproduced with permission.[138] Copyright 2018, Elsevier. (d) Mini sclerals fitted on an eye with chemical burn. Scale bar: 4.0 mm. Reproduced with permission.[139] Copyright 2012, Elsevier. (e) Mini sclerals fitted on an eye with Steven Johnson syndrome. Scale bar: 2.0 mm. Reproduced with permission.[139] Copyright 2012, Elsevier.

6.4. Contact lens sensors: from therapeutics to theranostics

Contact lens sensors have been primarily targeted as sensing platforms for point-of-care settings in glaucoma[8], and continuous monitoring of glucose in tears.[140, 141] The Triggerfish silicone lens was developed by Sensimed to monitor the intraocular pressure in glaucoma

patients.[142] Triggerfish underwent animal test and clinical trials, and received the FDA and CE approval to be worn for 24 consecutive hours. It integrates two strain gauge sensors, a microprocessor and a three-loop antenna. The sensor measures minute changes in the ocular dimensions through the strain gauge, recording for 30 seconds at 5 minutes intervals over 24 hours. The information is transmitted wirelessly from the sensor to the antenna, and then transferred via a wire to the recorder. The recorder is worn by the patient. The information can be retrieved from the recorder via a USB Bluetooth adapter.[142] A single-pixel GaN LED display was integrated within a contact lens and tested in rabbit eyes, powered by a remote radiofrequency transmitter.[143] Fluorescein tests showed no corneal epithelial damages. **Figure 10a** presents a prototype of a wearable contact lens sensors for continuous glucose monitoring.[16] Microstuctures with a periodicity of 1.6 were patterned on a glucose-selective hydrogel film functionalized with phenylboronic acid. Glucose binding induced a local volumetric increase, leading to a change in the Bragg diffraction. Graphene films were also used in contact lenses for various applications.[144, 145] An example of device for full-corneal electroretinagram (ERG) recording is shown in **Figure 10b.**[144] The device consisted on a contact lens-shaped parylene covered with a graphene layer on the concave side. Graphene was CVD-grown on a lens-shaped quartz mold to avoid the formation of wrinkles. ERGs were recorded on cynomolgus monkeys with a Ganzfeld flash stimulation, resulting in negligible corneal irritation. A contact lens glucose sensor featuring a LED display was recently reported **(Figure 10c)**.[128] The lens featured a reinforced region to host LED, rectifier, and glucose sensor. A transparent AgNF-based antenna and interconnects were located on an elastic region. In vivo test on a rabbit eye showed the turn-on and off states of the LED based on glucose concentration in the injected tear fluid. Several contact lens-compatible technologies have also been investigated. A potential power source for contact lenses consisted on a lactate/O_2 enzimatic biofuel cell (EBFC), based on flexible nano-porous

gold (NPG) electrodes.[146] The EBFCs was tested in artificial tears, exhibiting a decrease in performance in tears with respect to the buffer solution due to ascorbate interference, suggesting that a coating film on the biocathode might improve the performances in future developments. The response of the EBFC was limited by current density of the biocathode, which further improvements may enable the development of a self-powered lactate biosensor where the power density is correlated to lactate concentration. Stretchable photodetectors based on a crumpled graphene–gold nanoparticle (AuNP) hybrid structure were successfully integrated within contact lenses[147], exhibiting a plasmonically enhanced photoresponsivity of 1200% compared to a conventional flat graphene photodetector, and mechanical stretchability up to a 200% tensile strain. A new biomaterial for bio-friendly and green optoelectronics applications was recently demonstrated with soft contact lenses.[148] The lens was made of silk fibroid protein in hydrogel form for applications in light emitting diodes (LEDs). The optical properties of the resulting lens were influenced by the concentration of the protein as well as of the cross-linking agent. The lens showed a light extraction efficiency over 0.95 on a white LED. Recently, a stretchable electronic platform for contact lens smart applications was developed.[18] The electronics was based on thermoplastic polyurethane (TPU) with an outer diameter of 10mm and curvature radius of 9.0 mm featuring a silicon chip, an RF antenna and thin film interconnections placed in polymeric semirigid islands. The antenna was thought to be implemented at 13.56 MHz with near-field communication protocols for smart lenses applications. In the last decades, many efforts were put in the development of materials with high transparency, oxygen permeability, and outstanding mechanical stretchability, to be utilized in contact lens sensing systems.[149-152]

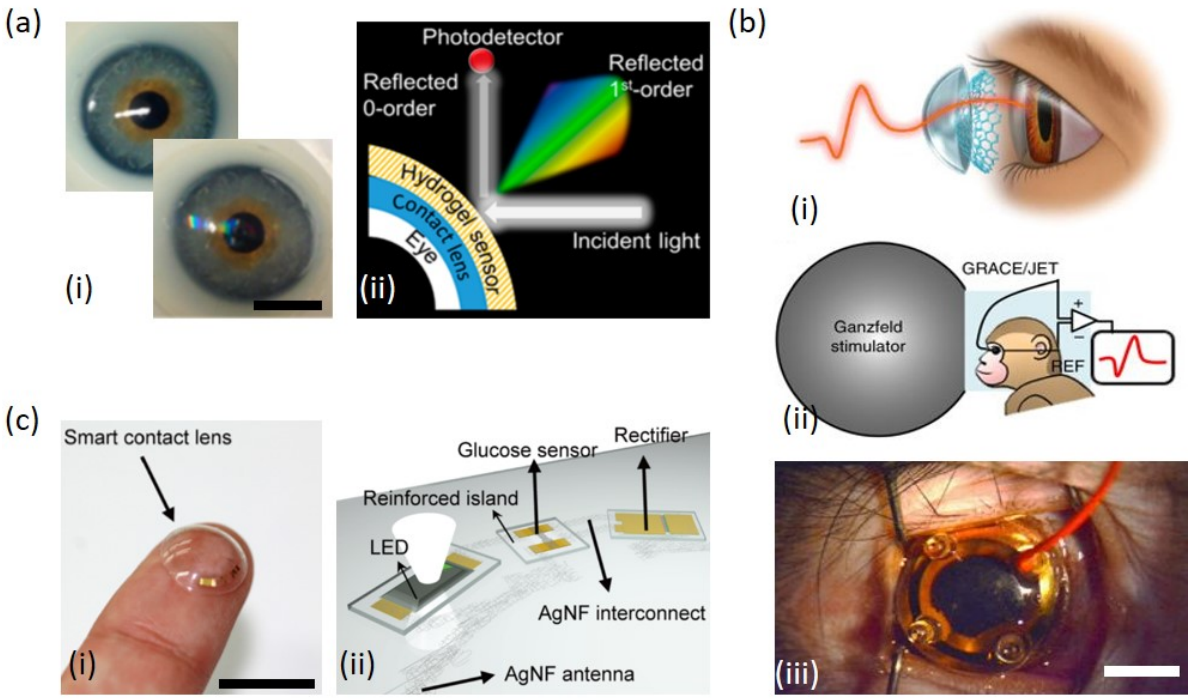

Figure 10. Selected contact lens sensors. (a) A contact lens for glucose continuous monitoring. Scale bar: 2.0 mm. Reproduced under the terms of the CC BY 4.0 license.[16] Copyright 2018, American Chemical Society. (b) Graphene contact lens electrode for ERG measurements. (i) Schematic drawing with ERG recording. (ii) Representation of a ffERG recording on cynomolgus monkeys with ganzfeld stimulation. (iii) Photograph of a Jet electrode applied to an eye of a cynomolgus monkey. Scale bar: 5 mm. Reproduced under the terms of the CC BY 4.0 license.[144] Copyright 2018, NPG. (c) A smart contact lens integrating wireless circuits with stretchable interconnects, a glucose sensor, and a display. (i) Photo of the contact lens sensor. Scale bar: 2.0 cm. (ii) Schematic of the sensor components. Reproduced under the terms of the CC BY NC license.[128] Copyright 2018, American Association for the Advancement of Science.

6.5. Contact lenses as drug delivery systems

Despite being an easily accessible organ, the physiology of the eye poses hard challenges in drug delivery.[153-155] The ocular environment acts as a barrier to external organisms. Hence,

ocular drug delivery must be designed to target specific tissues. Current drug delivery methods are primarily based on eye drops, emulsions, and gels. Innovative methods include implants, iontophoresis, and microneedles. Contact lenses provide a fascinating mean to achieve extended drug exposure time. Drugs can be loaded in contact lenses in different ways: soak-and-release, molecular imprinting (MI)[137], modification of lens matrix composition, and using colloidal and nano-carriers.[127] The soak-and-release method consists on soaking the lens in an aqueous drug solution, resulting in the drug being trapped in the hydrophilic matrix of the lens. This method is commonly used for delivery of anti-glaucoma drugs, anti-histamines and antibiotics.[126] The drug encounters a boost first release, followed by a gradual release. Soak-and-release method is being currently investigated for delivery of hyaluronic acid to treat dry eye disease.[153] To retard the release of hydrophilic drugs from contact lenses, Vitamin E was incorporated into the lens matrix to act as a hydrophobic barrier.[126] Molecular imprinting consists on etching nano-cavities to incorporate functional monomers within the lens. This enhanced the active area and maximized drug absorption within the lens. Using NSAIDs as a monomer, ibuprofen and antibiotics were delivered to ophthalmic tissues via contact lenses.[126] Self-responsive, molecular-imprinted contact lenses were used for the controlled release of timolol.[123] A visible color change was observable in the lens based on the amount of released drug (**Figure 11a**).

Modifying the lens matrix composition consists on obtaining specific binding sites on the surface of hydrogel lenses. Examples include hydrogel lenses with cationic functional groups to store anionic drugs and release them in physiological conditions. MAA was added to pHEMA lenses for extended release of naphazoline.[126] Drugs can also be inglobated into nanocarriers. Liposomes were used to carry hydrophilic and lipophilic drugs (ioxuridine, penicillin G, lidocaine, levofloxacin). Polymeric micelles were used as nanocarriers to deliver dexamethasone acetate.[156] Cyclodextrins were functionalized to carry hydrophobic

drugs.[157] Drug nanosuspensions were loaded in a contact lens for delivery of triamcinolone acetonide, showing significantly increased drug load capacity and releasing times.[158] Silicone hydrogel contact lenses functionalized with epalrestat were successful in addressing diabetic eye complications and cataract, by inhibiting aldose reductase (AR) and preventing protein glycation **(Figure 11b)**.[159] Nanogels were used as timolol maleate carriers and loaded into enzyme-responsive contact lenses, for tear lysozyme-activated release of timolol maleate for the treatment of glaucoma **(Figure 11c)**.[160] Nanoparticles were reported to allow extended delivery of lidocaine, timolol, meloxicam-nanoaggregates, antibacterial silver nano-particles, antifungal agent voriconazole and indomethacin.[126] An example is presented in **Figure 11d**, where an hybrid hydrogel-based contact lens comprising quaternized chitosan (HTCC), silver nanoparticles and graphene oxide (GO) was used for the treatment of fungal keratitis in mice.[125]

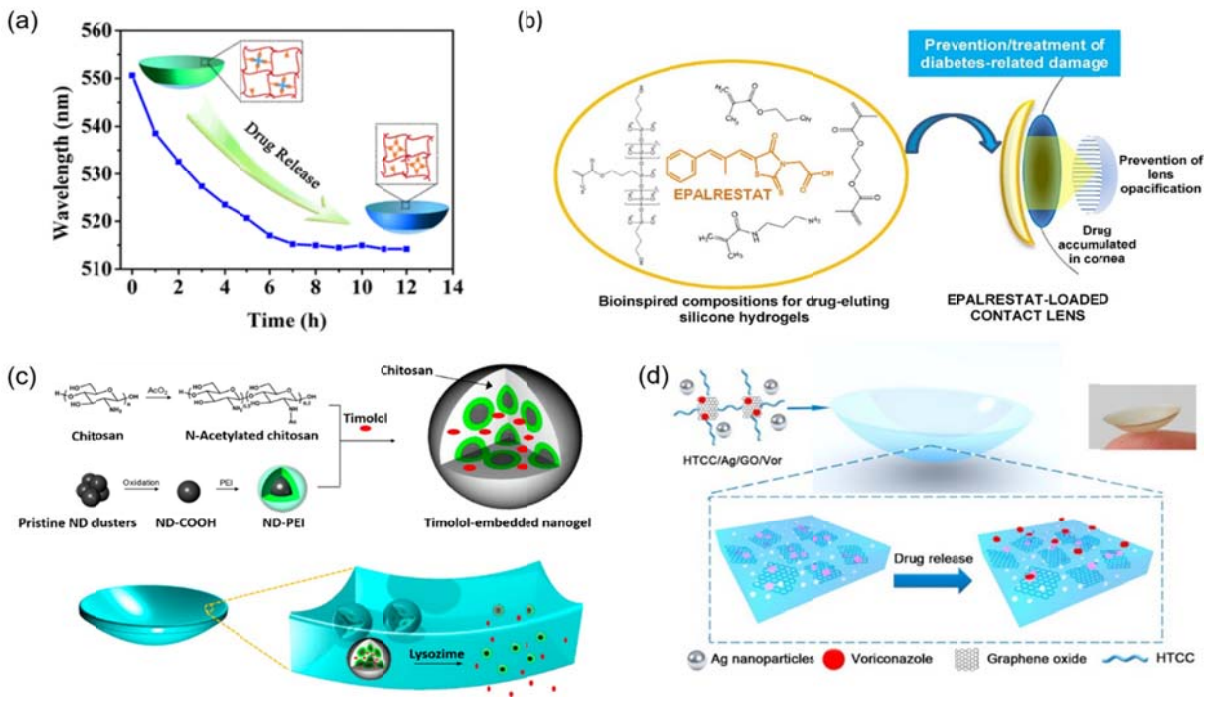

Figure 11. Selected contact lenses as drug delivery systems. (a) Self-responsive soft contact lens for timolol ophthalmic delivery, exhibiting a visible color change to monitor releasing times and quantities. Reproduced with permission.[123] Copyright 2018, American Chemical

Society. (b) Bioinspired composition of drug-eluting silicone hydrogel loaded into soft contact lenses for treating diabetic eye complications. Bovine tests showed drug accumulation within the cornea. Reproduced with permission.[159] Copyright, Elsevier. (c) Lysozyme-activated drug eluting contact lens. Drugs are loaded in ND nanogels by cross-linking PEI-acoated NDs and partially N-acetylated chitosan in presence of timolol maleate. Nanogels are further embedded within enzyme-responsive contact lenses. Tear lysozyme degrades the nanogel, resulting in timolol maleate release whilst leaving the lens intact. Reproduced with permission.[160] Copyright 2014, American Chemical Society. (d) Hybrid hydrogel-based contact lens comprising HTCC, silver nanoparticles and GO to treat fungal keratitis with targeted ophthalmic drug delivery. Reproduced with permission.[125] Copyright 2016, American Chemical Society.

7. Contamination in contact lenses

Bacteria are highly present in nature in the form of aggregates named biofilms, i.e. dense polymeric matrices where bacterial communities are entrapped. Biofilms act as a cohesion media for microbes, and as a vehicle to exchange nutrients, enriching and strengthening the biofilm itself.[161] Cells in biofilms have been found to be 100 to 1000 times more resistant to antibiotics with respect to planktonic cells.[162] The formation of a biofilm articulates in two steps: a first temporary adhesion mediated by Van der Waal forces, followed by an irreversible adhesion with the formation of a matrix.[161] Biofilm formation by pathogenic bacterial strain is a major cause of infections in medicine[163], dentistry[164, 165], food processing[166], and water treatment[167]. Surface modification is an emerging strategy to either prevent biofilm formation, or to induce bacterial detachment.[168] Microbial contamination of contact lenses is the cause of several eye diseases.[23, 95, 169] Both bacterial and contact lens material characteristics play an important role in the adhesion process. The most commonly isolated organisms from contact lenses are *Pseudomonas species, Serratia*

marcescens, coagulase-negative Staphylococci and Staphylococcus Aureus.[91] Treatment of *Pseudomonas Aeruginosa* eye infections often becomes a challenge due to the ability of this bacterium to be naturally resistant to some antibiotics, and its capacity to acquire mobile genetic elements (MGEs) that induce a rapid spread of drug resistance.[161] Despite *P. Aeruginosa*'s pili and flagella have shown to be involved in the adhesion process, both piliated and non-piliated *P. Aeruginosa* adhere to contact lenses, suggesting that other factors are involved.[170, 171] The main factors influencing bacteria adhesion are cell surface hydrophobicity, strain and suspension media, with *P. Aeruginosa* being the quickest to adhere and the one isolated in the highest percentage. Bacteria with a high surface hydrophobicity adhere more than hydrophilic organisms, indeed *P. Aeruginosa* adheres more than *Staphylococcus* (132° VS 20-35° contact angles) and other strains.[170] *P. aeruginosa* isolated from cornea during keratitis adhere more than when isolated from other body parts. *P. Aeruginosa* adhesion under different media has been studied, including using PBS, nutritionally rich media, and artificial tears to better simulate the ocular environment. Several bacterial strains can form a biofilm on the same surface and influence each other.[171] It has been shown that the presence of *S. epidermis* on hydrogel lenses affects the growth of *P. Aeruginosa*, but not vice-versa. The same *P. Aeruginosa* exposed to a contact lens for a second time have shown to adhere less than at the first exposure, suggesting that a selection of cells promote adhesion.[171] Characteristics of the targeted surface are also relevant to bacterial adhesion, the main being ionicity, water content, hydrophobicity, topography, and tear protein absorption. It has been demonstrated that both *P. Aeruginosa* and *S. Aureus* adhere more to ionic hydrogel lenses.[170] An inversely proportional dependence has been observed between bacterial adhesion and water content of the surface.[170, 172] Surfactant-laden contact lenses have a higher equilibrium water content (EWC) and a lower hydrophobicity which results in less bacterial attachment.[172] A higher surface roughness has

shown to favor adhesion, and contact lens wear has shown to induce surface roughness due to attachment of tear compounds. In particular, mucin, IgA, BSA, lysozyme and lactoferrin absorption enhance *P. Aeruginosa* adhesion.[172] Studies reported the ability of multiple bacteria genera to form biofilms on silicone hydrogel contact lenses in presence of dying neutrophils[173], which can be blocked using specific contact lens solutions.[174] A portable lens-free microscope for computational sensing of *S. Aureus* on contact lenses was recently developed, with a resolution of 16 CFU μL^{-1}.[175]

Several studies demonstrated changes in the ocular microbiota of contact lens wearers.[91, 95, 98, 176] Bacterial communities of the conjunctiva and skin under the eye of 20 subjects, 9 contact lens wearers and 11 controls were compared.[176] It resulted that dry conjunctival swabs from lens wearers featured more skin-like bacterial types, the most highly represented of which were *Methylobacterium, Lactobacillus, Acinetobacter and Pseudomonas.*[176] *Haemophilus, Streptocossus, Staphylococcus and Corynebacterium* have also been found, but they appeared in lower concentrations than in non-lens wearers.[176] The conjunctival microbiota of both lens and non-lens wearers had higher concentrations of hand-like bacteria than of face-like bacteria. Overall, the eye microbiota of contact lens wearers resembled the one of the skin, suggesting that there may be a transfer of bacteria from the skin to the ocular surface via contact lenses.[91, 176] Bacteria isolated from the eyes of non-contact lens wearers and bacteria isolated from contact lenses of asymptomatic patients are summarized in **Table 9**.

Table 9. The microbiota in conjunctiva, lids and tears of a healthy eye, and in contact lenses of asymptomatic patients.[91-99, 176]

Microbe	Healthy eye		Contact lenses
	Conjunctiva	Lids and tears	
Gram-positive bacteria			

Coagulase-negative staphylococci	**Yes**	**Yes**	**Yes**
Propionibacterium sp.	**Yes**	**Yes**	**Yes**
Corynebacterium sp.	**Yes**	**Yes**	**Yes**
Clostridium sp.	No	**Yes**	No
Bacillus sp.	**Yes**	**Yes**	**Yes**
Micrococcus sp.	**Yes**	**Yes**	**Yes**
S. Aureus	**Yes**	**Yes**	**Yes**
Stromatococcus sp.	No	No	**Yes**
Streptococcus sp.	No	**Yes**	No
Micrococcus sp.	No	No	No
Enterococcus sp.	**Yes**	No	No
Lactobacillus sp.	**Yes**	No	No
Peptococcus niger	**Yes**	No	No
Peptostreptococcus sp.	**Yes**	No	No
Gram-negative bacteria			No
Pseudomonas sp.	**Yes**	**Yes**	**Yes**
Enterobacter sp.	**Yes**	No	No
E. coli	**Yes**	No	No
Neisseria sp.	No	**Yes**	No
Proteus sp.	**Yes**	**Yes**	No
Acinetobacter sp.	**Yes**	No	No
Citrobacter sp.	**Yes**	No	No
Moraxella sp.	No	**Yes**	**Yes**
Fungi			
Fungus	**Yes**	**Yes**	**Yes**

7.1. Contamination of contact lens cases

Contamination of contact lens cases is reported to be a major cause of infection in contact lens wearers.[23, 177, 178] It has been found that over 90% of the subjects with contaminated case also had contaminated lens or solutions, suggesting that bacteria might be transferred from the case to the lens. Differently from contamination of contact lenses, which is primarily prompt by bacteria, contamination of contact lens cases includes bacteria, fungi, protozoa, and viruses in over the 70% of the cases.[177, 178] Lens cases can develop moderate or heavy contamination after two weeks of use. Biofilms in contact lens cases are thicker than the ones

formed on contact lenses.[178] Bacterial diversity in contact lens cases has shown to be related to the severity of the disease. So far, a threshold defining an acceptable contamination level has not been identified. Novel case designs to reduce microbial contamination are being studied.[179] Contact lenses handled inappropriately can adversely affect most anterior ocular structures.[20, 179, 180] The most frequent complications based on the eye site are summarized in **Table 10.** In **Figure 12,** clinical cases of corneal staining, conjunctival redness, and papillary conjunctivitis at different grading scales are presented.

Table 10. Contact lens complications based on eye site.[169, 181].

Complication	Eye site
Microcysts	Corneal epithelium
Epithelial staining	
Oedema	Corneal stroma
Neovascularization	
Keratitis [25, 26]	
Bedewing	Corneal endothelium
Blebs	
Polymegethism	
Meibomian gland dysfunctions	Eyelid
Lid wiper epitheliopathy	
Blinking rate variations	
Mucin balls	Tear film
Dry eye	
Conjunctival staining	Conjunctiva
Conjunctival redness	
Papillary conjunctivitis	
Limbal redness	Limbus
Vascularized limbal keratitis	
Limbal stem cells deficiency	

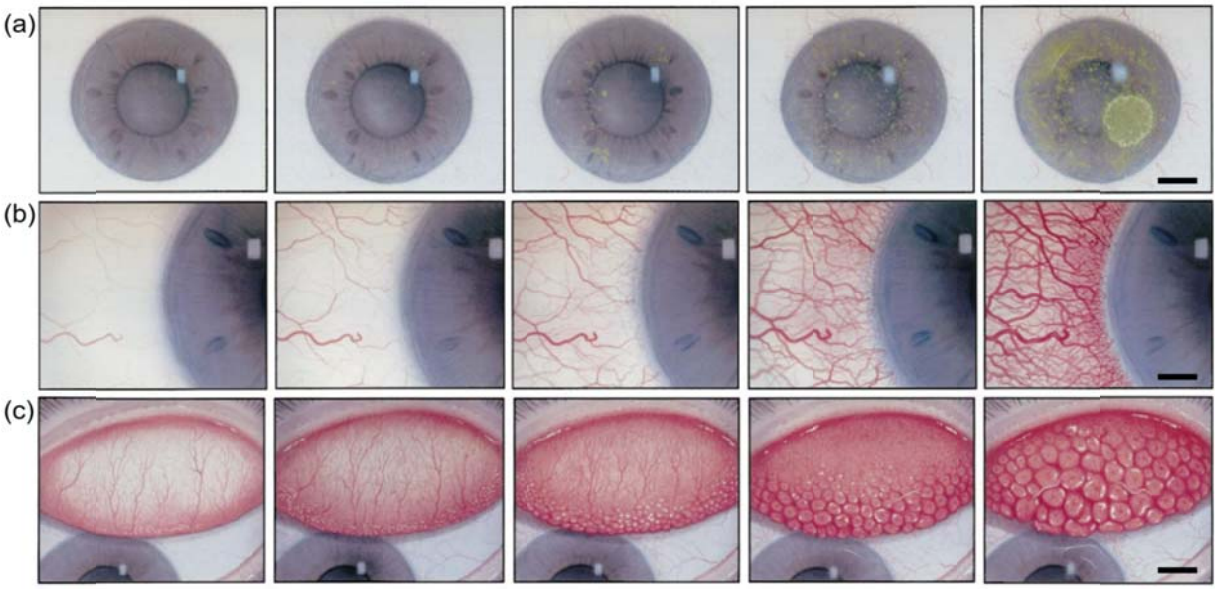

Figure 12. Contact lens complications. (a) Corneal staining. Scale bar: 3.0 mm. (b) Conjunctival redness. Scale bar: 1.5 mm. (c) Papillary conjunctivitis. Scale bar: 3.0 mm. Grading scale, from left to right: normal, trace, mild, moderate, severe. Reproduced with permission.[182] Copyright 2002, John Wiley and Sons.

7.2. Contact lens care

Antimicrobial methods can be generally classified into two main groups: active chemical strategies and passive chemical strategies, the first aimed in killing bacterial already attached to a surface by using microbicidal chemicals, the second based on preventing biofilm formation. Contact lenses and lens cases are mostly disinfected with hydrogen peroxide and multipurpose solutions (polyhexamethylene biguanide (PHMB) and Polyquad).[183, 184] The literature concerning the effectivity of hydrogen peroxide as a disinfection system is controversial. It has been demonstrated that *P. Aeruginosa* biofilms grown in vitro are better attacked by hydrogen peroxide[184, 185], but other studies report that *Staphylococci* is able to unbond hydrogen peroxide molecules, neutralizing its effect.[184, 186] *Serratia marcenses* can only be treated with hydrogen peroxide.[184] Polyquad has been found to reduce the transfer of bacteria from the case to the lens.[187, 188] A reduction in bacterial flora (>99%) on the surface

of the periocular skin without altering the bacterial species has also been recently demonstrated by using a hypochlorus acid hygiene solution.[189] The disinfection efficacy of CLEAR CARE, RevitaLens OcuTec, OPTI-FREE PureMoist and Biotrue solutions was compared. It resulted that CLEAR CARE cleaned lens cases exhibited much higher bacterial concentration than the ones cleaned with RevitaLens OcuTec.[190] The same result was observed comparing PureMoist with Biotrue. A recent study successfully demonstrated the use of a povidone-iodine as a disinfection system for contact lenses.[191] The case design might be also relevant to bacterial adhesion. Silver impregnated lens cases and selenium lens cases have been designed with anti-microbial purposes.[178] Other methods have been investigated for prevention and disinfection purposes, including the use of free-radical producing agents, quorum-sensing blockers, antimicrobial peptides, and non-steroidal anti-inflammatory drugs.[179] To minimize microbial contamination, hygiene measures have to be taken. These include disinfecting lens and cases frequently, replacing the case every two weeks, facing down the case during air drying, avoiding to use tap water and to top-off the contact lens solution, and wash hands before insertion and removal.[192]

8. Regulations of contact lenses

Contact lenses are prosthetic devices categorized as direct contact devices, i.e. “devices or device components that come into physical contact with body tissue” (ISO 10993-1).[193] To introduce a contact lens device to the market, standards and regulations must be fulfilled to assess its safety, functionality, and reliability. The International Organization for Standardization (non-acronymic abbreviation: ISO) is the world's largest developer of voluntary international standards to facilitate world trade by providing common standards between nations.[194] However, it has no role in enforcing its standards and it is not compulsory for marketed products to legally meet the ISO requirements.[195] Nevertheless,

governmental bodies exist to supervise and control medical devices, and they substantially adopt the ISO standard.[196, 197] Therefore, a device that fulfils ISO requirements is eligible to hit the market. In the US, regulations are established by the Food and Drug Administration (FDA), which from 2019 plans to officially use ISO 13485 as the basis for its legislation on medical devices.[196] Biocompatibility standards for medical devices are well stated in ISO 10993 – "Biological Evaluation of Medical Devices". ISO 10993-1 is the Guidance on Selection of Tests[193], ISO 10993-2 covers animal welfare requirements.[198] ISO 10993-10 assesses possible contact hazards from device-released chemicals that may produce skin and mucosal irritation, eye irritation and delayed contact sensitization.[199] ISO 10993-(3-19) states the guidelines for specific test procedures.[199-208] The most important tests in the biocompatibility assessment of a contact lens device are the *in vitro* test and the *in vivo* test. ISO 10993-5 describes the *in vitro* toxicological testing procedure [200], and ISO-9394 describes the biocompatibility test in rabbit eyes.[209]

8.1. In vitro toxicological test

The citotoxicity test can be performed either on an extract or on the entire sample, in direct contact mode with mammalian cells. The cell sample is prepared in accordance with ISO 10993-12[207] and handled aseptically throughout the procedure. Sterile, mycroplasma-free cell lines are obtained from living tissues and stored at −80 °C or below in the culture medium with cryoprotectant in the pH range 7.2-7.4. In qualitative evaluations, the text sample is exposed to a known amount of cell suspension through a vessel. Vessels can be cleaned and replenished with new culture medium. The culture is incubated at 37 ± 1 °C in air. Changes in morphology, vacuolization, detachment, cell lysis, and membrane integrity are evaluated by inspection under a microscope, using cytochemical staining. The interpretation of the results is done accordingly to the classification of the device, as given in

ISO 10993-1.[193] *In vitro* evaluation is primarily run to evaluate a potential *in vivo* toxicity. A reduction of cell viability higher than the 30% is considered cytotoxic. Direct contact cytotoxicity test is also performed on contact lens/contact lens solution combination in extended wear contact lenses.

8.2. In vivo animal test

Animal testing of contact lens devices is carried out in compliance with ISO-9394: "Ophthalmic optics — Contact lenses and contact lens care products: Determination of biocompatibility by ocular study with rabbit eyes.".[209] The irritant properties of materials which come in contact with ocular tissue are evaluated on rabbit eyes, complying to the regulations defining animal welfare (ISO 10933-2)[198] and good laboratory practice (ISO/IEC 17025)[210]. Animal test is performed after a positive outcome of the irritation and sensitization tests (ISO 10993-10)[199] and *in vitro* biocompatibility assessment (ISO-10993-2).[198] New Zealand white strain rabbits (male, female or mixed sexes) or equivalent albino rabbits are used to test contact lenses. Animal models are young adults, from a single strain, weighing more than 2.5 kg, and free from clinically significant ocular irritation or corneal retention of fluorescein stain. A minimum number of six animals need to be tested, and a 100% positive result has to be met. Each animal is uniquely identified by either a numbered ear tag, a tattoo, or a microchip. The animals are acclimatized to laboratory conditions for at least five days prior to testing. The lens is inserted in one eye of the rabbit and the other is used as a control. The lens is left on the eye's animal for 7 hours, then removed. This procedure is repeated for 21 days. Eyes are examined visually and evaluated according to both the Draize and the McDonald-Shadduck scoring systems. The eyes are excised and preserved in a fixation solution (e.g. 10 % neutral buffered formalin, Zenker's acetic fixative

or Davidson's solution). The eyes are further sectioned to divide cornea, conjunctiva, iris, and lens, and each part is stained for microscope evaluation.

9. Contact lens market

Contact lens technology gained increasing popularity and a broader range of applications since it was commercialized. The contact lens global market exceeded the value of 8.5 billion US dollars in 2018 with a growth over the 6%, and a continue transition to silicone hydrogel materials.[181] In 2018, the 69% of contact lens sales were silicone hydrogel contact lenses, followed by hydrogel lenses (19%), RGP (9%) and hybrid lenses (2%). Monthly and daily contact lenses were reported to be the most popular (41% and 35% respectively), over contact lenses with weekly (21%) or 3+ months (3%) replacement schedule (**Figure 13a**).[181] From data in 15 countries worldwide in 2018 resulted that a portion of contact lens patients are part-time wearers, with the highest percentages reported in Finland (34%), Czech Republic (30%), and Australia (29%) (**Figure 13b)**.[181] Over the last decade, a decrease in the use of hydrogen peroxide solutions was reported, but chemical care systems continued to dominate the market (**Figure 13c**).[213] Contact lens wearers in 2018 were over the 35% globally, with a higher net practice revenue when compared to the previous years in relation with the gross revenue. Weekly fits and refits were reported to increase comparing to the previous years. Contact lens wearers in 2018 were over the 35% globally, with a higher net practice revenue when compared to the previous years in relation with the gross revenue. Weekly fits and refits were reported to increase comparing to the previous years. In 2018, the US market of contact lens care was led by Clear Eyes, Bausch & Lomb with BioTrue, and Alcon with Opti□Free Pure Moist (**Figure 13d**).[211] The global contact lens market is estimated to grow from 12.4 billion USD in 2018 to 15.53 billion USD in 2021 and 19.45 billion USD in 2024 **(Figure 13e)**. **Figure 13f** presents the contact lens market value in 2018 in 20 countries.[213]

The US market was valued over 4.5 billion USD, with a net gap compared to the other countries.[10] An analysis of the new-born market of smart contact lenses revealed a value of 59.9 million USD in 2018, estimated to reach over one billion USD in 2022.[212]

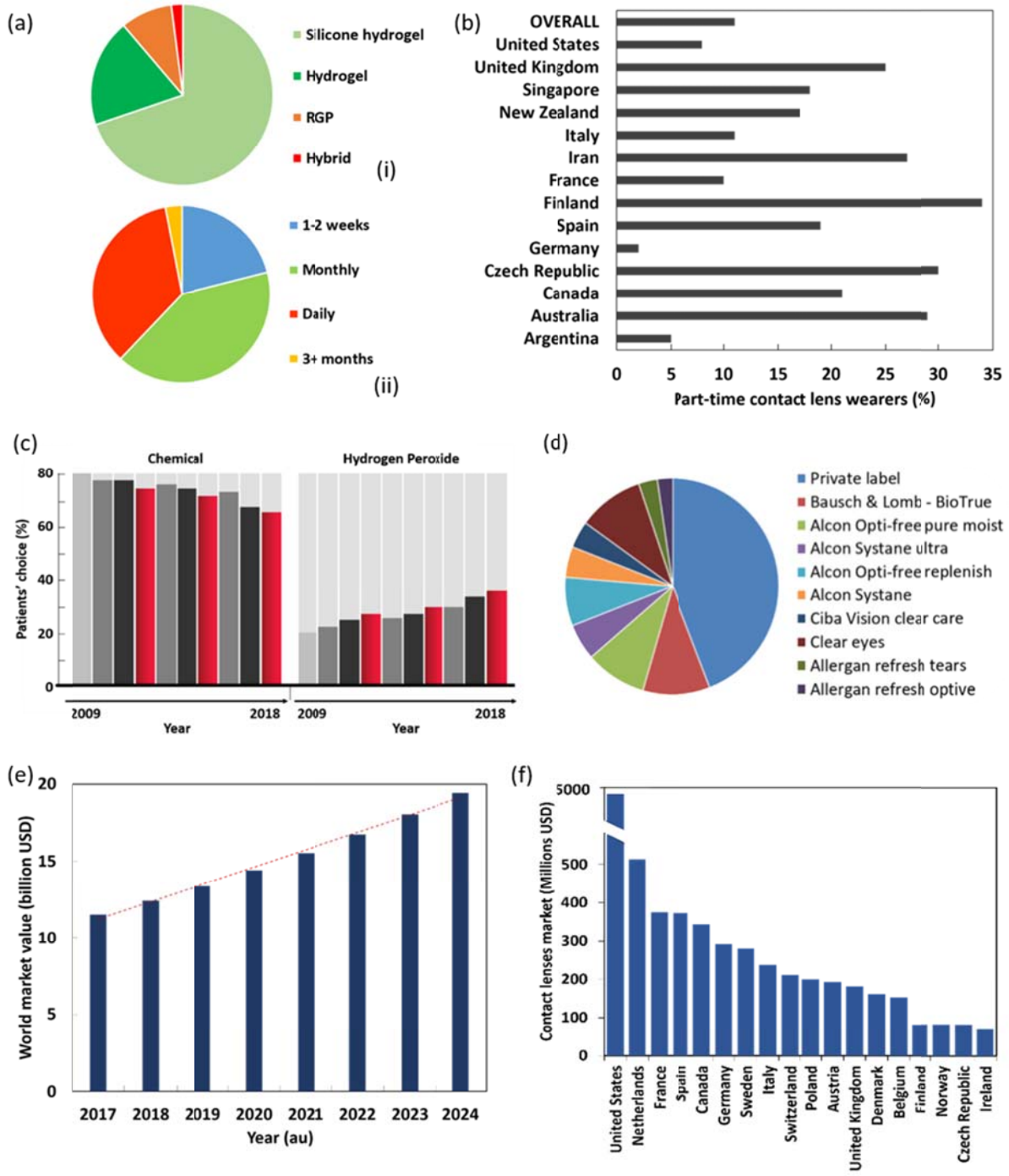

Figure 13. Contact lens market, as of January 2019. a) Contact lens fits and refits in 2018 based on i) material classes and ii) replacement schedule. Data from [181]. b) Part□time contact lens wearers in 2018 in 14 countries worldwide. Data from [181]. c) Contact lens care

trends from 2009 to 2019. Data from [213]. d) Unit sales of the leading eye and lens care solution brands in the United States (2018). The private label portion corresponds to 55 million USD. Data from [211]. e) Values and estimations of the global contact lens market from 2017 to 2024. Data from [10]. f) Contact lenses market analysis in 20 countries worldwide in 2018. Data from [213].

10. Conclusions

Contact lenses are a well-established, yet a constantly expanding technology. The global contact lens market in 2018 amounted to over 8 billion USD. Polymers in contact lenses have evolved to address the limitations with regard to ocular complications induced by contact lens wear. The choice of the polymer type utilized in contact lens manufacture is driven by the application, with RGP and soft contact lenses leading the market of ocular therapeutics and vision correction, respectively. In the last decade, contact lenses have been targeted as diagnostic wearable platforms with a variety of applications, including pressure sensors, glucose sensors, and drug delivery vehicles. Early stage investigations on tear fluid biomarkers may lay the foundations of a new pathway of contact lens technology that uses tears as a novel diagnostic media, to aid the management of in situ ocular diagnostics with a continuous monitoring method.

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Contact lenses

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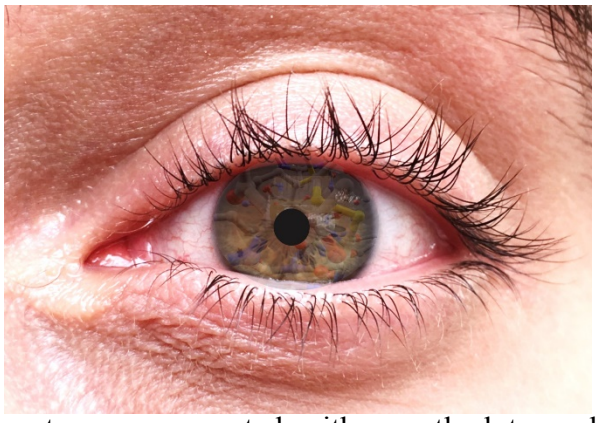
Contact lens technology: from Fundamentals to Applications



Contact lenses are prosthetic devices largely utilized worldwide. Here, contact lens technology is discussed from its conceptualization in 1508 to the evolution of polymeric materials, manufacturing techniques, applications, and complications associated to contact lens wear. The ocular environment is described with regards to the eye microbiota and the tear fluid composition. Recent advances in contact lenses as wearable bio-sensing platforms and drug delivery systems are presented, with an outlook toward future prospects.

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