

Silicone Hydrogels Materials for Contact Lens Applications

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Abstract

Silicone hydrogel (Si-Hy) materials combine the benefits of silicone or siloxane derivatives in terms of oxygen permeability and mechanical properties with those of hydrogels in terms of wettability and hydrophilicity. Such properties are critical when it comes to the application at the ocular surface in the form of contact lenses (CL) to correct visual dysfunctions, as bandage mechanism or as drug delivery devices. Nowadays, CL are used by over 100 million people worldwide.

Silicone hydrogel materials applied in the production of CL are a good example of how challenging the ocular surface environment is when it comes to the engineering of devices that will be well tolerated in this part of the human body. We now face the challenge of understanding the interaction between these materials and the disinfecting and cleaning systems, how these can impact the integrity of the ocular surface and the risks of inflammatory adverse events, and how wearing comfort can be improved.

Keywords: Biocompatibility, contact lens, silicone hydrogel, hydrophilic polymers

19.1 Introduction

The ocular surface is formed by the cornea, lids and conjunctiva. Tears are very important in keeping all these structures moistened and in gentle contact with each other. Contact lenses (CL) are applied directly to this anatomical region and are used by over 100 million people around the world. Despite this, the contact lens industry faces a high rate of drop-out from CL wear, mainly related to complaints of dryness and discomfort [1]. The CL polymers are required to meet several characteristics in order to avoid adverse effects to the ocular surface. One of the most critical ones is the need for oxygen and carbon dioxide permeability. A benefit of silicone is that it has long been recognized to increase the oxygen permeability of CLs. However, poor tolerance of this material at the ocular surface has been the motivation to try hybrid combinations of silicone (or siloxane) with other hydrophilic materials. After decades of failed

trials, silicone hydrogel (Si-Hy) CL were successfully introduced to the market in 1999. In less than 15 years they have become the main kind of soft CL material representing over 70% of all CL being fitted in the principal markets of North America, Northern Europe and Japan, among many others [2]. Although some authors claim that Si-Hy materials significantly improve comfort rates over the period of wear [3, 4], there does not seem to be evidence that Si-Hy materials by themselves can improve CL comfort [5]. Rather, the combination of lens material, surface and bulk properties, lens design, interaction with the cleaning and disinfection care regime, replacement schedule and other variables involved will interact with each other to define CL performance.

Since the introduction of the first two Si-Hy CL made of Lotrafilcon A material (Ciba Vision, Duluth, GA) and Balafilcon A material (Bausch + Lomb, Rochester, NY) the diversity of Si-Hy materials used in CL manufacturing has increased, with new formulations being launched almost

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every year. As a result, the knowledge of the properties of these materials and their clinical performance, benefits and limitations has expanded rapidly as revealed by the publication rate in this field illustrated in Figure 19.1.

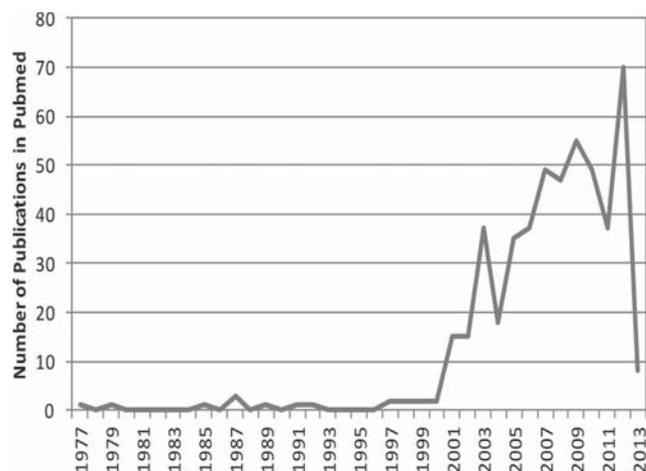


Figure 19.1 Publication rate (yearly) in the field of Si-Hy materials as retrieved from the National Library of Medicine search engine (www.pubmed.com) by January 2013.

19.2 Synthesis and Development of Materials

19.2.1 Polymer Structure

A CL polymer is a complex structure that consists of high molecular weight entities crosslinked in a three-dimensional amorphous network. If we can imagine polymer molecules as pieces of string loosely entangled, their interaction and entanglement governs the polymer's physical properties. The first step in the manufacture of CLs is the polymerization of the material. Polymerization is the process by which monomers are combined in the presence of crosslinkers and initiators in order to create a stable structure. In Si-Hy materials the main chain contains siloxane derivatives such as Polydimethylsiloxane (PDMS); 3-methacryloxy-2-hydroxypropyloxy propylbis(trimethylsiloxy)methylsilane (TRIS); tris-(trimethylsiloxy)silyl propylvinyl carbamate (TPVC); poly(dimethylsiloxy) di(silylbutanol) bis(vinyl carbamate) (PBVC). These and other materials also found in conventional hydrophilic contact lens materials such as *N,N*-dimethyl acrylamide (DMA); glycerol methacrylate (GMA); 2-hydroxyethyl methacrylate (HEMA); methacrylic acid (MA); methyl methacrylate (MMA); *N*-carboxyvinyl ester (NCVE); PC: phosphorylcholine or *N*-vinyl pyrrolidone (VP) are present in modern contact lens materials (Figure 19.2). However, contrary

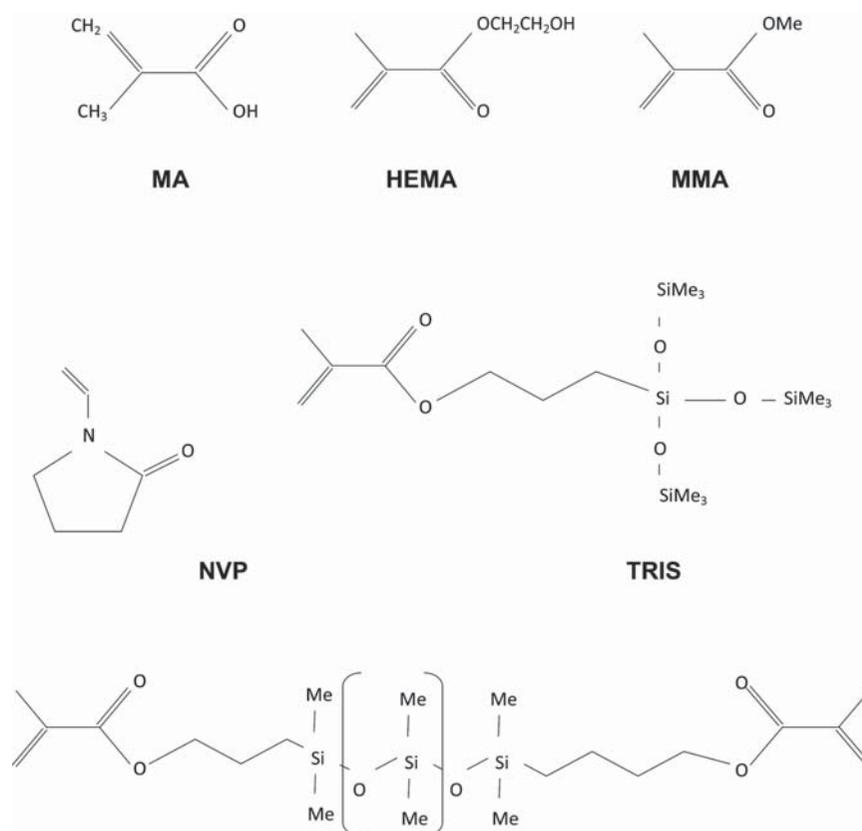


Figure 19.2 Different monomers used in current contact lens production. Me: methane or CH_3 ; MA: methacrylic acid; HEMA: 2-hydroxyethyl methacrylate; MMA: methyl methacrylate; VP: *N*-vinyl pyrrolidone; TRIS: 3-methacryloxy-2-hydroxypropyloxy propylbis(trimethylsiloxy)methylsilane; and PDMS: Polydimethylsiloxane used as the main chain for some Si-Hy CL materials.

to other hydrophilic materials, most of the details from the structure of these materials remain unknown [6]. Resulting CL polymers are named according to the criteria of the United States Adopted Names Council (USAN). A CL generic name has a unique prefix attached to a common suffix, “filcon” for hydrophilic materials and “focon” for hydrophobic materials. Despite the properties of silicone, Si-Hy materials are classified by USAN as hydrophilic materials.

Although proprietary manufacturing technologies are available, most current CLs are produced by cast molding and less frequently by lathe cutting. For lathe cutting, the material is first polymerized as solid rods to be cut into buttons for further processing in numerical computerized lathes to produce the lenses. In cast molding the polymerization also occurs by injecting the monomer mixture between convex and concave molds that will define posterior and anterior surfaces of the finished lens. In spite of improvements through computer-assisted control, lathe-cut technology is the most expensive method and is now used only to manufacture a limited amount of custom made designs for hydrophilic CL.

19.2.2 Current Materials

The search for Si-Hy materials for CL was driven by the belief that a high oxygen supply to the cornea will prevent most of the adverse events associated with contact lens wear [7, 8]. Ideally, such materials will also allow a safe extended or continuous CL wear (uninterrupted use of lenses day and night for 7 to 30 days) [9].

Two Si-Hy CL materials were initially available, Lotrafilcon A (Ciba Vision, Duluth GA) and Balafilcon A (Bausch + Lomb, Rochester, NY). They were characterized by high oxygen permeability (over 100×10^{-11} (cm²/sec) [mL O₂(STP)/(mL x mmHg)]) by increasing the content of siloxane moieties in the polymeric structure. As a result the materials had a low water content (24 and 36%, respectively), were stiffer (>0.8 MegaPascal) compared to previous hydrophilic materials based on poly-HEMA, and presented hydrophobic surfaces that required plasma surface treatments. Some mechanical interactions and comfort issues motivated a change in the direction for synthesis of the following Si-Hy materials. Nowadays, over 12 different Si-Hy materials are available in the marketplace. The main known characteristics of these materials are listed in Table 19.1. The relationship between water content and oxygen permeability of these materials represents quite well the changes in criteria used to produce such materials for the last 13 years. From a first inverse relationship between Dk and water content, the newer materials provide Dk values in the high range of the scale while keeping medium-high water content (>45%).

19.3 Surface Properties

Some of the most relevant characteristics for a material intended to be used as a CL are those related to the surface

wetability, electrostatic charge, surface topography, bulk equilibrium water content, oxygen permeability, properties related to the mechanical behavior, elastic modulus, and hydraulic and ionic permeability. A combination of these and other properties will dictate the biocompatibility of the CL with the surrounding tissues at the ocular surface [13].

19.3.1 Topography and Roughness

Surface roughness of devices contacting living systems will influence their biological reactivity. The relationship between surfaces is especially critical in CL applications as the polymer should interfere as least as possible with the epithelial surface of the cornea and with the lid conjunctiva. A smooth surface is essential to promote biocompatibility between CL and the ocular surface.

López-Alemaný *et al.* [15] observed substantial differences between Si-Hy lenses and conventional Hy lenses. The main difference is due to the plasma treatment to make the Si-Hy lenses wettable by tears. In this sense the Purevision lenses are treated by plasma oxidation, by deposition of a thin silicate (SiOx) surface on the lens [16]. Air Optix Night&Day lenses are treated by plasma polymerization process with a mixture of trimethylsilane, dry air and methane, which deposits a thin film of crosslinked hydrocarbon containing hydrophilic radicals on the surface [17]. In contrast to the early Si-Hy lens, most of the newest Si-Hy and conventional hydrogel lenses do not need surface treatment to improve wettability and are uniformly smooth with minor blister-like marks on the surface compared to Si-Hy where wrinkled morphology and rough surface were observed. As shown in Figure 19.3, this might not be the case with modern Si-Hy materials.

González-Meijome *et al.* [18, 19] evaluated several Si-Hy CLs using AFM microscopy by scanning areas ranging from 0.25 to 400 μm² in Tapping™ Mode. Mean roughness (*Ra*), root-mean-square roughness (*Rms*) and maximum roughness (*Rmax*) in nanometers (nm) were obtained. The higher roughness of balafilcon A was attributed to the plasma oxidation treatment used to improve wettability. Conversely, non-surface treated CL displayed a smoother surface. These observations could have implications in clinical aspects of Si-Hy CL wear such as lens degradation, resistance to bacterial adhesion or mechanical interaction with the ocular surface. Figure 19.3 illustrates the surface of five Si-Hy CLs observed with atomic force microscopy (AFM).

While the meaning of surface roughness on lens performance is not fully understood, Bruinsma *et al.* [20] demonstrated that surface roughness was one of the major determinants of *Pseudomonas aeruginosa* adhesion to etafilcon A [P(HEMA/MAA)] SCLs. Also, Baguet *et al.* [21] used AFM to monitor deposit formation on SCL surfaces and showed that as the deposits on the lens surface increased, the surface roughness also increased. More recently, González-Meijome *et al.* showed that deposits themselves may seriously impact the surface topography of Si-Hy contact lenses [22].

Table 19.1 Properties of the six Si-Hy materials currently available.

Brand	Air Optix Night & Day	Purevision	Acuvue Advance	Air Optix B	Acuvue OASYS	Biofinity	Avaira	PremiO	Acuvue TrueEye	Definitive	Clariti 1 Day	Dailies Total 1	Sil-O-Wet
Material (USAN)	lotrafilcon A	balafilcon A	galyfilcon A	lotrafilcon B	senofilcon A	comfilcon A	enfilcon A	asmoofilcon A	narafilcon A	efofilcon A	filcon II 3	delefilcon A	lucifilcon A
Year	1999	1999	2003	2004	2005	2006	2009	2007	2009	2008	2011	2012	2013
Manufacturer	Alcon Vision Care	Bausch & Lomb	J&J Vision Care	Alcon Vision Care	J&J Vision Care	Cooper-vision	Cooper-vision	Menicon	J&J Vision Care	Contamac	Sauflon	Alcon Vision Care	Paragon Vision Science
Dk	140	99	60	110	103	128	100	129	100	60	60	140	60
Central Thickness @-3.00 D (mm)	0.08	0.09	0.07	0.08	0.07	0.08	0.08	0.08	0.085	0.08	0.07	0.07	0.08
Dk/t (barrier/cm)	175	110	86	138	147	160	125	161	125	75	86	156	50
EWC (%)	24	36	47	33	38	48	46	40	46	74	58	32	65
Ionic (FDA group)	No (I)	Yes (III)	No(I)	No(I)	No(I)	No(I)	No(I)	No(I)	No(I)	No(II)	No(II)	No(I)	No(II)
Surface treatment	Plasma polymerization	Plasma oxydation	No	Plasma polymerization	No	No	No	Plasma oxydation	No	No	No disclosed	No	No
Elastic modulus (MPa)	1.4	1.1	0.43	1.2	0.72	0.8	0.5	0.91	0.66	0.35	0.5	0.7	-
Friction coefficient	0.394	0.443	0.028	0.361	0.024	0.057	0.018	0.207	-	-	0.014	-	-
Contact Angle(°)	80	95	65	78	68	-	-	-	-	-	-	-	-

Sources: manufacturer information; - Ross G *et al.*[10]; Tighe B.[11]; Roba *et al.* [12]; Jacob J. [13]; Karlgard *et al.*[6]; Tighe B.[14]
 FDA: Food & Drug Administration; USAN: United States Adopted Names Council; EWC: equilibrium water content; Dk: oxygen permeability in barrers 10^{-11} (cm²/sec)/[mL O₂(STP)/(mL x mmHg)];
 Dk/t= barrer/cm; Pa; pascal; MPa: megapascal; 1Pa = 1 N/m²; 1 kPa = 10³ N/m²; 1 MPa = 10⁶ N/m²; 100 N/cm² = 145 psi

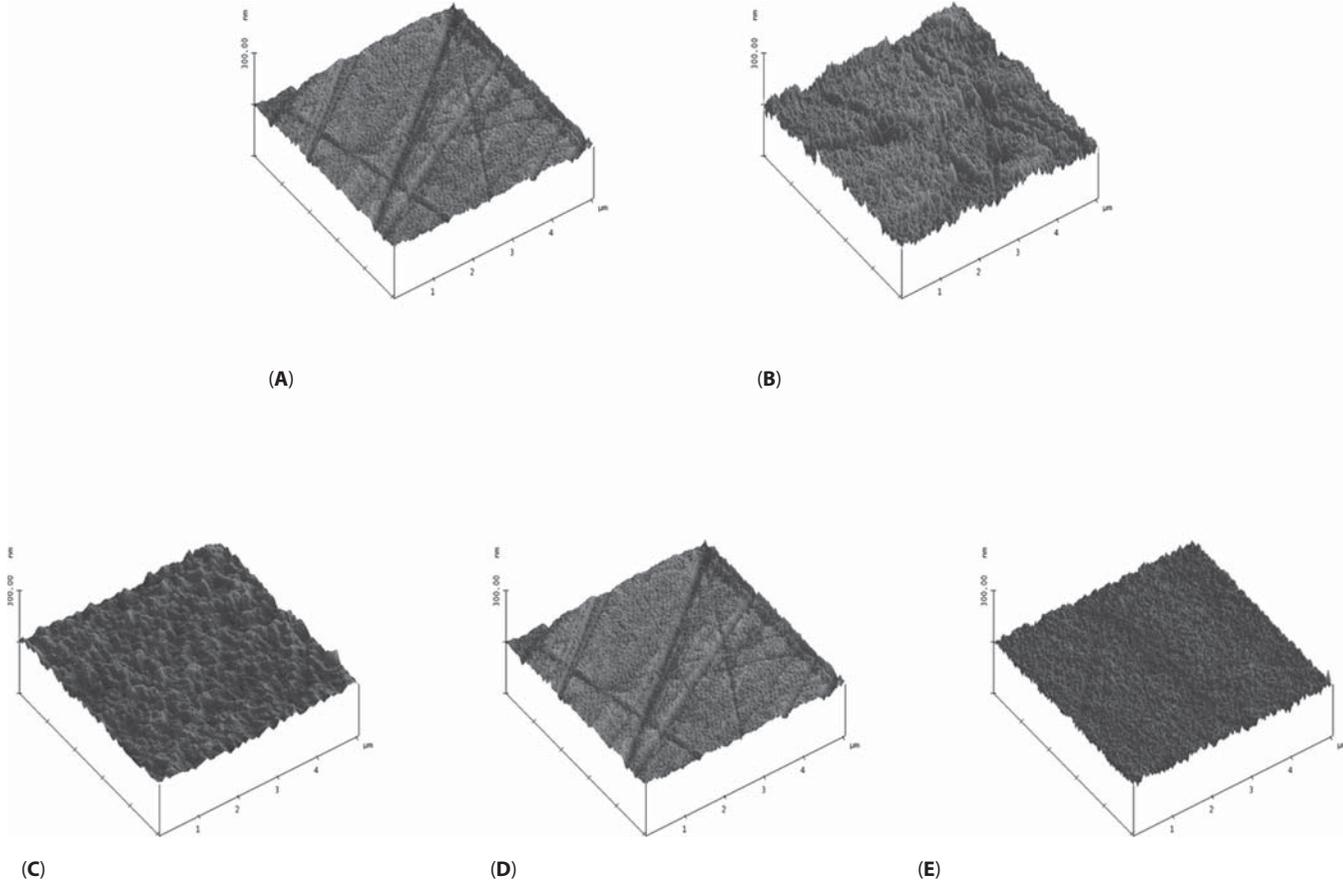


Figure 19.3 Surface appearance of five Si-Hy materials: lotrafilcon A (A), balafilcon A (B), galyfilcon A (C), lotrafilcon B (D) and senofilcon A (E) with atomic force microscopy (AFM) in tapping mode.

19.3.2 Friction

Friction is clinically relevant as it is believed to affect the interaction between the CL and the surrounding tissues—cornea, bulbar and tarsal conjunctiva—potentially influencing wearing comfort. As the lens dehydrates during the day or weeks of lens wear, because of exposure to dry environments and/or deposit formation, friction might increase and could be responsible for end-of-day discomfort, and palpebral reaction in the form of papillary conjunctivitis [16] or lid-wiper epitheliopathy [23]. Coefficient of friction, a measure of the lubricant properties, represents the amount of friction created at the lens surface from a load roughly equal to eyelid forces and oscillated at frequencies to mimic the normal blink. Values are then adjusted for hydrogel materials deformation and the fluid interface when measuring a wet lens [24].

Regarding Si-Hy, while first generation Si-Hy materials present higher values of friction coefficient compared to most HEMA-based lenses and modern Si-Hy materials [12], new materials are able to mimic the friction rates of conventional HEMA-based hydrophilic materials. It is assumed

that surface friction could be related with surface wettability, another relevant surface property for CL materials.

19.3.3 Wettability

Surface wettability is one of the main parameters defining CL interaction with the ocular surface [25] as it is believed to relate to comfort, ocular surface interaction and resistance to spoilage by tear deposits. The surfaces of first Si-Hy materials are naturally non-wettable by tears and because of the siloxane moieties migrating to the surface are hydrophobic, hence poorly tolerated. The oxygen-permeable components of these lens materials are the highly hydrophobic silicone, siloxysilane (TRIS) and perfluoro moieties. Therefore, the lenses were finished with surface treatments to obtain wettable surfaces by plasma oxidation in Balafilcon A [16] and plasma polymerization of a mixture of trimethylsilane, oxygen (air) and methane in Lotrafilcon A [17]. Materials that were developed after these do not need surface treatment to warrant wettability and this is currently the general trend for these materials (table 1). Achieving optimal wettability was a serious challenge with first plasma-treated Si-Hy CL.

Multiple strategies have emerged recently and in the past decades to create lens surfaces that are chemically similar to natural human tissue, a practice referred to as biomimesis. This is the case of so-called biomimetic materials used in several medical applications, including CLs. Such materials contain phosphatidilcholine (PC), a molecule found in the lipid layers of a cell membrane that gives the membrane a relatively neutral electrical charge, and the ability to bind water. It is said that CL polymers with phosphatidilcholine moieties, called “biocompatible,” minimize deposit formation and dehydration. Court *et al.* [26] applied this method to PDMS (Si-Hy) CL and significantly reduced the water contact angle (the lower the water contact angle on a surface, the higher is its wettability) and the protein uptake of the lens.

Understanding and improving wettability of contact lenses is still far from being achieved [25]. Its relationship with surface friction and resulting comfort of contact lenses might also be understood using appropriate testing procedures that mimic the challenging and highly dynamic ocular surface environment.

19.3.4 Surface Charge (Ionicity)

Depending on the monomers used, CL polymers and finished lenses can be ionic or non-ionic. An ionic hydrogel is defined as one containing more than 0.2% ionic constituents. The FDA created its Classification of Lens Groups for hydrogels based on EWC and electrostatic charge (ionicity) of the polymer, assuming that different hydrophilic lenses with similar water content and electrical charge would respond in a similar manner to the surrounding environment. Certain monomers used in the manufacture of CL almost invariably confer some degree of ionicity to the CL material, as is the case of methacrylic acid (MA). From the clinical perspective, this property is directly related to the level of protein (mainly lysozyme) adhesion, which is significantly higher in ionic materials as demonstrated by numerous studies, while lipid attraction was found to be independent of the ionicity of the material [27]. However, because most of the Si-Hy materials are non-ionic, their different properties made the FDA reconsider the classification of these materials into seven different groups which are presently under development [28].

19.4 Bulk Properties

19.4.1 Equilibrium Water Content and Water Activity

Several factors affect the *in vivo* equilibrium water content (EWC) of SCL including nominal EWC, lens thickness, pre-lens tear break-up time, ocular surface temperature, osmolarity, pH, relative environmental humidity, wearing

schedules, hydrogel material, blinking abnormalities, and cleaning regime [29]. The EWC of hydrogel CL also depends on the solution used to hydrate the material. For example, Refojo [30] has shown that EWC in distilled water is about 1.03 to 1.08 higher than in 0.9% saline solution, which is similar to the environment of the ocular surface

In hydrogels, the polymer network is filled with free water and bound water. Free water molecules are bound to each other and to hydrophilic radical in the polymer network. On the other hand, bound water molecules are more strongly attached to themselves and to the polymer network by both hydrogen and so-called hydrophobic bonds. Free water moves easily within and out of the polymer network, is easy to vaporize and is a good solvent for substances like some solutes in tears as sodium chloride, some medication in eye drops, etc. The solubility of compounds (i.e., ions, drugs, metabolites, etc.) in a hydrogel is a function of the content of “free water.” Conversely, “bound water” is strongly attached to the polymer network but in the right conditions can also be evaporated from the hydrogel but at a slower rate than the free water. A third type of water is described by some authors, called the “intermediate water” as it shows physicochemical properties somewhat between free and bound water because its molecular motion in the molecular space of the polymer shows behavior similar to that of bound water at lower temperatures and to that of free water with increasing temperature. This type of water is found loosely bound to hydrophobic groups or around the bound water molecules. Free and bound water are also known as freezing and non-freezing water [26].

The proportion of bound water ranged from 8.2 to 14.5% in soft lenses on the range from 32.7 to 60.2% EWC according to some authors. The same study concluded that although the material with NVP presented a slightly higher proportion of bound water, a correlation was not found between EWC and bound water except for those lenses where the main constituent was HEMA with no additional comonomers [31]. The proportions of bound and free water are believed to control the adsorption and desorption processes as lens dehydration, drug delivery, gas permeability in conventional hydrogels and hydraulic and ionic permeability. Adsorption of bound water and desorption of free water showed approximately an inverse relationship, especially for the glycerol methacrylate (GMA) group, which showed easy water uptake and slower water release. On the other hand, NVP shows a more difficult water uptake and easy release as shown by Yamada and Iwata, 1982 (referred by Kanome) [31].

Figure 19.4 presents examples of the dehydration process of three SCLs *in vitro*. Initial dehydration rate (DR) is similar for different materials, however, medium and high EWC lenses, maintain or even increase the DR for longer periods, while low EWC lens starts to decrease its DR faster.

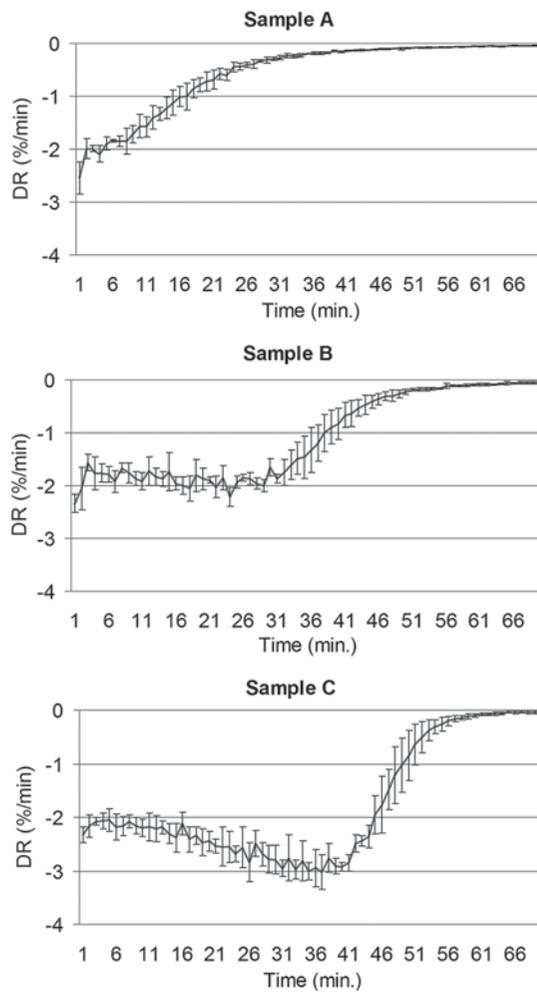


Figure 19.4 Dehydration curves representing dehydration rates (DR) during a period of 70 minutes for samples of three materials: sample A (low EWC), sample B (medium EWC) and sample C (high EWC).

19.4.2 Mechanical Properties

The mechanical properties of CL became particularly important after the marketing of the first Si-Hy contact lenses, as these materials induced changes to the ocular surface that were not commonly seen with less stiff HEMA-based materials. Most of these issues have been addressed by new Si-Hy materials while others need further investigation, such as the potential interaction of Si-Hy with the eyelids in the development of lid wiper epitheliopathy or meibomian gland dysfunction [32]. During the past 12 years, we learnt how critical mechanical properties are in the production of these materials.

Elastic modulus, or Young's modulus, represents the stress (force per unit of area) required to produce a unit of recoverable strain (elastic deformation) in a material. In other words, elastic modulus is a measure of how well a

material resists reversible deformation. It is defined by others as the force per unit area required to compress the material by a given amount [33]. Units are MPa (MegaPascal or 10^6 N/m²), and this material property has received increasing attention in the CL literature since the commercial use of Si-Hy materials [34].

Along with the relatively hydrophobic nature of Si-Hy materials, the tear film behind the lens is likely to be absent and the friction increases on the lens can bind over the ocular surface. First generation Si-Hy were found to induce mechanical changes in both cornea and conjunctiva, resulting in conjunctival indentation [35], trace central corneal flattening [36], and superior epithelial arcuate lesions [37]. Epithelial indentation was observed after removal of these high-Dk/t materials, and is presumably related to the increased incidence of spherical post-lens debris, which has been termed "mucin balls" or "lipid plugs" [38, 39]. The appearance of spherical debris behind the lens is probably linked to a higher modulus of Si-Hy CLs [16, 32]. Nowadays, Si-Hy materials present lower modulus while keeping high oxygen performance at the highest rates of the first Si-Hy lenses.

19.4.3 Oxygen Permeability and Transmissibility

Oxygen flux through CLs has been one of the most important parameters investigated in CL research for decades. This was indeed the main force driving Si-Hy production from the late 70s to the late 90s of the past century when they were finally introduced to the marketplace. According to the definition of Fatt [40], oxygen permeability is the ability of oxygen molecules to move within a polymeric material. This property defined as "Dk" is specific for each material and can be obtained by multiplying the coefficient of diffusion "D" that is related to the circulation of oxygen molecules through the CL, and coefficient of solubility "k" that describes how many oxygen molecules are dissolved per unit of CL volume. per unit of CL volume. per unit of CL volume. Due to the complexity of terms involved, units of oxygen permeability are better known as barrer= 10^{-11} cm²/sec)[mL O₂(STP)/(mL x mmHg)] or Fatt units.

Due to the potential impact of contact lenses on corneal physiology, oxygen diffusion through the cornea has been studied during the past 40 years and several models have been developed [41–45]. Three methods are most commonly used to measure oxygen transmissibility of contact lenses of given thickness "t" (Dk/t) of CLs: polarographic, coulometric and gas-to-gas techniques, each one having advantages and disadvantages [46–48]. The polarographic method was modified and used recently by Wichterlova *et al.* [49].

Oxygen transport is different in different CL materials. In conventional hydrogels whether they have low or high water content, oxygen delivery to the ocular surface takes place mainly through the water phase, so the higher the water content, the higher the permeability.

Thus, in these hydrogels EWC and Dk are directly and positively correlated [50, 51]. Conversely, in the Si-Hy materials, oxygen permeation occurs mainly through the silicone-siloxysilane portions of the solid phase in the hydrogel. the contribution of the aqueous phase to gas permeation is very low for the first Si-Hy materials Compañ *et al.* [52] found a slightly higher Dk value for the hydrated Si-Hy materials than for their xerogel (dry state).

The oxygen transmissibility of a CL to satisfy the physiological needs of the cornea was first provided by the Holden-Mertz criteria [53], which established minimum Dk/t of 24 barrer/cm to prevent corneal edema with hydrogel CL daily wear, and 87 to limit corneal edema under overnight CL wear to a level equal to the edema that occurs after overnight sleeping without CLs. More recently this criteria was revised and corrected by Harvitt and Bonanno [54], so that the Dk/t target to limit overnight corneal edema to the normal physiological levels should be modified to values higher than 35 and to 125 Dk/t units for open and closed eyes, respectively. Such numbers are so high that they approach the normal conditions of corneal edema and limbal redness without CL on the eye [55–57].

The biological apparent oxygen transmissibility (BOAT) concept arises from the need to reduce the scale of oxygen flux to the anterior corneal surface to the maximum of 7.5 mlO₂(STP)/cm²/hr, currently accepted as the maximum corneal oxygen consumption in the absence of any physiological barrier at sea level. The BOAT has been described by Fatt as the oxygen transmissibility measured for a sample modified by the biological properties of the cornea, which multiplied by the oxygen tension in air, gives the oxygen flux into the cornea. The BOAT is expressed in the same units as the Dk/t, but their values depart from each other as the transmissibility of the material increases [40, 58]. Figure 19.5

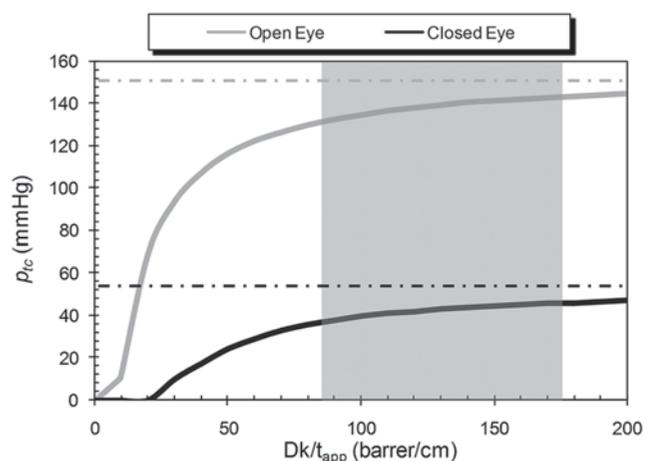


Figure 19.5 Partial pressure of oxygen under CLs (p_{1c}) of different Dk/t under open (light line) and closed eye conditions (dark line). Modified from [58]; shaded area corresponds to the range of Dk/t values for Si-Hy materials.

illustrates the relationship between the CL oxygen transmissibility (Dk/t) and the oxygen available at the corneal surface (p_{1c}) for open eyelids (upper curve) and close eyelids (lower curve).

Brennan [59] reported that values of Dk/t of 15 and 50 barrer/cm will be enough for the cornea to satisfy 96% of its normal oxygen consumption under daily wear and overnight wear conditions respectively. The findings of Compañ *et al.* [58] showed that CLs with oxygen transmissibility higher than 100 barrer/cm provide the lens-cornea interface with enough oxygen tension to substantially reduce additional oxygen flux onto the cornea. According to their results, in lenses with Dk/t > 70 barrer/cm, partial pressure of oxygen only reflects modest increase despite significant increase in Dk/t.

19.4.4 Hydraulic and Ionic Permeability

Ionic and hydraulic permeability are described together as ion transport can only happen dissolved in water. Nowadays, it is accepted by the scientific community that ion permeability in Si-Hy is essential to warrant lens movement on the eye, which is an important requirement for CL compatibility with the ocular surface. Some researchers agree that a certain level of ion permeability is necessary to avoid Si-Hy lens binding, but above that level, further permeability does not warrant an increase on the lens movement. However, although ion permeability and Si-Hy lens movement seem to be somewhat related, there is no scientific evidence to justify this dependence. It is clear that a tear layer behind the lens is essential to facilitate lens movement, but lens thickness seems to be less important [60]. In conventional hydrogels, water permeability follows a similar behavior to that of oxygen permeability because of their similar molecular size. Also, ions such as sodium and chloride diffuse through the aqueous phase of hydrogels, following a similar relationship. According to Tighe, the minimum EWC to warrant ion and water permeability in a CL is 20% [61]. The diffusion of small ions as sodium and chloride increases as the EWC of the hydrogel increases. Therefore, the diffusion of these ions in a 20% EWC hydrogel would be substantially smaller than that of 50% EWC hydrogels. In the pioneer Si-Hy launched to the marketplace between 1999 and 2003 the higher the Dk, the lower is the EWC, so one would think that the lower EWC in these materials the lower would be their water and ion permeability.

Recent research conducted by Weinmuller *et al.* [62] reported that water vapor diffusion coefficient (D) increases significantly with water concentration for polymacon (38% EWC) and hilafilcon A (70% EWC) (from approximately $0.3 \cdot 10^{-8}$ to $4.0 \cdot 10^{-8}$ cm²/s) because of augmented free volume related to higher EWC, whereas a more complex composition dependence was observed for alphafilcon A (66% EWC) and balafilcon A (36% EWC) probably as a consequence of a combined effect of polymer relaxation, plasticization, and water clustering. Balafilcon A shows the highest diffusivities at given water weight fraction ($3.5 \cdot 10^{-8}$ to $8.0 \cdot 10^{-8}$ cm²/s). This effect has been attributed by the authors to the great

water-vapor diffusion coefficient of PDMS in the SiHy lenses. This agrees with the results reported by Tighe [16] for the two first available Si-Hy materials. This author quoted a value of ionic permeability for lotrafilcon A and balafilcon A as being twice the ionic permeability of PHEMA (polymacon). The higher hydraulic permeability of these materials could be related with some degree of separation of hydrophobic and hydrophilic portions of the polymer network.

Different strategies have been considered to increase CL hydraulic permeability. Fenestration was the commonest assayed with PMMA impermeable hard lenses in the seventies [63]. The same approach was also followed with a new thick SCL for keratoconus with two fenestrations or pressure balancing holes (PBH) of which the primary goal was to avoid negative pressure, while the contribution of these features to the tear mixing under the CL is unknown. More recently, Miller *et al.* [64] performed 40 fenestrations 100 micron symbol in diameter in Si-Hy CLs, obtaining a significant improvement in tear mixing under the CLs.

19.5 Biological Interactions

The interaction of CL with the ocular surface is complex, involving immune and bacteriological interaction, mechanical interaction, metabolic stress and chemical interactions by the components of cleaning and disinfecting care solutions. Because different CL polymers are different in their chemical composition and physical properties, they may react differently to changes in pH, osmolality, temperature and the components of the various lens care products. The interaction of CL with the tear film forming deposits is also one of the main problems to be solved in current CL practice. Moreover, inter-individual variations in ocular surface shape and biological or metabolic needs would certainly account for different reactions to the same lens materials. Indeed, beyond the already mentioned mechanical interaction, Si-Hy materials have been demonstrated to behave quite differently from conventional p-HEMA-based hydrogels regarding uptake and release of care solutions biocides, adsorption of protein and lipids to their surfaces.

19.5.1 Microbial Contamination

CLs affect the balance in the biological environment of the ocular surface, disturbing the normal relationship between the ocular surface and the lids, introducing microorganisms that are not normally present, decreasing the oxygen availability and increasing the retention of metabolic debris and increasing tear evaporation rates. Sources of microbial contamination include poor hygiene during lens handling as well as contamination of the lens cases and care solutions [65]. Moreover, the presence of the CL affects the concentration and activity of immunological components of the ocular surface [66]. Also, CL surfaces can increase the chance

of bacteria attachment to the material, remaining for longer periods in contact with the ocular surface and increasing the chance of infection. The most threatening condition during CL wear is microbial keratitis (MK).

Several prospective epidemiological studies have been conducted since 2000 and have evaluated Si-Hy CL. These include the Australian national study [67, 68], a hospital-based study in Manchester [69] or a cohort study in the United States [70] investigating Si-Hy lenses used on an extended-wear basis.

The severity of disease ranges widely in contact-lens-related microbial keratitis, from the mildest disease lasting only a few days, associated with low costs and no reduction in vision in the affected eye, to large central scars reducing vision considerably with disease duration of some months and high costs [67]. Although the absolute risk of disease did not appear to be reduced with Si-Hy materials, it was hypothesized that without hypoxic stress, the cornea may be less vulnerable and the disease less severe. It has been suggested that corneal infiltrative events seen in a hospital clinic associated with Si-Hy materials tend to comprise a high proportion of mild disease [71]. Si-Hy contact lenses are particularly affected by non-severe forms of corneal complications [69, 72, 73]. A review recently published by Szczotka-Flynn and Chalmers established that the incidence of corneal infiltrative conditions is similar under extended and daily wear regimes, being 2–6% for symptomatic events and 6–25% if asymptomatic events are considered. These values are slightly lower for daily wear of Si-Hy CL [74]. Some of these adverse events related to CL wear and their incidence are shown in Table 19.2.

Vision loss is a possible long-term consequence of corneal infection, and this complication has been quoted as a measure of morbidity in contact-lens-related microbial keratitis and is relevant in 11% to 14% of cases of presumed microbial keratitis [70]. The absolute risk of vision loss is 0.3 to 3.6 per 10,000 wearers and depends on the lens type under consideration. Moreover, vision loss has been found to be 11.4 times (95% confidence interval, 4.2–30.9) more likely with highly pathogenic organisms, including gram-negative bacteria, *Nocardia* species, *Acanthamoeba*, and fungi [67].

The benefits of the elimination of hypoxia has also been well established to the structure and function of the cornea from *in vivo* observations [55, 79] and through laboratory experiments showing reduced bacterial binding to epithelial cells [80]. However, it is not well established that the CL material itself affects MK severity and pathogenesis [81]. Some evidence suggests that Si-Hy might be linked to similar or higher rates of adverse events [82] though less severe [69]; we cannot presently consider that Si-Hy materials protect against the most severe forms of CL-related adverse events [82, 83]. Currently, different surface and bulk modifications attempt to offer microbiological protection to modern contact lenses. Several approaches are under development including the use of selenium to reduce bacterial adhesion to CL materials, which is already being tested in animal models [84]. Silver-impregnated

Table 19.2 Prevalence of different CL-related changes in the ocular surface as quoted in different studies.

Definition	Most Likely Etiologic Links	Incidence & Bibliographic Source
CL related papillary conjunctivitis (CLPC)	Mechanical Deposits	1.7 [75] to 47, 5 [76] 4.6 to 7.2% (Si-Hy CW)
Superior Epithelial Aruate Lesion (SEAL)	Mechanical	4.5% (Si-Hy CW) [77]
CL peripheral ulcer (CLPU)	Bacteria	15–25%(Si-Hy CW) [77] 5.4% (CW) [77]
CL acute red eye (CLARE)	Bacteria	1–13% [78]
Asymptomatic Infiltrative Keratitis (AIK)	Bacteria	1–3.8% (Si-Hy CW) [77]
Infiltrative Keratitis (IK)	Bacteria	5% (Si-Hy CW) [77]
Superficial/punctuate keratitis (SK)	Dessication/ Mechanical/Toxicity	(see reference [69])
Microbial Keratitis (MK)	Bacteria/Fungi	0.01% (Si-Hy CW) [77, 69]

Si-Hy: silicone hydrogel; CW: continuous wear

contact lenses also have a demonstrated efficacy against microbial contamination [85]. More recently, other substances such as melamine [86] and protamine [87] have also proved to be effective against bacteria attachment to Si-Hy materials [88].

19.5.2 Mechanical Interactions

First generation Si-Hy materials, had higher elastic modulus. As a result, the ocular surface, particularly the corneal and conjunctival epithelium, is under a stronger mechanical stress because of lens movement during repeated blinking. More severe epithelial lesions can also be present in the form of superior epithelial arcuate lesions [37, 89], or conjunctival indentations. Flattening of corneal curvature [36, 90] and epithelial indentation from post-lens debris [39] have also been linked to the higher modulus of these materials.

In general, the incidence of CL-related corneal erosion is greater with EW than with DW and greater with first-generation Si-Hy CLs than with conventional hydrogel lenses [91]. The underlying mechanism leading to CL-related corneal erosion has yet to be understood, but several hypotheses regarding lens characteristics and corneal physiology have been proposed to support a mechanical cause. Some lens characteristics have been reported to be the causative factors in corneal erosion. Specifically, a tight-fitting lens can result in lens adhesion, and when nudged loose on blinking or on lens removal, the lens can force the epithelium to be pulled away from the corneal surface [77]. The cause can be a combination of mechanical and physiologic events that result in the gradual weakening of adhesion complexes that causes the corneal epithelium alteration [92]. It has been suggested that matrix metalloproteinases (MMPs) may facilitate CL-induced erosion, especially after overnight CL wear [93]. Matrix metalloproteinase-9 (MMP-9) is the primary matrix-degrading enzyme produced by the basal epithelial cells and is known to be active against major components of the basement membrane, including the fibrils

that anchor the basement membrane to the stroma [94]. Thus, if present in uncontrolled amounts, these enzymes can have collagen-degrading effects and may increase the risk of epithelial erosion. It has been reported that a substantial upregulation of MMP-9 occurs before awakening compared with the open-eye state, which implies that the removal of a CL after overnight wear can cause mechanical harm to a cornea that is already susceptible to erosion [92]. However, recent research which investigated changes in tear film MMP-9 after 12 months of CW of Si-Hy CL found a marginal, but not statistically significant, higher MMP-9 concentration in the Si-Hy lens group than the non-lens wearing control group [95]. However, levels of tear MMP-9 were significantly associated ($p=0.042$) with the degree of myopia, suggesting a possible increased erosion risk for the more myopic patients, presumably related with the thicker lenses or tighter fitting in some visual correction strategies.

The mechanical interaction of CL on the ocular surface has also been suggested as a cause for the increase of Langerhans cells in the epithelium of guinea pigs, a sign of inflammatory response [96], as well as loss of keratocyte density in the corneal stroma [97, 98]. However, when pro-inflammatory markers have been studied in tears after 12 months of CW of Si-Hy CL, only a marginal increase, thought not statistically significant, has been found compared with the non-lens wearing control group [95, 98]. Finally, these authors found changes in the epidermal growth factor (EGF) tear concentration after CW of Si-Hy CL, suggesting a causative mechanical effect with a compensative increased epithelial cell growth being that this effect increased in most myopic wearers when compared with low myopias and non-wearing controls.

19.5.3 Interaction with Tears

Several characteristics of polymers affect their interaction with tear contaminants, particularly the electrostatic

charge, surface wettability and EWC. The electrostatic charge of the polymer surface and the EWC of the bulk depend on the monomers included, and this is essential to understand the formation of deposits of different biochemical nature in soft contact lens (SCL) polymers. In the case of the FDA group IV materials, the presence of methacrylic acid (MA) in most of them is the major factor contributing to the anionic nature of the lens surface [99]. The chemical configuration of other monomers as N-vinyl pyrrolidone (NVP) have also been associated with a higher incidence of lipid deposits in FDA group II CL [100]. Jones *et al.* [101] observed that once lens material is taken into account, protein deposits display a small inter- and intra-subject variation. Conversely, the same study showed that lipid deposits display a higher patient-related variability. Finally, the deposition of lipids and proteins on contact lenses is time dependent [102, 103].

19.5.3.1 Protein Deposits

Protein deposition on SCL is a material-dependent process [104]. The ionic nature of FDA group IV containing MA significantly adhere more proteins (particularly lysozyme) than copolymers of HEMA with NVP or acrylamide [105]. The most commonly accepted mechanism for lysozyme binding in group IV CL materials is the electrostatic affinity between the anionic material and the positively charged lysozyme at physiological pH [99]. Furthermore, the level of ionicity in the CL surface seems to be related with the amount of proteins deposited [27]. Surprisingly, the higher incidence of lysozyme deposits on ionic materials compared to Si-Hy materials was associated with a lower incidence of denaturation [106]. Despite lower deposits of protein in Si-Hy materials, the higher proportion of denatured entities could also add some support to the etiology of increased papillary reaction seen with Si-Hy, primarily associated with the higher modulus of first Si-Hy materials [77].

There are other types of proteins that adhered to the CL surface such as albumin or lactoferrin, whose mechanism of adhesion seems to be different from lysozyme. However, because of the large molecular weight of albumin compared to lysozyme, this protein only forms deposits on the lens surface without penetration into the lens matrix [108]. Quantities of proteins recovered from worn CL are on the order of <50 µg per lens for non-ionic materials to more than 500 µg per lens for ionic group IV materials [101, 109].

19.5.3.2 Lipid Deposits

Lipid deposits have received increased attention recently [110] because there are evidences that Si-Hy CL are more sensitive to build-up this kind of deposits [61, 106]. Larger inter-subject variability regarding lipid deposit formation [101] agrees with the clinical finding of large variability in the front surface wettability of worn CLs [111]. Group I materials demonstrated less inter-subject variability than group IV lenses regarding lipid deposition. The authors explained this finding

by the lower number of polar sites available to bind lipids in the group I lens material, which would produce a higher competition for lipid elements, thus not allowing inter-subject variations to be evident. However, in group IV material, with larger availability for lipid binding, the inter-subject differences will have a chance to become evident [104].

Previous *in vitro* studies have demonstrated that lotrafilcon B material has the lowest affinity for major tear lipids such as nonpolar (cholesterol) and polar (phosphatidylethanolamine) lipids compared to other silicone hydrogel materials [103] after 20 days of incubation in artificial tear formulation. Similar results were found by Subbaraman *et al.* for lysozyme adsorption in lenses incubated for 28 days, with Lotrafilcon A and B family of Si-Hy lenses showing the lowest amount of lysozyme deposition [102]. The amount of deposits collected from lotrafilcon B in the previous studies were in the range of <5 mg lipids/lens and <10 mg lysozyme/lens. Collection of cholesterol and lysozyme from lotrafilcon B lenses worn by volunteers during a one month period showed even lower values than those obtained *in vitro* [112]. According to the same authors, the amount of deposits can vary between materials cared with the same cleaning and disinfecting product.

Previous *in vitro* studies have confirmed the affinity of certain deposits for certain materials [102, 103]. Furthermore, an *in vivo* study has shown that despite significant interaction between lens material and care system, the main contributor to the amount of cholesterol and lysozyme deposited on silicone hydrogel materials is lens material [112]. This effect was particularly remarkable for lotrafilcon B that deposited between 0.1 to 0.5 mg of cholesterol irrespective of the care system used. Polar and non-polar lipids show differences in their pattern of adhesion to different Si-Hy CL materials [103, 113].

Clinical evaluation of surface wettability and front surface deposits was not significantly different between Si-Hy lenses worn continuously for 6 nights or 30 nights [114]. Maziarz *et al.* [115] found that the amount of cholesterol recovered from balafilcon A lenses worn overnight or under a daily wear schedule were similar. However, while lenses worn overnight presented values of cholesterol between 10 to 30 µg/lens, lenses worn on a daily wear schedule presented values that in the majority of patients were between 10 to 20 µg/lens. This study concluded that cholesterol was the lipid most frequently adhered to CLs of different types including Si-Hy and conventional hydrogel materials, while other authors obtained opposite results [106].

19.5.4 Interaction with CL Care Solutions

Despite initially being marketed for continuous wear up to 1 month (CW) or extended wear (EW) up to 15 days without removal, Si-Hy are most commonly prescribed and used on a daily wear (DW) basis where the lens is removed for disposal or cleaning every night. daily wear (DW) basis where the lens

is removed for disposal or cleaning every night [116]. The DW schedules introduce the need for an effective lens care product for cleaning and disinfection. The majority of lens care products prescribed for use with Si-Hy CL are multipurpose solutions [116]. Multipurpose disinfecting solutions (MPDS) require an antimicrobial active component or components such as polyquaraterium-1 (Polyquad), myristaminodopropyl dimethylamine (Aldox; Alcon Laboratories, Fort Worth, TX), and polyhexamethylene biguanide (PHMB; Bausch + Lomb, Rochester, NY). Different manufacturers have alternatively referred to PHMB as polyhexanide or DYMED [117]. In addition to the antimicrobial agents, the lens care products contain buffer systems, surfactants, and preservatives to provide an effective lens care solution, and all of these can have their own impact on the viability of the epithelial cells as shown in *in vitro* models [118]. It is well established that different materials interact differently with different biocides regarding their uptake and release process [119]. These kinetics modulate the interaction between biocides and other care systems' constituents with the ocular surface of contact lens wearers, but overall, they prolong the contact time and might be the origin of clinical allergic or toxic reactions to these products. The molecular size, electrostatic charge and hydrophilic or hydrophobic nature of the biocides seem to be determinant in the interaction with CL materials of different water content and surface charge [119].

Lens care product components have the potential to affect the physiological response and comfort of Si-Hy CLs. The most common clinical presentation of the chemical interaction between CL solutions and the ocular surface is the so-called solution-induced corneal staining (SICS) that has been observed with Si-Hy CL, particularly when PHMB-preserved care solutions are used (Figure 19.6). It has been observed that Si-Hy materials when used with care systems containing

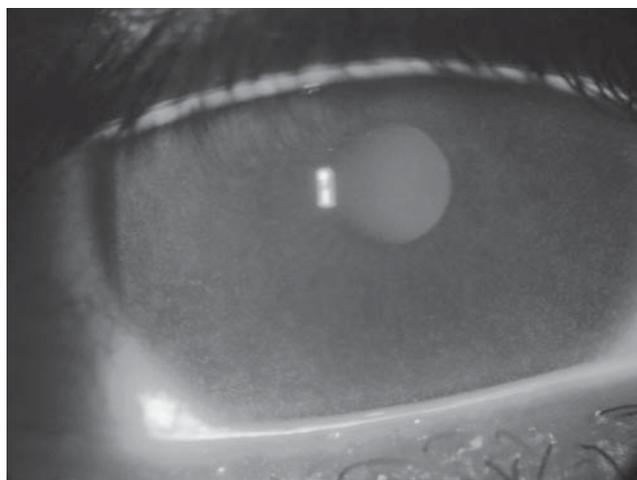


Figure 19.6 Diffuse punctate keratitis seen as bright green spots across the peripheral corneal surface during Si-Hy CL wear along with a preserved multipurpose solution.

PHMB as a preservative are associated to higher corneal toxicity than other products that do not use this molecule [120]. Similar results were found by Garofalo *et al.* [117] with Si-Hy and FDA group II hydrogel SCL, particularly within the first two hours of wear. Jones *et al.* [120] evaluated the physiological and subjective responses of subjects wearing a balafilcon A Si-Hy lens and compared the ocular response to use of a lens care product containing Polyquad/Aldox with one containing PHMB. The PHMB lens care product was associated with more corneal and conjunctival staining and more stinging or burning on lens insertion compared with the product containing Polyquad, which conversely showed less limbal hyperemia. Further research in this area has shown that certain lens/solution combinations are associated with the production of corneal staining, with a combination of balafilcon A lenses and a PHMB-containing solution usually having the highest levels [121, 122]. Recently Willcox *et al.* [123] have demonstrated that lens care products (Polyquad/Aldox or PHMB) can change corneal staining and comfort responses during wear of Si-Hy CL. These changes seem to be associated with the release of material soaked into lenses or changes to the lens surface composition. That study has demonstrated that lotrafilcon B and galyfilcon A Si-Hy CL caused corneal staining (solution-induced corneal staining) if soaked in the PHMB containing MPDS, but not when soaked in the Polyquad/Aldox containing multipurpose disinfecting solutions. However, other recent studies do not support the association between PHMB and superficial punctate keratitis [124]. The interactions between different components of different solutions containing the same biocide agent, the limitations of the current *in vitro* models and the lack of parallelism between *in vitro* and *in vivo* results regarding compatibility of solutions with CL materials, limit our present understanding of its mechanisms and how to prevent such interactions [125, 126]. This understanding is urgent considering that a number of studies have found a significant association between Si-Hy materials and inflammatory events [127]. Part of this association might be related with solution-induced reactions on the ocular surface [128, 129].

19.6 Load and Release of Products from Contact Lenses

The load and release of active agents (moisture agents or drugs) through CL attempts to increase the time of residency of the substance in the ocular surface compared with the application of ocular drops. The controlled release of drugs will provide a more effective way to increase the therapeutic activity of the substance for longer periods, while the use of moisture agents is expected to improve the ocular tolerance to CL itself. There is a lot of hope in this technology to solve the most common causes of CL dropout, dryness and discomfort [1, 130, 131]. Daily disposable contact lenses are the best option to implement these strategies, as the moisture agent can be loaded in the blister package and a new lens is

used every day. For planned replacement lenses, the use of active agents in the care solution might be an alternative way to achieve a release effect during the day after the lens being soaked overnight. However, it is still to be demonstrated if this strategy could improve the tolerance of a contact lens over the month of wear [132].

19.6.1 Release of Moisture Agents from Si-Hy Contact Lenses

Release of poly(vinyl alcohol) (PVA) from SCL is currently being used as a form to extend CL comfort though the day by continuous release [133]. Other agents such as PVP are used by Johnson & Johnson in their "Acuvue Moist" lenses or Acuvue Advance Plus. Hyaluronic acid has also been used as a moisture agent to be released from the material of the contact lens. An example of this is the Fusion™ technology by Safilens (Italy). More recently, Pitt *et al.* have showed that load and release of phospholipids from Si-Hy CLs might help to improve dryness symptoms in CL wearers by improving tear film stabilization [134]. The use of moisture additives to CL might also be the reason for lowering the friction coefficients measured by Roba *et al.* in Si-Hy lenses such as Acuvue Advance Plus (Galyfilcon A), Air Optix Night & Day Aqua (Lotrafilcon A) or Air Optix Aqua (Lotrafilcon B) compared to their "non-treated" counterparts [12].

19.6.2 Drug Release from Si-Hy Contact Lenses

The use of polymeric materials for the release of ocular drugs is not a new field [135] but is gaining increasing relevance with the possibility of changing the properties of the materials to optimize the treatment purposes (functionalization) [136], including contact lenses [137] and also in other areas of the biomedical sciences and bioengineering [138].

Several pharmacological agents have already been tested with Si-Hy materials, including hypotensors for glaucoma treatment [139], anti-inflammatory and anti-allergy drugs such as 0.1% dexamethasone phosphate [140] cromolyn sodium, ketotifen fumarate, ketorolac tromethamine and dexamethasone sodium phosphate [141], antibiotic drugs [142, 143] and tear secreting natural molecules [144].

It is expected that modifications of CL composition and using new approaches for drug load and controlled release of drugs will allow the production of really tunable devices for each application, dosage and treatment period. In this sense, Hiratani and Alvarez-Lorenzo [145] modulated the composition of the lenses to adapt the drug loading and release behavior for the treatment of specific pathological processes. Indeed, the ability of different CL polymers to load and release different substances presents great variability even for materials with similar equilibrium water content [140]. These authors showed how the percentage of dexamethasone released from two different Si-Hy materials could change from 44 to 65% of the total loaded, despite their similarity in equilibrium

water content (38% for senofilcon A and 36% for balafilcon A). The same study showed that the uptake of dexamethasone by alphafilcon A (a pHEMA base hydrogel) and lotrafilcon A (a first generation Si-Hy) could be similar (102 and 118 mg, respectively), but their percentage of delivery radically different (56% vs 11%, respectively). Loading kinetics expressed as the time to achieve maximum load can also be significantly different among materials. Further modification strategies such as molecular imprinting [146] and nanoparticle encapsulation [144] will be of much importance in the future of these applications [146, 147].

19.7 Conclusions

Surface properties are as important, if not more important, than bulk properties in materials intended for use in CL production. The wellbeing of the ocular surface in terms of its interaction with CLs depends in part on the lens surfaces, including facilitating removal of metabolic debris by tear exchange at the lens-cornea interface, but also in good part on the bulk properties of the CL material. Thus, a CL to be used at the ocular surface should: a) be permeable to oxygen and carbon dioxide to promote normal corneal metabolism; b) have appropriate mechanical properties so that the lens is stable, easy to handle and resistant to mechanical stress during blinking, handling or care, and to maintain its integrity to avoid compromising ocular integrity and comfort; c) resist abnormal dehydration so that the lens be comfortable and not compromise the integrity of the corneal and conjunctival epithelium; d) hydrogel and Si-Hy CLs should have water and ion permeability for good hydrodynamic behavior and to avoid lens binding to the cornea; e) have a highly hydrophilic surfaces for good tear wettability and comfort, and to diminish protein and lipid deposits; f) be able to maintain a stable tear film between blinks not only for comfort but also for good optical quality; g) be able to avoid bacterial attachment and deposit formation on lens surface; and h) will not accumulate components from care solutions that could be an irritant to the eye when reaching a certain concentration.

Silicone-hydrogel CLs have demonstrated to be able to overcome some of their early limitations, and currently a wide range of materials warrant a high oxygen permeability to the anterior corneal surface, while they also provide smooth surfaces to interact with the ocular tissues in a gentle way and are less stiff than their predecessors. The use of Si-Hy CL as vehicles for controlled drug delivery is gaining increasing interest [137, 147]. The use of moisture agents in the blister package of daily disposable contact lenses might be an additional strategy to improve the CL tolerance and avoid CL dropout. Aspects such as optimal load and loading time, as well as a fine control of delivery kinetics, are mandatory in order to warrant optimal therapeutic effect.

The production of a high volume of Si-Hy CLs at lower costs is not provided for Si-Hy daily disposable CL, which is an excellent option to reduce the incidence of deposits and

superficial punctate keratitis related with care systems. This modality is imperative for use of moisture agents in the blister package to be delivered through the day.

Disclosure

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References

1. K. Dumbleton, C.A. Woods, L.W. Jones, and D. Fonn, *Eye Contact Lens*, Vol. 39, p. 92, 2013.
2. P.B. Morgan, C.A. Woods, I.G. Tranoudis, M. Helland, N. Efron, C.N. Grupcheva, D. Jones, K.-O. Tan, A. Pesinova, O. Ravn, J. Santodomingo-Rubido, F. Malet, M. Vegh, N. Erdinest, H.I. Hreinsson, G. Montani, P. Chande, M. Itol, G. Montani, M. Itol, B.S. Chu, J. Bendoriene, E. van der Worp, S. Awasthi, W. Lam, J. M. Gonzalez-Méijome, S. Radu, V. Belousov, O. Johansson, M.S. Silih, J. Hsiao, and J.J. Nichols, *Contact Lens Spectrum*, Vol. 26, 2012.
3. C. Riley, G. Young, and R. Chalmers, *Eye Contact Lens*, Vol. 32, p. 281, 2006.
4. B.M. Aakre, A.E. Ystenaes, M.J. Doughty, O. Austrheim, B. Westerfell, and M.T. Lie, *Ophthalmic Physiol Opt.*, Vol. 24, p. 130, 2004.
5. M. Guillon, *Eye Contact Lens*, Vol. 39, p. 85, 2013.
6. C.C.S. Karlgard, D.K. Sarkar, L.W. Jones, C. Moresoli, and K.T. Leung, *Applied Surface Science*, Vol. 230, p. 106, 2004.
7. T.J. Liesegang, *CLAO J.*, Vol. 28, p. 12, 2002.
8. E.C. Poggio, R.J. Glynn, O.D. Schein, J.M. Seddon, M.J. Shannon, V.A. Scardino, and K.R. Kenyon, *N. Engl. J Med.*, Vol. 321, p. 779, 1989.
9. D.F. Sweeney, L. Keay, N. Carnt, and B.A. Holden, *Clin Exp. Optom*, Vol. 85, p. 161, 2002.
10. G. Ross, M. Nasso, V. Franklin, F. Lydon, and B. Tighe, Silicone hydrogels: Trends in products and properties, Presented at BCLA 29th Clinical Conference & Exhibition, Brighton, UK, 2005.
11. B. Tighe, Trends and developments in silicone hydrogel materials. www.siliconehydrogels.org, September, 2006.
12. M. Roba, E.G. Duncan, G.A. Hill, N.D. Spencer, and S.G.P. Tosatti, *Tribol. Lett.*, Vol. 44, p. 387, 2011.
13. J.T. Jacob, *Eye Contact Lens*, Vol. 39, p. 12, 2013.
14. B.J. Tighe, *Eye Contact Lens*, Vol. 39, p. 3, 2013.
15. A. López-Alemaný, V. Compañ, and M.F. Refojo, *J. Biomed. Mater. Res.*, Vol. 63, p. 319, 2002.
16. B. Tighe, "Silicone hydrogel materials – How do they work?," in: D.F. Sweeney, ed., *Silicone Hydrogels. The Rebirth of Continuous Wear Contact Lenses*, Oxford: Butterworth-Heinemann, 2000, p. 1.
17. C.M. Weikart, Y. Matsuzawa, L. Winterton, and H.K. Yasuda, *J. Biomed. Mater. Res.*, Vol. 54, p. 597, 2001.
18. J. Gonzalez-Meijome, A. Lopez-Alemaný, J. Almeida, and M. Parafita, *Invest. Ophthalmol. Vis. Sci.*, Vol. 46, p. 909, 2005.
19. J.M. Gonzalez-Meijome, A. Lopez-Alemaný, J.B. Almeida, M.A. Parafita, and M.F. Refojo, *J. Biomed. Mater. Res. B Appl. Biomater.*, Vol. 76, p. 412, 2006.
20. G.M. Bruinsma, M. Rustema-Abbing, J. de Vries, B. Stegenga, H.C. van der Mei, M. L. van der Linden, J.M. Hooymans, and H.J. Busscher, *Invest. Ophthalmol. Vis. Sci.*, Vol. 43, p. 3646, 2002.
21. J. Bagnuet, F. Sommer, V. Claudon-Eyl, and T.M. Duc, *Biomaterials*, Vol. 16, p. 3, 1995.
22. J.M. Gonzalez-Meijome, A. Lopez-Alemaný, J.B. Almeida, M.A. Parafita, and M.F. Refojo, *J. Biomed. Mater. Res. B Appl. Biomater.*, Vol. 76, p. 419, 2006.
23. D.R. Korb, J.V. Greiner, J.P. Herman, E. Hebert, V.M. Finnemore, J.M. Exford, T. Glonek, and M.C. Olson, *CLAO J.*, Vol. 28, p. 211, 2002.
24. R. Steffen and C. Schneider, *Optician*, Vol. 227, p. 23, 2004.
25. N. Keir and L. Jones, *Eye Contact Lens*, Vol. 39, p. 99, 2013.
26. J.L. Court, R.P. Redman, J.H. Wang, S.W. Leppard, V.J. Obyrne, S.A. Small, A.L. Lewis, S.A. Jones, and P.W. Stratford, *Biomaterials*, Vol. 22, p. 3261, 2001.
27. C. Maissa, V. Franklin, M. Guillon, and B. Tighe, *Optom. Vis. Sci.*, Vol. 75, p. 697, 1998.
28. J.C. Hutter, J.A. Green, and M.B. Eydelman, *Eye Contact Lens*, Vol. 38, p. 358, 2012.
29. J.J. Nichols, G.L. Mitchell, and G.W. Good, *Optom. Vis. Sci.*, Vol. 80, p. 447, 2003.
30. M.F. Refojo, *Contact Intraocular Lens Med. J.*, Vol. 1, p. 153, 1975.
31. S. Kanome, "Fundamental chemistry and physical properties of polymer material," in: Menicon Toyo Contact Lens Co. Ltd., ed., *Menicon Toyo's 30th Anniversary Compilation of Research Reports*, Nagoya, Japan, 1982, p. 109.
32. M.C. Lin and T.N. Yeh, *Eye Contact Lens*, Vol. 39, p. 114, 2013.
33. A. Franklin, *Optician*, Vol. 227, p. 27, 2004.
34. C.R. Horst, B. Brodland, L.W. Jones, and G.W. Brodland, *Optom. Vis. Sci.*, Vol. 89, p. 1468, 2012.
35. M. Covey, D.F. Sweeney, R. Terry, P.R. Sankaridurg, and B.A. Holden, *Optom. Vis. Sci.*, Vol. 78, p. 95, 2001.
36. K.A. Dumbleton, R.L. Chalmers, D.B. Richter, and D. Fonn, *Optom. Vis. Sci.*, Vol. 76, p. 845, 1999.
37. B.A. Holden, A. Stephenson, S. Stretton, P.R. Sankaridurg, N. O'Hare, I. Jalbert, and D.F. Sweeney, *Optom. Vis. Sci.*, Vol. 78, p. 9, 2001.
38. K. Dumbleton, L. Jones, R. Chalmers, D. Williams-Lyn, and D. Fonn, *CLAO J.*, Vol. 26, p. 186, 2000.
39. N. Pritchard, L. Jones, K. Dumbleton, and D. Fonn, *Optom. Vis. Sci.*, Vol. 77, p. 68, 2000.
40. I. Fatt, *CLAO J.*, Vol. 22, p. 25, 1996.
41. N.A. Brennan, *Clin. Exp. Optom.*, Vol. 88, p. 103, 2005.
42. N.A. Brennan, *Cornea*, Vol. 20, p. 104, 2001.
43. M. Chhabra, J.M. Prausnitz, and C.J. Radke, *Optom. Vis. Sci.*, Vol. 86, p. 454, 2009.
44. M. Chhabra, J.M. Prausnitz, and C.J. Radke, *J. Biomed. Mater. Res. B Appl. Biomater.*, Vol. 90, p. 202, 2009.

45. X. Larrea and P. Buchler, *Invest. Ophthalmol. Vis. Sci.*, Vol. 50, p. 1076, 2009.
46. W.J. Benjamin, "Oxygen transport through contact lenses," in: M. Ruben and M. Guillon, eds., *Contact Lens Practice*, London: Chapman & Hall, 1994, p. 43.
47. N.A. Brennan, N. Efron, B.A. Holden, and I. Fatt, *Ophthalmic Physiol. Opt.*, Vol. 7, p. 485, 1987.
48. C.F. Morgan, N.A. Brennan, and L. Alvord, *Optom. Vis. Sci.*, Vol. 78, p. 19, 2001.
49. J. Wichterlova, K. Wichterle, and J. Michalek, *Polymer*, Vol. 46, p. 9974, 2005.
50. N.A. Brennan, N. Efron, B.A. Weissman, and M.G. Harris, *CLAO J.*, Vol. 17, p. 169, 1991.
51. V. Compañ, J. Guzman, and E. Riande, *Biomaterials*, Vol. 19, p. 2139, 1998.
52. V. Compañ, A. Andrio, A. Lopez-Aleman, E. Riande, and M.F. Refojo, *Biomaterials*, Vol. 23, p. 2767, 2002.
53. B.A. Holden and G.W. Mertz, *Invest. Ophthalmol. Vis. Sci.*, Vol. 25, p. 1161, 1984.
54. D.M. Harvitt and J.A. Bonanno, *Optom. Vis. Sci.*, Vol. 76, p. 712, 1999.
55. E.B. Papas, C.M. Vajdic, R. Austen, and B.A. Holden, *Curr. Eye Res.*, Vol. 16, p. 942, 1997.
56. C. Maldonado-Codina, P.B. Morgan, C.M. Schneider, and N. Efron, *Optom. Vis. Sci.*, Vol. 81, p. 911, 2004.
57. D.F. Sweeney, *Eye Contact Lens*, Vol. 29, pp.S22-S25, 2003.
58. V. Compañ, A. Lopez-Aleman, E. Riande, and M.F. Refojo, *Biomaterials*, Vol. 25, p. 359, 2004.
59. N.A. Brennan, *Optom. Vis. Sci.*, Vol. 82, p. 467, 2005.
60. P.C. Nicolson and J. Vogt, *Biomaterials*, Vol. 22, p. 3273, 2001.
61. B. Tighe, "Silicone hydrogels: Structure, properties and behaviour," in: D.F. Sweeney, ed., *Silicone Hydrogels: Continuous-Wear Contact Lenses*, London: Butterworth-Heinemann, 2004, p. 1.
62. C. Weinmuller, C. Langel, F. Fornasiero, C.J. Radke, and J.M. Prausnitz, *J. Biomed. Mater. Res. A*, Vol. 77, p. 230, 2006.
63. A.G. Sabell, "The history of contact lenses," in: A.J. Phillips and L. Speedwell, eds., *Contact Lenses*, Oxford: Butterworth-Heinemann, 1997, p. 1.
64. K.L. Miller, K.A. Polse, and C.J. Radke, *Invest. Ophthalmol. Vis. Sci.*, Vol. 44, p. 60, 2003.
65. J.J. Durban, E.H. Villaverde, M. Monteoliva-Sanchez, and A. Ramos-Cormenzana, *Optom. Vis. Sci.*, Vol. 73, p. 529, 1996.
66. R.A. Sack, S. Sathe, and A. Beaton, *Eye Contact Lens*, Vol. 29, pp. S80-S82, 2003.
67. L. Keay, K. Edwards, T. Naduvilath, K. Forde, and F. Stapleton, *Invest. Ophthalmol. Vis. Sci.*, Vol. 47, p. 4302, 2006.
68. L. Keay, K. Edwards, T. Naduvilath, H.R. Taylor, G.R. Snibson, K. Forde, and F. Stapleton, *Ophthalmology*, Vol. 113, p. 109, 2006.
69. P.B. Morgan, N. Efron, E.A. Hill, M.K. Raynor, M.A. Whiting, and A.B. Tullo, *Br. J. Ophthalmol.*, Vol. 89, p. 430, 2005.
70. O.D. Schein, J.J. McNally, J. Katz, R.L. Chalmers, J.M. Tielsch, E. Alfonso, M. Bullimore, D. O'Day, and J. Shovlin, *Ophthalmology*, Vol. 112, p. 2172, 2005.
71. P.B. Morgan, N. Efron, N.A. Brennan, E.A. Hill, M.K. Raynor, and A.B. Tullo, *Invest Ophthalmol. Vis. Sci.*, Vol. 46, p. 3136, 2005.
72. L. Szczotka-Flynn, B.A. Benetz, J. Lass, M. Albright, B. Gillespie, J. Kuo, D. Fonn, A. Sethi, and A. Rimm, *Cornea*, Vol. 30, p. 535, 2011.
73. N. Efron, P.B. Morgan, E.A. Hill, M.K. Raynor, and A.B. Tullo, *Optom. Vis. Sci.*, Vol. 82, p. 519, 2005.
74. L. Szczotka-Flynn and R. Chalmers, *Eye Contact Lens*, Vol. 39, p. 47, 2013.
75. M.R. Allansmith, D.R. Korb, J.V. Greiner, A.S. Henriquez, M.A. Simon, and V.M. Finnemore, *Am. J. Ophthalmol.*, Vol. 83, p. 697, 1977.
76. A.L. Alemany and P. Redal, *Contactologia*, Vol. 13, p. 14, 1991.
77. K. Dumbleton, *Cont. Lens Anterior Eye*, Vol. 25, p. 137, 2002.
78. B.A. Holden, P.R. Sankaridurg, and I. Jalbert, "Adverse events and infections: Which ones and how many?," in: D.F. Sweeney, ed., *Silicone Hydrogels - The Rebirth of Continuous Wear Contact Lenses*, Oxford: Butterworth-Heinemann, 2000, p. 150.
79. L. Keay, D.F. Sweeney, I. Jalbert, C. Skotnitsky, and B.A. Holden, *Optom Vis. Sci.*, Vol. 77, p. 582, 2000.
80. H.D. Cavanagh, P. Ladage, K. Yamamoto, S.L. Li, W.M. Petroll, and J.V. Jester, *Eye Contact Lens*, Vol. 29, pp. S14-S16, 2003.
81. D.J. Evans and S.M. Fleiszig, *Eye Contact Lens*, Vol. 39, p. 72, 2013.
82. F. Stapleton, L. Keay, K. Edwards, T. Naduvilath, J. K. Dart, G. Brian, and B. A. Holden, *Ophthalmology*, 115, 1655, 2008.
83. F. Stapleton, L. Keay, K. Edwards, and B. Holden, *Eye Contact Lens*, Vol. 39, p. 78, 2013.
84. S.M. Mathews, J.E. Spallholz, M.J. Grimson, R.R. Dubielzig, T. Gray, and T.W. Reid, *Cornea*, Vol. 25, p. 806, 2006.
85. M.D.P. Willcox, E.B.H. Hume, A.K. Vijay, and R. Patcavich, *J. Optom.*, Vol. 3, p. 148, 2010.
86. D. Dutta, N. Cole, N. Kumar, and M.D. Willcox, *Invest. Ophthalmol. Vis. Sci.*, Vol. 54, p. 175, 2013.
87. A.K. Vijay, M. Bandara, H. Zhu, and M.D. Willcox, *Optom. Vis. Sci.*, Vol. 90, p. 119, 2013.
88. M.D. Willcox, *Eye Contact Lens*, Vol. 39, p. 60, 2013.
89. N. O'Hare, F. Stapleton, T. Naduvilath, I. Jalbert, D.F. Sweeney, and B.A. Holden, *Adv. Exp. Med. Biol.*, Vol. 506, p. 973, 2002.
90. J.M. Gonzalez-Meijome, J. Gonzalez-Perez, A. Cervino, E. Yebra-Pimentel, and M.A. Parafita, *Optom. Vis. Sci.*, Vol. 80, p. 440, 2003.
91. M.D. Willcox, T.J. Naduvilath, P.K. Vaddavalli, B.A. Holden, J. Ozkan, and H. Zhu, *Eye Contact Lens*, Vol. 36, p. 340, 2010.
92. M. Markoulli, E. Papas, N. Cole, and B. Holden, *Cont. Lens Anterior Eye*, Vol. 35, p. 2, 2012.
93. J.J. Reidy, M.P. Paulus, and S. Gona, *Cornea*, Vol. 19, p. 767, 2000.
94. K. Fukuda, Y. Fujitsu, N. Kumagai, and T. Nishida, *Invest. Ophthalmol. Vis. Sci.*, Vol. 47, p. 2857, 2006.
95. J. Gonzalez-Perez, C. Villa-Collar, J.M. Gonzalez-Meijome, N.G. Porta, and M.A. Parafita, *Invest. Ophthalmol. Vis. Sci.*, Vol. 53, p. 5301, 2012.
96. A. Zhivov, J. Stave, B. Vollmar, and R. Guthoff, *Cornea*, Vol. 26, p. 47, 2007.
97. N. Efron, I. Perez-Gomez, and P.B. Morgan, *Clin. Exp. Optom.*, Vol. 85, p. 156, 2002.
98. P. Kallinikos and N. Efron, *Invest. Ophthalmol. Vis. Sci.*, Vol. 45, p. 3011, 2004.
99. C.E. Soltys-Robitaille, D.M. Ammon, Jr., P.L. Valint, Jr., and G.L. Grobe, III, *Biomaterials*, Vol. 22, p. 3257, 2001.
100. A.R. Bontempo and J. Rapp, *CLAO J.*, Vol. 20, p. 242, 1994.
101. L. Jones, K. Evans, R. Sariri, V. Franklin, and B. Tighe, *CLAO J.*, Vol. 23, p. 122, 1997.

102. L.N. Subbaraman, M.A. Glasier, M. Senchyna, H. Sheardown, and L. Jones, *Curr. Eye Res.*, Vol. 31, p. 787, 2006.
103. F.P. Carney, W.L. Nash, and K.B. Sentell, *Invest. Ophthalmol. Vis. Sci.*, Vol. 49, p. 120, 2008.
104. A.R. Bontempo and J. Rapp, *CLAO J.*, Vol. 27, p. 75, 2001.
105. J.L. Bohnert, T.A. Horbett, B.D. Ratner, and F.H. Royce, *Invest. Ophthalmol. Vis. Sci.*, Vol. 29, p. 362, 1988.
106. L. Jones, M. Senchyna, M.A. Glasier, J. Schickler, I. Forbes, D. Louie, and C. May, *Eye Contact Lens*, Vol. 29, pp. S75-S79, 2003.
107. L. Michaud and C. Giasson, *Cont. Lens Anterior Eye*, Vol. 21, p. 104, 1998.
108. Q. Garrett, R.C. Chatelier, H.J. Griesser, and B.K. Milthorpe, *Biomaterials*, Vol. 19, p. 2175, 1998.
109. L. Jones, A. Mann, K. Evans, V. Franklin, and B. Tighe, *Optom. Vis. Sci.*, Vol. 77, p. 503, 2000.
110. J.J. Nichols, *Eye Contact Lens*, Vol. 39, p. 19, 2013.
111. L. Jones, V. Franklin, K. Evans, R. Sariri, and B. Tighe, *Optom. Vis. Sci.*, Vol. 73, p. 16, 1996.
112. Z. Zhao, N.A. Carnt, Y. Aliwarga, X. Wei, T. Naduvilath, Q. Garrett, J. Korth, and M.D. Willcox, *Optom. Vis. Sci.*, Vol. 86, p. 251, 2009.
113. M. Heynen, H. Lorentz, S. Srinivasan, and L. Jones, *Optom. Vis. Sci.*, Vol. 88, p. 1172, 2011.
114. J. Stern, R. Wong, T.J. Naduvilath, S. Stretton, B.A. Holden, and D.F. Sweeney, *Optom. Vis. Sci.*, Vol. 81, p. 398, 2004.
115. E.P. Maziarz, M.J. Stachowski, X.M. Liu, L. Mosack, A. Davis, C. Musante, and D. Heckathorn, *Eye Contact Lens*, Vol. 32, p. 300, 2006.
116. P.B. Morgan and N. Efron, *Cont. Lens Anterior Eye*, Vol. 29, p. 59, 2006.
117. R.J. Garofalo, N. Dassanayake, C. Carey, J. Stein, R. Stone, and R. David, *Eye Contact Lens*, Vol. 31, p. 166, 2005.
118. J. Santodomingo-Rubido, O. Mori, and S. Kawaminami, *Ophthalmic Physiol. Opt.*, Vol. 26, p. 476, 2006.
119. L. Jones and C.H. Powell, *Eye Contact Lens*, Vol. 39, p. 28, 2013.
120. L. Jones, N. MacDougall, and L.G. Sorbara, *Optom. Vis. Sci.*, Vol. 79, p. 753, 2002.
121. G. Andrasko and K. Ryen, *Optometry*, Vol. 79, p. 444, 2008.
122. N.A. Carnt, V.E. Evans, T.J. Naduvilath, M.D. Willcox, E.B. Papas, K.D. Frick, and B.A. Holden, *Arch. Ophthalmol.*, Vol. 127, p. 1616, 2009.
123. M.D. Willcox, B. Phillips, J. Ozkan, I. Jalbert, L. Meagher, T. Gengenbach, B. Holden, and E. Papas, *Optom. Vis. Sci.*, Vol. 87, p. 839, 2010.
124. J. Santodomingo-Rubido, *Ophthalmic Physiol. Opt.*, Vol. 27, p. 168, 2007.
125. M. Gorbet and C. Postnikoff, *Eye Contact Lens*, Vol. 39, p. 41, 2013.
126. D.M. Robertson, *Eye Contact Lens*, Vol. 39, p. 66, 2013.
127. N. Carnt and F. Stapleton, *Eye Contact Lens*, Vol. 39, p. 36, 2013.
128. N.A. Carnt, M.D.P. Willcox, V.E. Evans, T.J. Naduvilath, D. Tilia, E.B. Papas, D.F. Sweeney, and B.A. Holden, *Contact Lens Spectrum*, Vol. 22, p. 38, 2007.
129. N. Carnt, I. Jalbert, S. Stretton, T. Naduvilath, and E. Papas, *Optom. Vis. Sci.*, Vol. 84, p. 309, 2007.
130. L. Jones, N.A. Brennan, J. González-Méijome, J. Lally, C. Maldonado-Codina, T.A. Schmidt, L. Subbaraman, G. Young, J.J. Nichols, members of the TFOS International Workshop on Contact Lens Discomfort. *Invest Ophthalmol Vis Sci*. Vol. 54, TFOS37, 2013.
131. G. Young, J. Veys, N. Pritchard, and S. Coleman, *Ophthalmic Physiol. Opt.*, Vol. 22, p. 516, 2002.
132. J.M. Gonzalez-Meijome, A.C. da Silva, H. Neves, D. Lopes-Ferreira, A. Queiros, and J. Jorge, *Cont. Lens Anterior Eye*, 2012.
133. L.C. Winterton, J.M. Lally, K.B. Sentell, and L.L. Chapoy, *J. Biomed. Mater. Res. B Appl. Biomater.*, Vol. 80, p. 424, 2007.
134. W.G. Pitt, D.R. Jack, Y. Zhao, J.L. Nelson, and J.D. Pruitt, *Optom. Vis. Sci.*, Vol. 88, p. 502, 2011.
135. D. Gulsen and A. Chauhan, *Invest. Ophthalmol. Vis. Sci.*, Vol. 45, p. 2342, 2004.
136. B.G. Short, *Toxicol. Pathol.*, Vol. 36, p. 49, 2008.
137. K. Singh, A.B. Nair, A. Kumar, and R. Kumria, *Journal of Basic and Clinical Pharmacology*, Vol. 2, p. 87, 2011.
138. M.S. Fernandes, N.S. Dias, A.F. Silva, J.S. Nunes, S. Lanceros-Mendez, J.H. Correia, and P.M. Mendes, *Biosens. Bioelectron.*, Vol. 26, p. 80, 2010.
139. C.C. Peng, A. Ben-Shlomo, E.O. Mackay, C.E. Plummer, and A. Chauhan, *Curr. Eye Res.*, Vol. 37, p. 204, 2012.
140. A. Boone, A. Hui, and L. Jones, *Eye Contact Lens*, Vol. 35, p. 260, 2009.
141. C.C. Karlgard, N.S. Wong, L.W. Jones, and C. Moresoli, *Int. J. Pharm.*, Vol. 257, p. 141, 2003.
142. A. Hui, A. Boone, and L. Jones, *Eye Contact Lens*, Vol. 34, p. 266, 2008.
143. J.B. Ciolino, T.R. Hoare, N.G. Iwata, I. Behlau, C.H. Dohlman, R. Langer, and D.S. Kohane, *Invest. Ophthalmol. Vis. Sci.*, Vol. 50, p. 3346, 2009.
144. C.O. Dominguez-Godinez, A. Martin-Gil, G. Carracedo, A. Guzman-Arangué, J.M. González-Méijome, J. Pintor, *J. Optom*, 2013; Vol. 6, p. 205, 2013.
145. H. Hiratani and C. Alvarez-Lorenzo, *Biomaterials*, Vol. 25, p. 1105, 2004.
146. C.J. White, M.K. McBride, K.M. Pate, A. Tieppo, and M.E. Byrne, *Biomaterials*, Vol. 32, p. 5698, 2011.
147. A. Guzman-Arangué, B. Colligris, and J. Pintor, *J. Ocul. Pharmacol. Ther.*, , 2012.