1

Types of Lenses

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1.1 History of Contact Lenses

A history of contact lenses spanning over almost 500 years has been detailed (1, 2). It is based on historical works, scientific papers and journal articles and looks at both the modern disposable lens as well as the hard and soft lenses that came before. Some important events are collected in Table 1.1.

Table 1.1 History of contact lenses (2).

Year	Inventor	Issue
1508	Leonardo da Vinci	Corneal neutralization
1637	René Descartes	Fluid-filled tube
1685	Philippe de La Hire	Neutralization of cornea
1801	Thomas Young	Three color theory of perception
1827	George Biddell	Theory of astigmatism
1845	Sir John F. W. Herschel	Convex lenses
1846	Carl Zeiss	Optical instruments
1851	Johann Nepomuk Czermak	Water-filled goggle
1887	Adolf Eugen Fick	First successful contact lens
1961	Otto Wichterle	Soft contact lenses
1979	Kyoichi Tanaka	Silicone hydrogel materials

In 1508, Leonardo da Vinci first had the idea of placing a corrective lens directly onto the surface of the eye (3–5). In 1637, René Descartes proposed another idea in which a glass tube filled with liquid is placed in direct contact with the cornea.

In 1887, Adolf Eugen Fick, a German physiologist, created the first successful contact lens (6). Glass-blown scleral lenses remained the only form of contact lens until 1938, when poly(methyl methacrylate) (PMMA) was developed, and Mullen and Obring used the plastic to manufacture scleral lenses. Obring developed the Plexiglass series in New York in 1940 (4).

In 1961, the Czech chemist Otto Wichterle invented soft contact lenses (7, 8). In 1970, rigid gas-permeable contact lenses were developed, and widely accepted for the advantages of small diameter (about 9 *mm*) and gas permeability. Silicone hydrogel materials were developed in 1979 (9). In 1999, an important development was the launch of the first silicone hydrogels onto the market. These new materials showed an extremely high oxygen permeability with comfort performance (4).

The factors that influenced the development of special materials have been reported (10). Accounts of early attempts to improve vision by use of a lens contacting the eye are limited to a few isolated observations (11). Practical success was not realized until techniques for fabrication of lenses from glass were sufficiently developed (12). PMMA replaced glass in the late 1930s. This material is more durable, more readily fabricated and was claimed by some authors to show a better ocular compatibility (13). During the same broad period of time, there was also a change in emphasis from scleral to corneal contact lenses, which placed different demands on material design and development.

More is demanded from ophthalmic treatments using contact lenses, which are currently used by over 125 million people around the world (14). Improving the material of contact lenses is currently a rapidly evolving discipline (10).

A search has been performed of the titles of papers in the Scopus database to identify contact lens-related articles published this century (15). The ten most highly cited papers were determined from the total list of 4,164 papers found. Rank-order lists by count were assembled for the *top 25* in each of four categories: authors, institutions, countries and journals. A 20-year subject-specific contact lens h-index was derived for each author, institution, country and journal to serve as a measure of impact in the field. The top 10 constituents (of the top 25) of each category were ranked and tabulated (15).

1.2 Materials

Contact lens materials (10) are typically based on polymer- or silicone-hydrogel, with additional manufacturing technologies employed to produce the final lens. These processes are simply not enough to meet the increasing demands for contact lenses and the ever-increasing number of contact lens users (14).

An advanced perspective on contact lens materials has been presented, with an emphasis on materials science employed in developing new contact lenses (14, 16). The future trends for contact lens materials are to graft, incapsulate, or modify the classic contact lens material structure to provide new or improved functionality. Also, some of the fundamental material properties are discussed, and the outlook for related emerging biomaterials is presented.

Contact lens materials and lens types, treatment for contact lens and tear film complications, and myopia correction and contact lenses for abnormal ocular conditions have been detailed (17). Current topics in this field are miniscleral lenses, keratoconus, corneal crosslinking, and pediatric, cosmetic and prosthetic contact lenses. Furthermore, simulation programs for scleral lens fitting, sagittal values, soft toric mislocation, front vertex power, orthokeratology and rigid lens design are discussed.

1.3 Monomers

The monomers that can be used for contact lenses, which are described in the following sections and in both tables and references, are collected in Table 1.2.

These issues will be detailed in the following sections of this chapter.

1.3.1 Monomers for Block Copolymers

A block copolymer that contains both hydrophobic and hydrophilic blocks with amino acid groups has been described (18).

The principal monomers for such block copolymers are a combination of two monomers capable of forming a hydrogel; such monomers are collected in Table 1.3.

Table 1.2 Monomers for contact lenses.

Monomers and monomer types	Usage	References
2-Hydroxyethyl methyacrylate *N*-Vinyl-2-pyrrolidone Methyl methacrylate Isobornyl methacrylate *tert*-Butylcyclohexyl methacrylate	Soft lenses	(19)
Hydrophobic monomers	Strengthening agents	Table 1.8
Hydrophilic monomers		Table 1.8
Hydrophilic monomers	Hydrogels	Table 1.10
Azlactones	Surface treatment	Table 1.12
Acrylamide *N*-Hydroxyethyl acrylamide *N*-Isopropyl acrylamide 2-Acrylamido-2-methylpropanesulfonic acid 2-Hydroxyethyl methacrylate 2-Hydroxyethyl acrylate	Macromers	(20)
Acryl monomers	Water absorbable	Table 1.16
Poly(siloxane)	Water absorbable	Table 1.17
4-(Phenyldiazenyl) phenyl methacrylate	Blue-light blocking	(21)
Acrylates	UV-blocking	Table 1.22
Silicone hydrogel	Multifocal lenses	Table 1.23
Acrylates	Non-silicone hydrogel	Table 1.25
Crosslinking agents	Non-silicone hydrogel	Table Table 1.26
Oxyperm	Oxygen permeable	Table 1.32
Ionoperm	Oxygen permeable	Table 1.32

Table 1.3 Monomers (18).

Monomer	Monomer
2-Ethylphenoxy acrylate	2-Ethylphenoxy methacrylate
2-Ethylthiophenyl acrylate	2-Ethylthiophenyl methacrylate
2-Ethylaminophenyl acrylate	2-Ethylaminophenyl methacrylate
Phenyl acrylate	Phenyl methacrylate
Benzyl acrylate	Benzyl methacrylate
2-Phenylethyl acrylate	2-Phenylethyl methacrylate
3-Phenylpropyl acrylate	3-Phenylpropyl methacrylate
3-Propylphenoxy acrylate	3-Propylphenoxy methacrylate
4-Butylphenoxy acrylate	4-Butylphenoxy methacrylate
4-Phenylbutyl acrylate	4-Phenylbutyl methacrylate

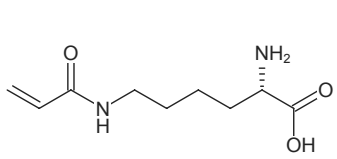
Side-chain-linked amino acids are collected in Table 1.4. Some of these compounds are shown in Figure 1.1.

Table 1.4 Side-chain-linked amino acids (18).

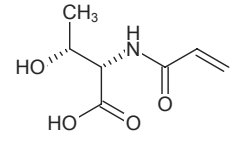
Monomer	Monomer
Acryloyl-*L*-lysine	Acryloyl-*L*-serine
Acryloyl-*L*-threonine	Acryloyl-*L*-tyrosine
Acryloyl-*L*-amino-phenylalanine	Acryloyl-*L*-cysteine
Acryloyl-*L*-oxy-proline	Nϵ-acryloyl-Nα-Oelityl-L-Lysine

The synthesis of a variety of such monomers has been detailed (18). For example, the synthesis of (*S*)-6-acrylamido-2-aminohexanoic acid monomers is performed via a copper complex (18):

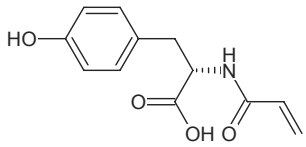
Preparation 1–1: L-lysine (14.62 *g*; 100 *mmol*) was dissolved in 150 *ml* deionized water and heated to about 80°C. Copper carbonate (16.6 *g*; 75 *mmol*) was added in portions over a period of 30 *min*. The reaction was stirred for an additional 30 *min*. The hot, deep-blue suspension was filtered through silica gel. The filter was washed with a small amount of water. On the following day, the lysine copper complex containing the combined filtrate was cooled in an ice bath, and 100 *ml* tetrahydrofuran was added. A solution of acryloyl chloride in methyl-*tert*-butylether (8.9 *ml*, 110 *mmol*) was added dropwise during a period of 1 *h*. The pH was initially maintained between 8 and 10 by parallel, dropwise addition of 10% sodium hydroxide solution. After half of the acryloyl chloride solution had been added, the product began to precipitate. When most of the acryloyl chloride had been added, addition of sodium hydroxide was



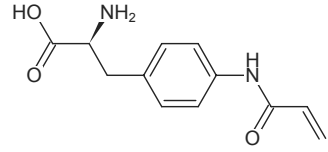
Acryloyl-*L*-lysine



Acryloyl-*L*-threonine



Acryloyl-*L*-tyrosine



Acryloyl-*L*-amino-phenylalanine

Figure 1.1 Monomers for side-chain-linked amino acids.

slowed down to allow the pH to drop to about 6 and the temperature of the reaction mixture was allowed to reach room temperature. The blue suspension was stirred for an additional 2 *h* and was then filtered. The solid material retained on the filter was washed with water and acetone and then dried. A yield of 6.5 *g* of acryloyl-*L*-lysine copper complex was obtained. Acryloyl-*L*-lysine copper complex (29.5 *g*) was suspended in 300 *ml* deionized water and cooled in an ice bath. H_2S gas was bubbled into the suspension until copper sulfide precipitation was complete; then 3 *g* of active charcoal was added to the suspension. The suspension was heated briefly to 100°C. After cooling to room temperature, 500 *ml* acetone was added to the suspension which was then filtered on silica gel. The clear filtrate was put in a rotary evaporator. After evaporation of the solvent, the solid product was recrystallized from 200 *ml* of 50% aqueous acetone. A yield of 17.76 *g* (69.76%) of white powder was obtained. The structure of the compound was verified by nuclear magnetic resonance spectroscopy and LC-MS spectroscopy.

The preparation of a block copolymer containing a hydrophilic cellophil polymer and a lipid-like copolymer was done by raft polymerization as follows (18):

Preparation 1–2: Step A

In a 50 *ml* round-bottom flask, a solution of 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid (6.13 *mg*, 0.017 *mmol*), *N*,*N*-Dimethyl acrylamide (0.624 *ml*, 6.05 *mmol*), and *iso*-decyl acrylate (0.163 *ml*, 0.673 *mmol*) in 10 *ml N*,*N*-dimethylformamide was degassed using ultrasonic treatment. Subsequently, 2-benzyl-2-(dimethylamino)-4′-morpholinobutyrophenone (6.40 *mg*, 0.017 *mmol*) was added, and polymerization was induced by UV light. After 4 *h* of polymerization under stirring, the reaction mixture was purified by extensive dialysis against deionized water using a membrane with a 3.5 *kDa* MWCO. The mixture was subsequently lyophilized. The average molecular weight (12 *kDa*) and PDI (1.19) of the block copolymer was verified by GPC measurement.

Step B

The lyophilized macro-CTA prepared in step A (300 *mg*, 6.82 *μmol*) was mixed with acryloyl-*L*-lysine (100 *mg*, 0.499 *mmol*) in 10 *ml* deionized water. The mixture was degassed using ultrasonic treatment. 2,2′-Azobis(2-methylpropionamidine) dihydrochloride (4.62 *mg*, 0.017 *mmol*) was added to the mixture. The polymerization was induced by heating the mixture in a reaction vessel to 50°C. After 4 *h* of polymerization at 50°C, the resulting block copolymer was purified by extensive dialysis against deionized water using a membrane with a 3.5 *kDa* MWCO. The cellophil block copolymer was subsequently lyophilized. The average molecular weight (18 *kDa*) and PDI (1.25) of the block copolymer were verified by GPC measurement. Larger block copolymers (32 *kDa*, PDI 1.28; 58 *kDa*, PDI 1.24) were obtained by decreasing the ratio of CTA to monomers in step A from 1/100 to 1/200 (32 *kDa*) and 1/400 (58 *kDa*), respectively, whereas the molar ratios of *i*-decylacrylate (7.5 *mol* of 5), DMA (63.9 *mol* of 5) and AK (28.6 *mol* of 5) were kept constant.

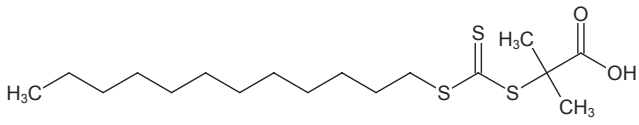
Some of the compounds mentioned in Preparation 1–2 are shown in Figure 1.2.

1.3.2 Silicone Acrylamides

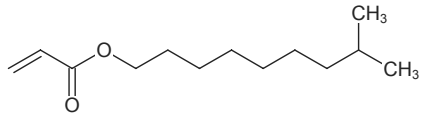
Examples of hydrophilic methacrylamide monomers are collected in Table 1.5. Some of these compounds are shown in Figure 1.3. Also, several other similar monomers have been detailed (22).

These alkyl and aryl groups can be straight or branched. Of these monomers, the *N*-(2-hydroxyethyl)methacrylamide monomer is preferable from a perspective of increasing the transparency of the so obtained polymer.

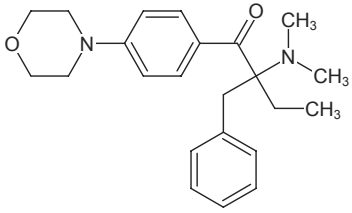
The monomer mixture for synthesizing the polymer additionally may contain between about 1% and about 30% of a hydrophilic



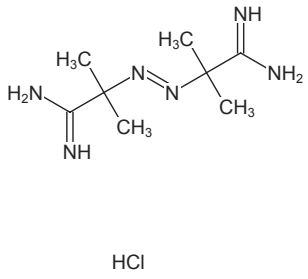
2-(Dodecylthiocarbonothioylthio)-2-methylpropionic acid



iso-Decyl acrylate

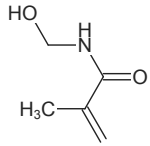


2-Benzyl-2-(dimethylamino)-
4′-morpholinobutyrophenone

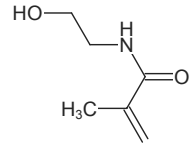


2,2′-Azobis(2-methylpropion-
amidine) dihydrochloride

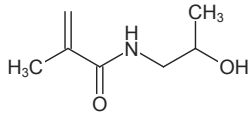
Figure 1.2 Compounds for a block copolymer.



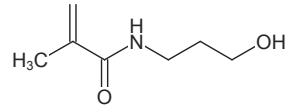
N-Hydroxymethyl methacrylamide



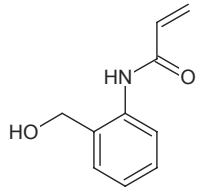
N-(2-Hydroxyethyl) methacrylamide



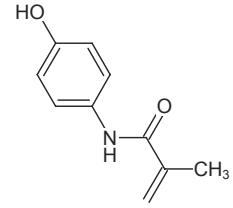
N-(2-Hydroxypropyl) methacrylamide



N-(3-Hydroxypropyl) methacrylamide



N-(2-Hydroxymethylphenyl) methacrylamide



N-(4-Hydroxymethylphenyl) methacrylamide

Figure 1.3 Hydrophilic methacrylamide-based monomers.

Table 1.5 Hydrophilic methacrylamide-based monomers (23).

Compound
N-Hydroxymethyl methacrylamide
N-(2-Hydroxyethyl) methacrylamide
N-(2-Hydroxypropyl) methacrylamide
N-(3-Hydroxypropyl) methacrylamide
N-(2-Hydroxybutyl) methacrylamide
N-(3-Hydroxybutyl) methacrylamide
N-(4-Hydroxybutyl) methacrylamide
N-(2-Hydroxymethylphenyl) methacrylamide
N-(3-Hydroxymethylphenyl) methacrylamide
N-(4-Hydroxymethylphenyl) methacrylamide

polymer with a molecular weight of about 1000 *Dalton* or higher in the monomer and polymer component of the monomer mixture in order to enhance the wettability, resistance to adhesion of proteins, resistance to adhesion of lipids and combinations thereof.

Examples of hydrophilic polymers that can be used in the polymer are shown in Table 1.6. Some of the monomers of these compounds are shown in Figure 1.4.

Hydrophilic polymers selected from poly(vinyl pyrrolidone), poly(*N*,*N*-dimethyl acrylamide), poly(acrylic acid), and poly(vinyl alcohol) may be particularly effective for enhancing the wettability of silicone hydrogels (23). Poly(vinyl pyrrolidone) and poly(*N*,*N*-dimethyl acrylamide) provide a balance between the wettability and the compatibility of the polymerization mix in certain formulations.

The polymer can also include a monomer with two or more reactive groups as a copolymerization component. In this case, the polymer becomes solvent resistent.

Preferable monomers with two or more vinyl groups include bifunctional and polyfunctional acrylates. Examples are shown in Table 1.7. Some bisacrylamide monomers are shown in Figure 1.5. Polyfunctional methacrylate compounds are shown in Figure 1.6.

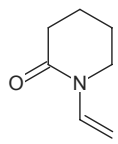
A polymerization initiator may be added to enhance the polymerization traction. Suitable initiators include thermal polymerization initiators, such as a peroxide compound or an azo compound, or

Table 1.6 Hydrophilic polymers (23).

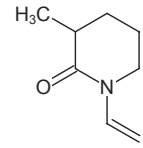
Polymer compound
Poly(*N*-vinyl pyrrolidone)
Poly(*N*-vinyl-2-piperidone)
Poly(*N*-vinyl-2-caprolactam)
Poly(*N*-vinyl-3-methyl-2-caprolactam)
Poly(*N*-vinyl-3-methyl-2-piperidone)
Poly(*N*-vinyl-4-methyl-2-piperidone)
Poly(*N*-vinyl-4-methyl-2-caprolactam)
Poly(*N*-vinyl-3-ethyl-2-pyrrolidone)
Poly(*N*-vinyl-4,5-dimethyl-2-pyrrolidone)
Poly(2-vinylimidazole)
Poly(*N*-vinyl formamide)
Poly(*N*-vinyl acetamide)
Poly(*N*-methyl-*N*-vinyl acetamide)
Poly(*N*,*N*-dimethyl acrylamide)
Poly(*N*,*N*-diethyl acrylamide)
Poly(*N*-isopropyl acrylamide)
Poly(vinyl alcohol)
Poly(acrylate)
Poly(ethylene oxide)
Poly(2-ethyl oxazoline)
Heparine Polysaccharide
Poly(acryloyl morpholine)

Table 1.7 Multifunctional monomers (23).

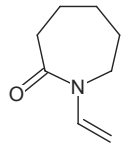
Compound	Compound
Ethylene glycol acrylate	Ethylene glycol dimethacrylate
Diethylene glycol diacrylate	Diethylene glycol dimethacrylate
Triethylene glycol diacrylate	Triethylene glycol dimethacrylate
Neopentyl glycol diacrylate	Neopentyl glycol dimethacrylate
Tetraethylene glycol diacrylate	Tetraethylene glycol dimethacrylate
Glyceryl triacrylate	Glyceryl trimethacrylate
Pentaerythritol tetraacrylate	Pentaerythritol tetramethacrylate
Trimethylol propane triacrylate	Trimethylol propane trimethacrylate
N,*N*′-Methylene bisacrylamide	*N*,*N*′-Ethylene bisacrylamide
N,*N*′-Propylene bisacrylamide	



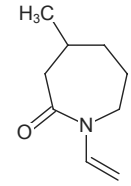
N-Vinyl-2-piperidone



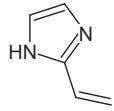
N-Vinyl-3-methyl-2-piperidone



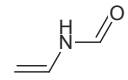
N-Vinyl-2-caprolactam



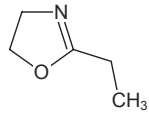
N-Vinyl-4-methyl-2-caprolactam



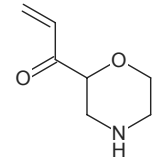
2-Vinylimidazole



N-Vinyl formamide

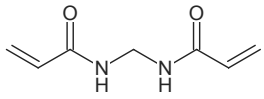


2-Ethyl oxazoline

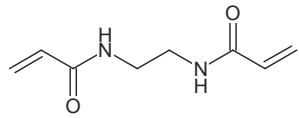


Acryloyl morpholine

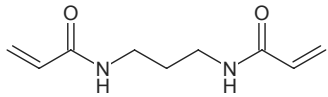
Figure 1.4 Monomers for hydrophilic polymers.



N,*N*′-Methylene bisacrylamide



N,*N*′-Ethylene bisacrylamide



N,*N*′-Propylene bisacrylamide

Figure 1.5 Bisacrylamide monomers.

photopolymerization initiators. Also, photoinitiators can be added in order to enhance the polymerization.

Several examples of the polymerization procedure have been detailed (23).

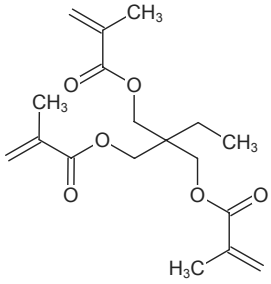
1.4 Soft Lenses

1.4.1 Hydrogels

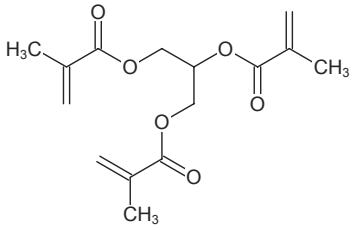
Soft contact lens materials are made by polymerizing and crosslinking hydrophilic monomers such as 2-hydroxyethyl methyacrylate, *N*-vinyl-2-pyrrolidone, and combinations thereof (19).

The polymers produced by polymerizing these hydrophilic monomers exhibit significant hydrophilic character themselves, and are capable of absorbing a significant amount of water in their polymeric matrices. Due to their ability to absorb water, these polymers are often referred to as *hydrogels*.

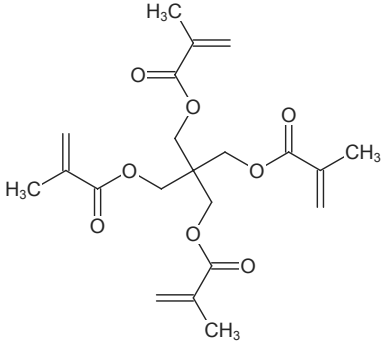
These hydrogels are optically clear and, due to their high levels of water of hydration, are particularly useful materials for making soft contact lenses. However, the high levels of water of hydration of hydrogels contributes to their relative lack of physical strength, which results in hydrogel contact lenses being relatively easy to tear (19).



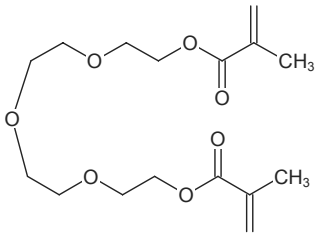
Trimethylol propane trimethacrylate



Glyceryl trimethacrylate



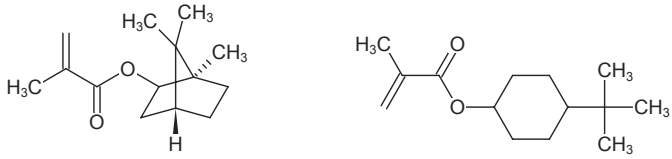
Pentaerythritol tetramethacrylate



Tetraethylene glycol dimethacrylate

Figure 1.6 Polyfunctional methacrylate compounds.

Various hydrophobic monomers have been copolymerized with these hydrophilic monomers in order to obtain polymers with an improved physical strength. Such hydrophobic monomers include styrene, and various acrylates and methacrylates such as methyl methacrylate, isobornyl methacrylate, and *tert*-butylcyclohexyl methacrylate. The last two compounds are shown in Figure 1.7.



Isobornyl methacrylate *tert*-Butylcyclohexyl methacrylate

Figure 1.7 Hydrophobic monomers.

While these hydrophobic monomers do increase the physical strength of hydrogel polymers, they also produce polymers with lower levels of water of hydration than the unmodified hydrogels.

So, an attempt was made to provide polymeric materials with an increased physical strength and high levels of water of hydration (19).

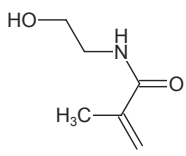
It has been found that certain hydrophobic monomers act as strengthening agents when copolymerized with hydrophilic monomers and crosslinkers. Examples of these monomers are shown in Table 1.8 and in Figures 1.8, 1.9, and 1.10.

Most preferred contact lenses have an oxygen transport rate of at least about 2×10^{-6} $cm^3 sec^{-1} cm^{-2} atm^{-1}$, which makes them hydrolytically stable, biologically inert, transparent, and resilient. Furthermore, they should preferably have a softness of about 60 or below on the Shore hardness A scale when hydrated. The more preferred materials have a Shore hardness between 25 to 35 on the A scale.

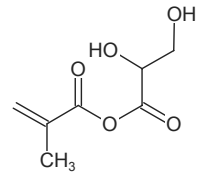
The tensile modulus of elasticity of these hydrated polymers is at least about 50 $g\,mm^{-2}$, preferably from about 75 $g\,mm^{-2}$ to about 100 $g\,mm^{-2}$, and the tear strength is at least about 2.0 $g\,mm^{-1}$ thickness, preferably from about 2.0 $g\,mm^{-1}$ to about 250 $g\,mm^{-1}$ thickness.

Table 1.8 Monomers (19).

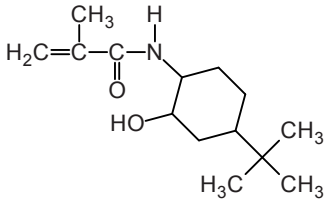
Hydrophilic monomers
2-Hydroxyethyl methacrylate
N-(2-Hydroxy ethyl)-methacrylamide
N-Vinyl-2-pyrrolidone
Glyceryl methacrylate
N-Methacryloyl glycine
2-Hydroxyl-3-methacryl(propyl)-4-methoxy phenyl ether
2-Hydroxy cyclohexyl methacrylate
Hydrophobic strengthening agent monomers
4-*tert*-Butyl-2-hydroxycyclohexyl methacrylate
4-*tert*-Butyl-2-hydroxycyclopentyl methacrylate
Methacryloylamino-4-*tert*-butyl-2-hydroxycyclohexane
6-Isopentyl-3-hydroxycyclohexyl methacrylate
Methacryloylamino-2-isohexyl-5-hydroxy cyclopentane
Crosslinking monomers
Allyl methacrylate
Ethylene glycol dimethacrylate
Divinyl ethylene urea
1,3-Bis(4-methacryloxybutyl) tetramethyl disiloxane



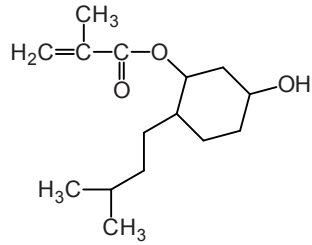
N-(2-Hydroxy ethyl)-methacrylamide



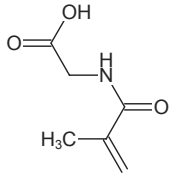
Glyceryl methacrylate



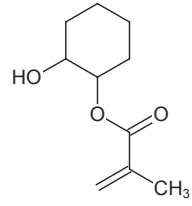
Methacryloylamino-4-*tert*-butyl-2-hydroxycyclohexane



6-Isopentyl-3-hydroxy cyclohexyl methacrylate

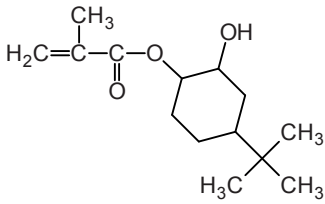


N-Methacryloyl glycine

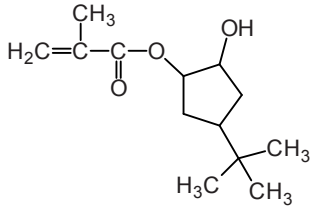


2-Hydroxy cyclohexyl methacrylate

Figure 1.8 Hydrophilic monomers.

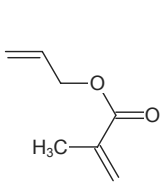


4-*tert*-Butyl-2-hydroxy-cyclohexyl methacrylate

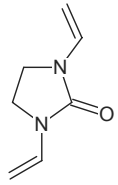


4-*tert*-Butyl-2-hydroxy-cyclopentyl methacrylate

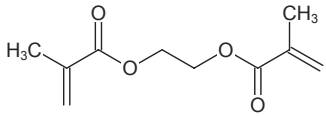
Figure 1.9 Hydrophobic strengthening monomers.



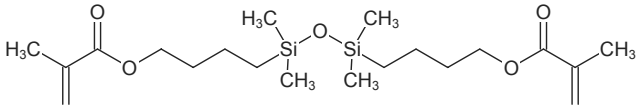
Allyl methacrylate



Divinyl ethylene urea



Ethylene glycol dimethacrylate



1,3-Bis(4-methacryloxybutyl) tetramethyl disiloxane

Figure 1.10 Crosslinking monomers.

High tensile modulus of elasticity is desirable for strength and durability. High tear strength is desirable in order to prevent damage to the contact lens due to tearing during patient use, i.e., the removing and placing of the lens on the eye, and to prevent damage to the lens during cleansing and disinfecting.

A soft contact lens formulation is illustrated in the following example (19):

Preparation 1–3: A mixture was made containing 77.0 *g* of glyceryl methacylate, 22.5 *g* of 4-*tert*-butyl-2-hydroxycyclohexyl methacrylate, and 0.5 *g* of ethylene glycol dimethacrylate. To this mixture was added 0.5 *g* of benzoin methyl ether, an ultraviolet-induced polymerization initiator. The solution was cast between glass plates separated by a Teflon perfluoro polymer gasket, 0.3 *mm* thick and cured. After curing, the film was released from the glass plates and hydrated and extracted in hot distilled water for 4 *h*.

Then, the film was placed in a borate buffered saline solution for testing. The resultant material was optically clear and had a water content of 53% and an oxygen permeability of 18×10^{-11} $cm^3 cm sec cm^2 mm Hg^{-1}$.

The mechanical properties were measured according to the following test methods and gave the results shown in Table 1.9.

Table 1.9 Mechanical properties (19).

Standard	Ref.	Name	Value
ASTM-D 1708	(24)	Young's modulus of elasticity	60 $g\,mm^{-2}$
ASTM-D 1708	(24)	Tensile strength	84 $g\,mm^{-2}$
ASTM-D 1708	(24)	% Elongation	164 %
ASTM-D 1938	(25)	Tear Initiation	3.8 $g\,mm^{-1}$

1.4.1.1 Polymerizable Contact Lens Formulations

Hydrogel contact lenses, polymerizable compositions useful for making such lenses, packaging systems for use with such lenses and methods of producing such lenses have been discovered (26). These contact lenses have a relatively low surface friction and are able to release hydrophilic polymers present in the contact lenses for prolonged periods of time.

The contact lenses have a lens body. The lens body is the reaction product of a polymerizable composition containing one or

more monomers, and a crosslinker that crosslinks the monomers during a polymerization reaction to form a first polymer component. The polymerizable composition also contains a hydrophilic polymer component, which is substantially unreactive during the polymerization.

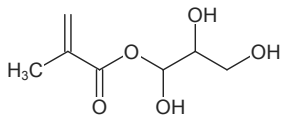
Thus, the resulting lens body includes a first polymer component formed from the one or more monomers present in the polymerizable composition, and the second polymer component, the hydrophilic polymer component that is physically entangled with the first polymer component in the lens body.

The hydrophilic polymer component is unreactive or substantially unreactive during the polymerization process. Thus, the resulting hydrogel lens body can be understood to be a network of a first polymeric component, formed from the monomers present in the polymerizable composition, and a second polymeric component, the hydrophilic polymer component, in which the hydrophilic polymer component is substantially physically entrapped by the first polymer component. Although there may be some small amounts of reactivity of the hydrophilic polymer component, the reactivity is not sufficient to prevent leaching or release of the hydrophilic polymer from the lens body. The present contact lenses can be understood to consist of an interpenetrating polymer network where the formation of the first polymer component occurs in the presence of the hydrophilic polymer component. However, as discussed herein, in the present contact lenses, it is possible for the hydrophilic polymer component to be released from the lens body even though it is entrapped by the first polymer component.

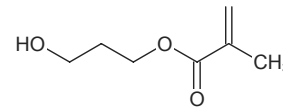
Examples of these monomers are shown in Table 1.10 and in Figure 1.11.

Polymerization initiators can be used in the polymerizable composition. Thermal initiators that may be used are azo or peroxide compounds, such as those having a half-life at the polymerization temperature of at least 20 *min*. Examples of initiators are shown in Table 1.11 and in Figure 1.12.

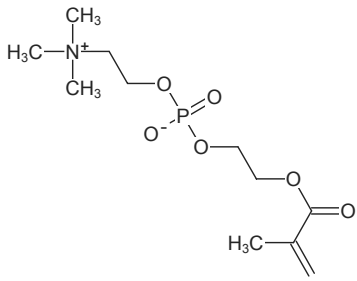
A tinting agent can be any agent that imparts a visibility to the otherwise clear hydrogel lens body. The tinting agent may be a water-soluble dye, or particles of pigment, or combinations thereof. Some examples of tinting agents include copper phthalocyanine



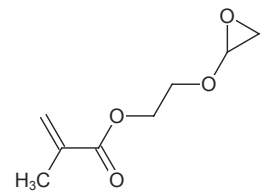
Glycerol mono methacrylate



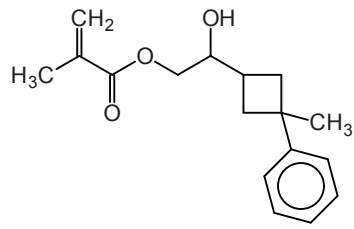
3-Hydroxypropyl methacrylate



2-Methacryloyloxyethyl phosphorylcholine



Methacryloyloxyethyl ethylene oxide

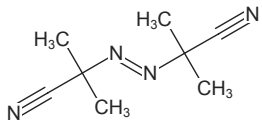


2-(3-Phenyl-3-methylcyclobutyl)-2-hydroxyethyl methacrylate

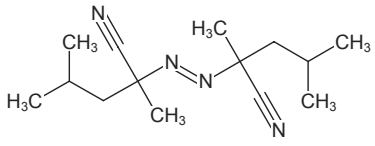
Figure 1.11 Monomers and comonomers.

Table 1.10 Monomers (26).

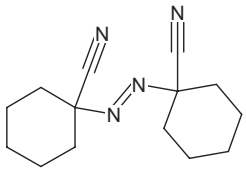
Monomers for the first polymer
2-Hydroxyethyl methacrylate 2-(3-Phenyl-3-methylcyclobutyl)-2-hydroxyethyl methacrylate 2-Hydroxyethyl acrylate 2-Hydroxypropyl methacrylate 2-Hydroxypropyl acrylate 3-Hydroxypropyl methacrylate Glycerol mono acrylate Glycerol mono methacrylate *n*-Vinyl pyrrolidone Acrylamide
Hydrophilic monomers for the second polymer
2-Methacryloyloxyethyl phosphorylcholine
Hydrophilic comonomers for the second polymer
n-Butyl methacrylate Methacryloyloxyethyl ethylene oxide Methacryloyloxyethyl propylene oxide



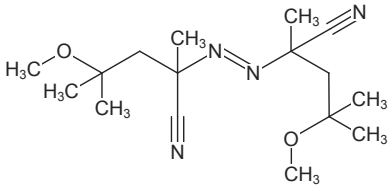
2,2′-Azo-bis-isobutyronitrile



2,2′-Azo-bis(2,4-dimethyl-valeronitrile)



1,1′-Azo-bis(cyclohexane carbonitrile)

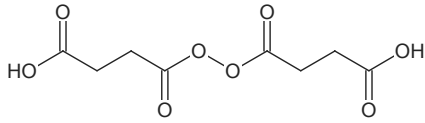


2,2′-Azo-bis(2,4-dimethyl-4-methoxy-valeronitrile

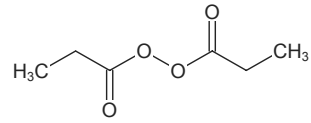
Figure 1.12 Azo initiators.

Table 1.11 Initiators (26).

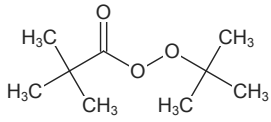
Azo initiators
2,2′-Azo-bis-isobutyronitrile
2,2′-Azo-bis(2,4-dimethylvaleronitrile)
1,1′-Azo-bis(cyclohexane carbonitrile)
2,2′-Azo-bis(2,4-dimethyl-4-methoxyvaleronitrile)
Peroxy initiators
Isopropyl percarbonate
tert-Butyl peroctoate
Benzoyl peroxide
Lauroyl peroxide
Decanoyl peroxide
Acetyl peroxide
Succinic acid peroxide
Methyl ethyl ketone peroxide
tert-Butyl peroxyacetate
Propionyl peroxide
2,4-Dichlorobenzoyl peroxide
tert-Butyl peroxypivalate
Pelargonyl peroxide
2,5-Dimethyl-2,5-bis(2-ethylhexanoylperoxy)hexane
p-Chlorobenzoyl peroxide
tert-Butyl peroxybutyrate *tert*-Butyl peroxymaleic acid
tert-Butyl-peroxyisopropyl carbonate
Bis(1-hydroxycyclohexyl)peroxide
Photoinitiators (23, 26)
Diethoxyacetophenone
1-Hydroxycyclohexyl phenyl ketone
2,2-Dimethoxy-2-phenylacetophenone
Phenothiazine
Diisopropylxanthogen disulfide
Benzoin
Benzoin methyl ether
2-Hydroxy-2-methyl-1-phenyl-propan-1-one
Bis(2,6-dimethoxybenzoyl)-2,4-4-trimethylpentyl phosphine oxide
Bis(2,4,6-trimethylbenzoyl)-phenyl phosphine oxide
2,4,6-Trimethylbenzoyl diphenylphosphine oxide



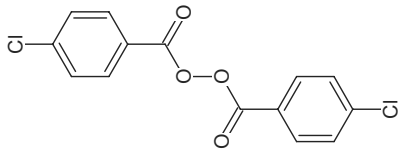
Succinic acid peroxide



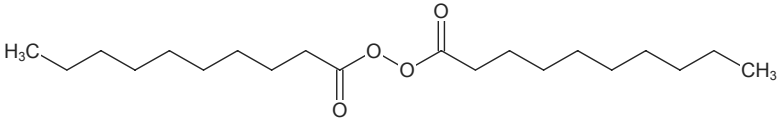
Propionyl peroxide



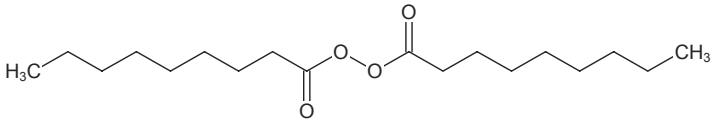
tert-Butyl peroxypivalate



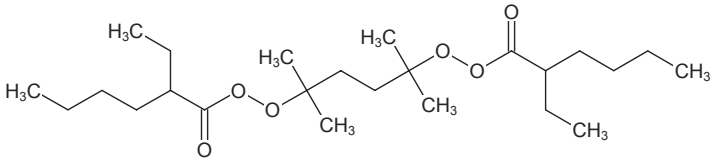
p-Chlorobenzoyl peroxide



Decanoyl peroxide

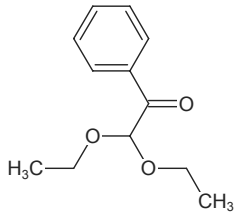


Pelargonyl peroxide

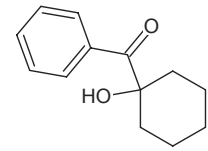


2,5-Dimethyl-2,5-bis(2-ethylhexanoylperoxy)hexane

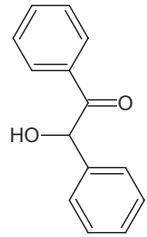
Figure 1.12 (cont) Peroxy initiators.



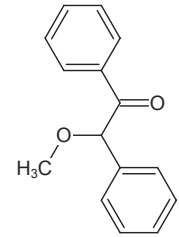
Diethoxyacetophenone



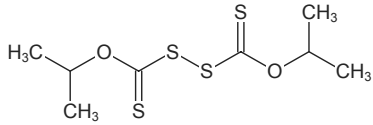
1-Hydroxycyclohexyl phenyl ketone



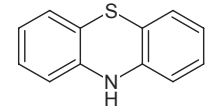
Benzoin



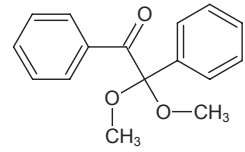
Benzoin methyl ether



Diisopropylxanthogen disulfide

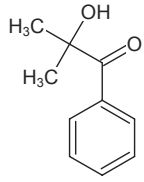


Phenothiazine

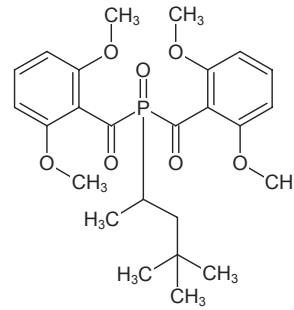


2,2-Dimethoxy-2-phenylacetophenone

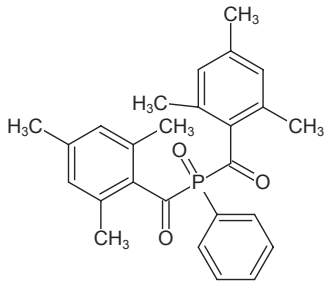
Figure 1.12 (cont) Photoinitiators.



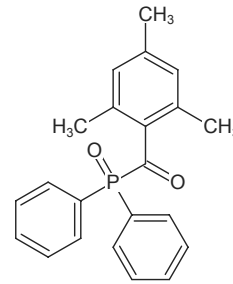
2-Hydroxy-2-methyl-1-phenyl-propan-1-one



Bis(2,6-dimethoxybenzoyl)-2,4-4-trimethylpentyl phosphine oxide



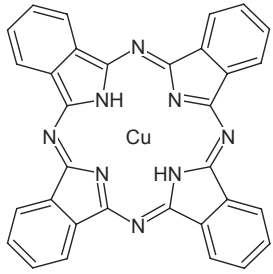
Bis(2,4,6-trimethylbenzoyl)-phenyl phosphine oxide



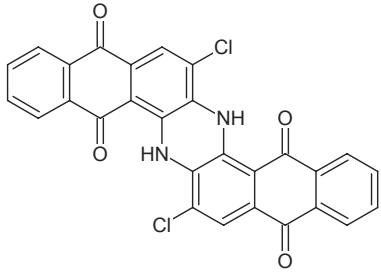
2,4,6-Trimethylbenzoyl diphenylphosphine oxide

Figure 1.12 (cont) Photoinitiators.

blue, Vat Blue 6, Reactive Blue 4, and Reactive Blue 19. These compounds are shown in Figure 1.13.



Copper phthalocyanine blue



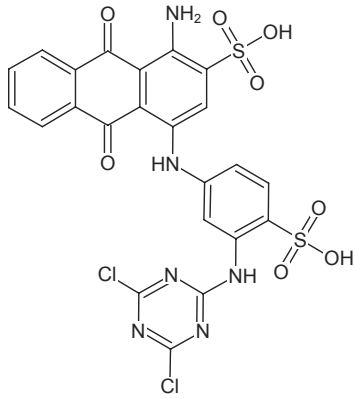
Vat Blue 6
7,16-Dichloro-6,15-dihydrodinaphtho[2,3-a:2′,3′-h]
phenazine-5,9,14,18-tetrone

Figure 1.13 Tinting agents.

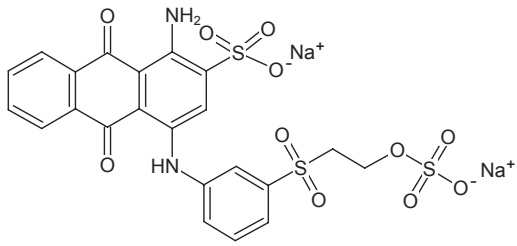
An effective amount of the tinting agent used can vary depending on factors such as the type of tinting agent, the reactive monomer composition, or the non-reactive polymers present in the composition. In general, the amount of tinting agent used may be up to about 15% of the polymerizable composition (26).

1.4.1.2 Surface Treatment for Silicone Hydrogel Contact Lenses

The usage of transparent silicone rubber for corneal contact lenses was first described in 1966 (27).



Reactive Blue 4
1-Amino-4-((3-((4,6-dichloro-1,3,5-triazin-2-yl)amino)-4-sulfophenyl)amino)-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid



Reactive Blue 19
Disodium 1-amino-9,10-dioxo-4-[(3-{[2-(sulfonatooxy)ethyl]sulfonyl}phenyl)amino]-9,10-dihydroanthracene-2-sulfonate

Figure 1.13 (cont) Tinting agents.

Silicone lenses have been subjected to plasma surface treatment to improve their surface properties; for example, to make the surface more hydrophilic, deposit-resistant, or scratch-resistant (28).

A method of surface treatment has been described that consists of coating the device with a carbon layer, followed by the attachment of hydrophilic polymer chains to the surface of the carbon layer. Then, the carbon layer is plasma treated to form reactive functionalities containing oxygen, nitrogen, and/or sulfur. Complementary reactive functionalities in monomeric units along a hydrophilic reactive polymer are then reacted with the reactive functionalities on the carbon layer. Also, a contact lens surface can be pretreated with an oxidizing plasma prior to deposition of the carbon layer in order to improve adhesion of the carbon layer.

Silicone hydrogels generally have a water content of 10% to 80%. Such materials are usually prepared by polymerizing a mixture containing at least one silicone-containing monomer and at least one hydrophilic monomer. Either the silicone-containing monomer or the hydrophilic monomer may function as a crosslinking agent. Examples of silicon-containing monomeric units are bulky polysiloxanylalkyl(meth)acrylic monomers.

Plasma surface treatments involve passing an electrical discharge through a gas at low pressure (28). The electrical discharge may be at radio frequency (typically 13.56 *MHz*), although microwave and other frequencies can be used. Electrical discharges produce ultraviolet radiation, in addition to being absorbed by atoms and molecules in their gas state, resulting in energetic electrons and ions, atoms, molecules, and radicals. So, a plasma is a complex mixture of atoms and molecules in both ground and excited states, which reach a steady state after the discharge is begun. The circulating electrical field causes these excited atoms and molecules to collide with one another as well as the walls of the chamber and the surface of the material being treated.

The deposition of a coating from a plasma onto the surface of a material has been shown to be possible from high-energy plasmas without the assistance of sputtering. Monomers can be deposited from the gas phase and polymerized in a low pressure atmosphere, at preferably 0.001 *torr* to 1.0 *torr*, onto a substrate utilizing continuous or pulsed plasmas, suitably as high as about 1000 *W*. A modulated plasma may be applied 100 *ms* on then off. In addition,

liquid nitrogen cooling has been utilized to condense vapors out of the gas phase onto a substrate and subsequently use the plasma to chemically react these materials with the substrate. However, plasmas do not require the use of external cooling or heating to cause the deposition. Low or high wattage (20 *W* to 500 *W*) plasmas can coat even the most chemical-resistant substrates, including silicones.

The method of fabrication can be done as follows (28):

1. Subjecting the surface of a lens substrate to a plasma polymerization deposition with a C_1 to C_{10} saturated or unsaturated hydrocarbon to form a polymeric carbonaceous layer (or *carbon layer*) on the lens surface,
2. Forming reactive functionalities on the surface of the carbon layer, and
3. Attaching hydrophilic polymer chains to the carbon layer by reacting the reactive functionalities on the carbon layer with complementary isocyanate or ring-opening reactive functionalities along a reactive hydrophilic polymer.

It has been found that in the case of silicone hydrogels, the use of diolefins, such as 1,3-butadiene or isoprene, are particularly preferred, resulting in coatings that are more flexible and expandable in water (28). More flexible coatings are especially preferred for high-water lenses that expand considerably upon hydration.

There are various ways to attach a polymer chain to a carbon layer, including plasma oxidation or other means to provide surface reactive functional groups that can react with the polymer. Preferably, a nitrogen-containing gas is used to form amine groups on the carbon layer. However, oxygen- or sulfur-containing gases may alternatively be used to form oxygen- or sulfur-containing groups, such as hydroxy or sulfide groups or radicals, on the carbon layer. Thus, the carbon layer is rendered reactive (functionalized) to promote the covalent attachment of the hydrophilic polymer to the surface.

To create a reactive functional group on the carbon layer, such an oxidation preferably utilizes a gas composition consisting of an oxidizing media such as ammonia, ethylene diamine, C_1 to C_8 alkyl amine, hydrazine, or other oxidizing compounds. Preferably, the oxidation of the hydrocarbon layer is performed for a period of about 1 *min* to 10 *min*, a discharge frequency of 13.56 *MHz* at about

20 *W* to 500 *W* and about 0.1 *torr* to 1.0 *torr*. The lens substrate may be treated on both sides at once or each side sequentially.

The hydrophilic reactive polymer may contain monomeric units derived from azlactone-functional, epoxy-functional and acid-anhydride-functional monomers. Azlactone monomers are listed in Table 1.12 and in Figure 1.14.

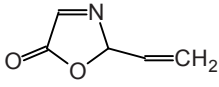
Table 1.12 Azlactone monomers (28).

2-Alkenyl azlactones
2-Ethenyl-1,3-oxazolin-5-one
2-Ethenyl-4-methyl-1,3-oxazolin-5-one
2-Isopropenyl-1,3-oxazolin-5-one
2-Isopropenyl-4-methyl-1,3-oxazolin-5-one
2-Ethenyl-4,4-dimethyl-1,3-oxazolin-5-one
2-Isopropenyl-4-dimethyl-1,3-oxazolin-5-one
2-Ethenyl-4-methyl-ethyl-1,3-oxazolin-5-one
2-Isopropenyl-4-methyl-4-butyl-1,3-oxazolin-5-one
2-Ethenyl-4,4-dibutyl-1,3-oxazolin-5-one
2-Isopropenyl-4-methyl-4-dodecyl-1,3-oxazolin-5-one
2-Isopropenyl-4,4-diphenyl-1,3-oxazolin-5-one
2-Isopropenyl-4,4-pentamethylene-1,3-oxazolin-5-one
2-Isopropenyl-4,4-tetramethylene-1,3-oxazolin-5-one
2-Ethenyl-4,4-diethyl-1,3-oxazolin-5-one
2-Ethenyl-4-methyl-4-nonyl-1,3-oxazolin-5-one
2-Isopropenyl-methyl-4-phenyl-1,3-oxazolin-5-one
2-Isopropenyl-4-methyl-4-benzyl-1,3-oxazolin-5-one
2-Ethenyl-4,4-pentamethylene-1,3-oxazolin-5-one
Cycloalkyl azlactones
2-Isopropenyl-4,4-dimethyl-2-oxazolin-5-one
2-Vinyl-4,4-dimethyl-2-oxazolin-5-one
Spiro-4′-(2′-isopropenyl-2′-oxazolin-5-one) cyclohexane
Cyclohexane-*spiro*-4′-(2′-vinyl-2′-oxazol-5′-one)
2-(1-Propenyl)-4,4-dimethyl-oxazol-5-one

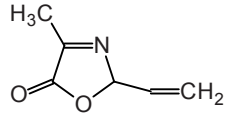
The synthesis of such monomers has been described in detail (29). The synthesis of 2-isopropenyl-4,4-dimethyl-2-oxazolin-5-one can be done as follows (29):

Preparation 1–4: 1. Methacryloylation:

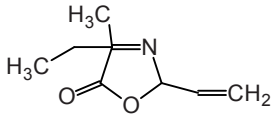
In a 500 *ml* 3-neck round-bottom flask equipped with a mechanical stirrer, thermometer and an addition funnel, 51.5 *g* (0.5 *mol*) of



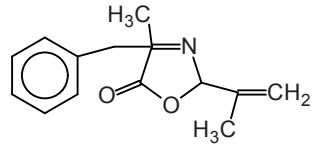
2-Ethenyl-
1,3-oxazolin-5-one



2-Ethenyl-4-methyl-
1,3-oxazolin-5-one

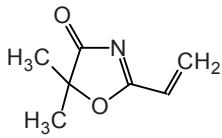


2-Ethenyl-4-methyl-ethyl-
1,3-oxazolin-5-one

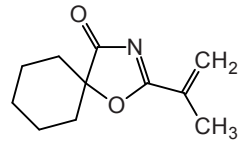


2-Isopropenyl-4-methyl-4-benzyl-
1,3-oxazolin-5-one

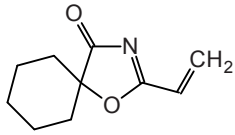
Figure 1.14 2-Alkenyl azlactones.



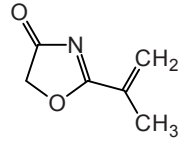
2-Vinyl-4,4-dimethyl-2-
oxazolin-5-one



Spiro-4′-(2′-isopropenyl-2′-
oxazolin-5-one) cyclohexane



Cyclohexane-*spiro*-4′-(2′-vinyl-2′-
oxazol-5′-one)



2-(1-Propenyl)-4,4-dimethyl-
oxazol-5-one

Figure 1.14 (cont) Cycloalkyl azlactones.

α-aminoisobutyric acid and 40 *g* (1 *mol*) of NaOH were dissolved in 150 *ml* of H_2O. The reaction flask was cooled to 0°C to 5°C in a CH_3OH ice bath and 0.5 *mol* of methacrylate chloride was added dropwise while the temperature of the reaction mixture was kept below 0°C. After stirring for an additional hour, the reaction mixture was acidified with concentrated HCl with a pH of 3 to precipitate out the intermediate, which was then filtered, washed with cold H_2O and air dried. Further drying was accomplished in a vacuum oven at 80°C overnight to obtain 44.9 *g* (0.26 *mol* 53%) *N*-methacryloyl-α-aminoisobutyric acid, which was suitable for the synthesis of 2-isopropenyl-4,4-dimethyl-2-oxazolin-5-one.

Cyclization, synthesis of 2-isopropenyl-4,4-dimethyl-2-oxazolin-5-one:

In a 500 *ml* dry 3-neck round-bottom flask, 0.26 *mol* of *n*-methacryloyl-α-aminoisobutyric acid was dispersed in 300 *ml* of dry hexane and allowed to react with mechanical stirring by dropwise addition of triethylamine (0.52 *mol*) while the temperature of the reaction mixture was maintained at 45°C to 0°C. During the addition, the copious evolution of carbon dioxide and the formation of white precipitate of TEA-HCl were observed. The reaction mixture was stirred for an additional 2 *h*. After cooling to room temperature, a white precipitate was filtered off and hexane evaporated off yielding an oil. Pure 2-isopropenyl-4,4-dimethyl-2-oxazolin-5-one was obtained after being recrystallized twice in hexane at dry ice/acetone temperature. The yield was 29 *g* (73%).

2-Isopropenyl-4,4-dimethyl-2-oxazolin-5-one is shown in Figure 1.15.

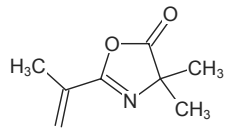


Figure 1.15 2-Isopropenyl-4,4-dimethyl-2-oxazolin-5-one.

Azlactone-functional monomers can be copolymerized with other monomers in various combinations of amounts (28). Using a monomer of similar reactivity ratio to that of an azlactone monomer will result in a random copolymer. Alternatively, use of a comonomer having a higher reactivity to that of an azlactone will tend to result in a block copolymer chain with a higher concentration of azlactone functionality near the terminus of the chain.

After producing a lens with the desired final shape, it is desirable to remove residual solvent from the lens before edge-finishing operations. This is because, typically, an organic diluent is included in the initial monomeric mixture in order to minimize phase separation of the polymerized products produced by polymerization of the monomeric mixture and to lower the glass transition temperature of the reacting polymeric mixture, which allows for a more efficient curing process and ultimately results in a more uniformly polymerized product. Sufficient uniformity of the initial monomeric mixture and the polymerized product are of particular concern for silicone hydrogels, primarily due to the inclusion of silicone-containing monomers which may tend to separate from the hydrophilic comonomer.

Suitable organic diluents include, for example, monohydric alcohols, such as *n*-hexanol and *n*-nonanol (cf. Figure 1.16), diols such as ethylene glycol, polyols such as glycerin, ethers such as diethylene glycol monoethyl ether (cf. Figure 1.17), ketones such as methyl ethyl ketone, esters such as methyl enanthate (cf. Figure 1.18), and hydrocarbons such as toluene.

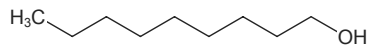


Figure 1.16 *n*-Nonanol.

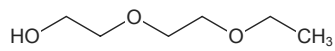


Figure 1.17 Diethylene glycol monoethyl ether.

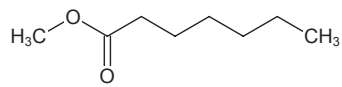


Figure 1.18 Methyl enanthate or Methyl heptanoate.

Preferably, the organic diluent is sufficiently volatile to facilitate its removal from a cured article by evaporation at or near ambient

pressure. Generally, the diluent is included at 5% to 60% of the monomeric mixture, with 10% to 50% being especially preferred.

The cured lens is then subjected to solvent removal, which can be accomplished by evaporation at or near ambient pressure or under vacuum. An elevated temperature can be employed to shorten the time necessary to evaporate the diluent. The time, temperature and pressure conditions for the solvent removal step will vary depending on such factors as the volatility of the diluent and the specific monomeric components, as can be readily determined by one skilled in the art. According to a preferred embodiment, the temperature employed in the removal step is preferably at least 50°C. A series of heating cycles in a linear oven under inert gas or vacuum may be used to optimize the efficiency of the solvent removal. The cured article after the diluent removal step should preferably contain not more than 5%.

After solvent removal, the lens is next subjected to mold release and optional machining operations. The machining step includes, for example, buffing or polishing a lens edge and/or surface. Finally, the lens is subjected to a surface treatment (28).

1.4.1.3 Hydrophilicity Improvement

The hydrophilicity of the surface of a silicone hydrogel lens can be improved with a poly(oxy ethylene) derivative with a plurality of hydroxyl groups (30). The surface treatment can be done as follows (30):

Preparation 1–5: First, 60 parts by mass of 3-[tris(trimethylsiloxy)silyl] propyl methacryloyloxyethyl succinate, shown in Figure 1.19, 39 parts by mass of 2-hydroxyethyl methacrylate, 0.5 part by mass of ethylene glycol dimethacrylate, and 0.5 part by mass of azobisisobutyronitrile were mixed and dissolved. Then the solution was flowed into a cell sandwiched between a glass plate and a polypropylene plate through the use of a poly(ethylene terephthalate) sheet having a thickness of 0.1 *mm* as a spacer. After an oven had been purged with nitrogen, the solution was heated at 100°C for 2 *h* to be polymerized, followed by molding into a film shape. After polymerization, the cured film was removed from the cell, and was immersed in a mixed liquid containing ethyl alcohol and ion-exchanged water at a ratio of 3/1 for 12 *h*, and in ion-exchanged water for 12 *h* to produce a water-containing film. The produced water-containing film was placed in a discharging apparatus, and the pressure in a chamber

was reduced to about 2.66 *Pa*. After that, a plasma discharge treatment was performed under an oxygen gas atmosphere at about 13.3 *Pa* for 10 *min* (frequency: 13.56 *MHz*, high-frequency output: 50 *W*). After that, a peroxide (peroxide group) was produced on the surface of the water-containing film by storing it under an oxygen gas atmosphere for a minimum of 10 *min*.

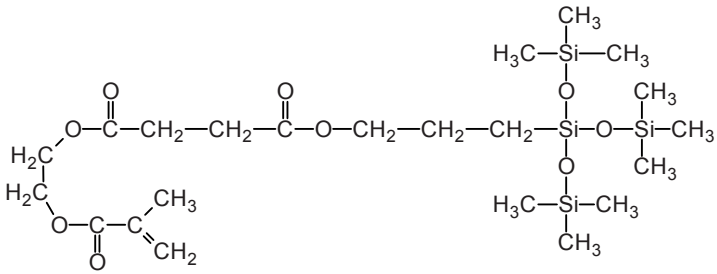


Figure 1.19 3-[Tris(trimethylsiloxy)silyl]propyl methacryloyloxyethyl succinate.

Examples of preferred monomers for use in the base material of a silicone hydrogel contact lens to control the water content include water-soluble monomers. These materials are collected in Table 1.13.

Table 1.13 Monomers for controlling water content (30).

Compound	Compound
(Meth)acrylic acid	Itaconic acid
Crotonic acid	Cinnamic acid
Vinylbenzoic acid	Glycerol (meth)acrylate
N-Vinylformamide	*N*-Vinylacetamide
2-Hydroxyethyl (meth)acrylate	2,3-Dihydroxypropyl (meth)acrylate
N-Methyl-*N*-vinylacetamide	*N*-Vinyl-2-pyrrolidone
2-(Meth)acryloyloxyethyl phosphorylcholine	
Polyalkylene glycol mono(meth)acrylate	
Polyalkylene glycol monoalkyl ether (meth)acrylate	

The usage amount of any monomer in Table 1.13 is typically from 10 parts by mass to 50 parts by mass, preferably from 20 parts by mass to 40 parts by mass with respect to 100 parts by mass of the

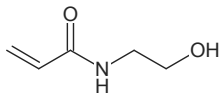
monomer composition of the silicone hydrogel contact lens base material (30).

1.4.1.4 Interpenetrating Polymer Network Hydrogel Contact Lenses

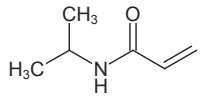
Interpenetrating polymer network hydrogels have been described that have high oxygen permeability, strength, water content, and resistance to protein adsorption (20).

The hydrogels include two interpenetrating polymer networks. The first polymer network is based on a hydrophilic telechelic macromonomer. The second polymer network is based on a hydrophilic monomer. The hydrophilic monomer is polymerized and crosslinked to form the second polymer network in the presence of the first polymer network.

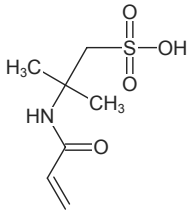
The telechelic macromonomer is preferably poly(ethylene) glycol diacrylate or poly(ethylene) glycol dimethacrylate. The hydrophilic monomer can be acrylic acid, acrylamide, *N*-hydroxyethyl acrylamide, *N*-isopropyl acrylamide, methacrylic acid (MA), 2-acrylamido-2-methylpropanesulfonic acid, 2-hydroxyethyl methacrylate, or 2-hydroxyethyl acrylate, cf. Figure 1.20.



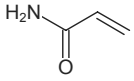
N-(2-Hydroxyethyl) acrylamide



N-Isopropyl acrylamide



2-Acrylamido-2-methylpropanesulfonic acid



Acrylamide

Figure 1.20 Monomers for telechelic macromonomers (20).

One surface of the interpenetrating polymer network hydrogel

should be surface modified. Preferably, at least one surface is modified with a layer of poly(ethylene) glycol macromonomers, polymerized poly(ethylene) glycol diacrylate, or polymerized poly(ethylene) glycol dimethacrylate.

The steps required for synthesis of an interpenetrating polymer network hydrogel are as follows (20):

The starting material for the hydrogel is a solution of telechelic macromonomers with functional end groups. The telechelic macromonomers are polymerized to form a first polymer network. Next, hydrophilic monomers are added to the first polymer network. Hydrophilic monomers are then polymerized and crosslinked in the presence of the first polymer network to form a second polymer network.

1.4.1.5 Poly(olefin) Contact Lenses

New lens molds and methods useful in producing soft contact lenses have been discovered. Poly(propylene) (PP) contact lens molds and methods of making such soft contact lenses, such as hydrogel contact lenses, by using such molds have been described (31).

The present molds and methods provide contact lenses with consistent high optical quality; for example, producing lenses with fewer surface defects and with less severe surface defects or a reduced optical distortion caused by surface defects. Furthermore, the present molds and methods use reduced amounts of energy, shorten contact lens production cycle time and achieve reduced machinery wear and tear. Such advantageous results are relative to producing identical soft contact lenses from molds made of thermoplastic poly(olefin), in particular PP, resin having a melt flow rate of less than 10 $g\,(10min)^{-1}$, for example, 1.9 $g\,(10min)^{-1}$.

The term *melt flow rate* denotes the industry known standard ASTM D1238-13 (32). This parameter is usually available from suppliers of commercial resins. Such mold member or members may be conventionally produced, for example, by injection molding processing. Preferably, both mold members are injection molded from one or more of such resins.

These benefits of producing soft contact lenses can be obtained without requiring molds made from thermoplastic poly(olefin)

resins having a melt flow rate of at least about $g\,(10min)^{-1}$, as described in a previous publication (33) for rigid gas-permeable contact lenses. Also, molds made out of Ziegler-Natta catalyst-based poly(olefin) resin are not required, as noted in a publication of Ansell and Yin (34).

Here, methods of producing soft contact lens products, e.g., soft hydrophilic or hydrogel contact lens products, are provided. These methods consist of placing a soft lens-forming composition in a cavity formed between a first mold member and a second mold member, subjecting the soft lens-forming composition in the cavity to conditions effective to form a contact lens product from the lens-forming composition, and repeating the placing and subjecting steps a plurality of times, for example, at least about 100 times or at least about 1000 times or at least about 10,000 times, thereby producing a plurality of soft contact lens products.

At least the first mold members, and advantageously all of the first and second mold members, consist of a nucleated thermoplastic poly(olefin) resin having a melt flow rate in a range of 10 $g\,(10min)^{-1}$ to about 40 $g\,(10min)^{-1}$ (31).

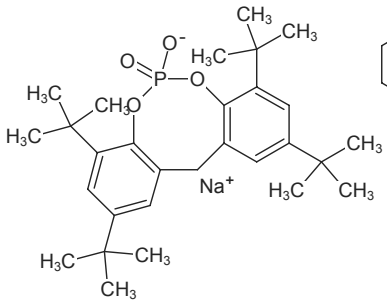
A nucleating agent is specifically utilized to increase the rate of crystallization of the poly(olefin) component as it cools from the melt as compared to the same or identical poly(olefin) component without the nucleating agent. Many nucleating agents are suitable for inclusion with the thermoplastic poly(olefin) resin formulations useful in the present invention.

Nucleating agents for PP have been described (35, 36). Examples of suitable nucleating agents are collected in Table 1.14 and shown in Figure 1.21.

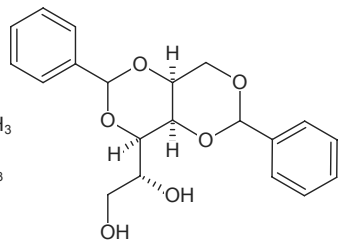
The thermoplastic poly(olefin) resin acts to reduce the time required for crystallization of the poly(olefin) resin and/or to produce smaller crystals of the poly(olefin) resin relative to an identical thermoplastic poly(olefin) resin without the nucleating agent. Reducing poly(olefin) crystallization time is believed to allow for better and more precise control of poly(olefin) resin crystallization. Producing smaller poly(olefin) resin crystals is believed to allow the poly(olefin) resin (crystallized) to more closely conform to the desired shape of the mold member or members, in particular to the desired shape of the surface or surfaces of the mold member or

Table 1.14 Nucleating agents (31).

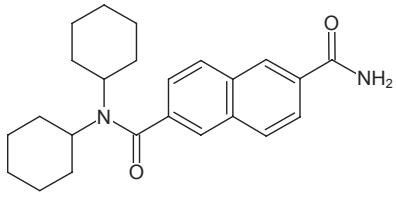
Compound
Sodium benzoate
Sodium sulfate
Sodium 2,2′-methylenebis(4,6-di-*tert*-butylphenyl) phosphate
Aluminum 2,2′-methylenebis(4,6-di-*tert*-butylphenyl) phosphate
Dibenzylidene sorbitol
Di(*p*-tolylidene) sorbitol
Di(*p*-ethylbenzylidene) sorbitol
Bis(3,4-dimethylbenzylidene) sorbitol
N′,*N*′-Dicyclohexyl-2,6-naphthalenedicarboxamide
Salts of disproportionated rosin esters



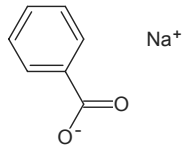
Sodium 2,2′-methylenebis(4,6-di-*tert*-butylphenyl) phosphate



Dibenzylidene sorbitol



N′,*N*′-Dicyclohexyl-2,6-naphthalenedicarboxamide



Sodium benzoate

Figure 1.21 Nucleating agents (31).

members which are shaped to produce the anterior and/or posterior surfaces of the contact lens product.

In addition, many other types of additives can be included in the thermoplastic poly(olefin) resin formulations. Such additives include lubricants, antistatic agents, slip agents, antiblocking agents, colorants, metal deactivators, mold release agents, fillers and reinforcements, fluorescent whitening agents, biostabilizers, and mixtures thereof.

These methods produce a plurality of soft contact lens products having fewer surface defects and/or less severe surface defects and/or reduced optical distortion caused by surface defects relative to an identical plurality of soft contact lens products produced in identical molds in which the first mold members comprise a thermoplastic poly(olefin) resin having a melt flow rate of less than 10 $g\,(10min)^{-1}$, for example, 1.9 $g\,(10min)^{-1}$.

Also, a method of producing soft hydrophilic cast-molded contact lenses having enhanced surface quality is assessed. Such a method consists of (31):

1. Providing first and second mold members structured to be assembled together to form a lens-shaped cavity therebetween, each of the first and second mold members comprises a nucleated, thermoplastic poly(olefin) resin having a melt flow rate in a range of about 10 $g\,(10min)^{-1}$ to about 40 $g\,(10min)^{-1}$,
2. Placing a soft hydrophilic contact lens-forming composition in the cavity,
3. Forming a soft hydrophilic contact lens product from the soft hydrophilic contact lens-forming composition in the cavity,
4. Removing the soft hydrophilic contact lens product from the first and second mold members; and repeating the above-noted providing, placing, forming and removing steps a plurality of times.

This method can produce a plurality of soft hydrophilic contact lens products having enhanced surface quality relative to an identically produced plurality of soft contact lens products made using first and second mold members consisting of thermoplastic olefin resin having a melt flow rate of 1.9 $g\,(10min)^{-1}$.

In an aspect, a method of producing soft hydrophilic contact lenses is provided which includes forming a plurality of soft hydrophilic contact lens products from a soft hydrophilic contact lens-forming composition in cavities formed by first and second mold members and removing the soft hydrophilic contact lens products from the first and second mold members. This method consists of using first and second molds consisting of a nucleated thermoplastic poly(olefin) resin having a melt flow rate in a range of about 10 $g\,(10min)^{-1}$ to about 40 $g\,(10min)^{-1}$, and producing a soft hydrophilic contact lens with enhanced surface quality (31).

A cross-sectional view of a contact lens mold assembly is shown in Figure 1.22.

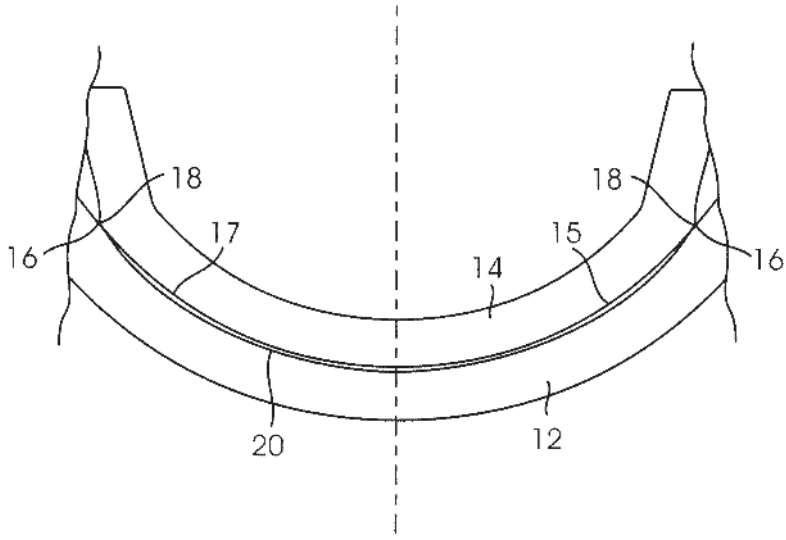


Figure 1.22 Cross-sectional view of a contact lens mold assembly (31).

The contact lens mold assembly, shown in Figure 1.22, includes a first or female mold member 12 coupled to a second or male mold member 14 to form a lens-shaped cavity 15 which has a circular periphery. In addition, the first and second mold members 12 and 14 can be structured to produce a contact lens having a rounded posterior lens edge surface. However, other embodiments of the mold members 12 and 14 may form non-rounded lens edge surfaces. As shown in Figure 1.22, lens-shaped cavity 15 contains a polymeriz-

able contact lens precursor composition 17, which is discussed in detail elsewhere herein. The first and second mold members 12 and 14 are made of thermoplastic poly(olefin) resin and are interference fitted together. In particular, first and second mold members 12 and 14 are press fitted together at first peripheral region 16 (of first mold member 12) and second peripheral region 18 (of second mold member 14). Thus, first and second peripheral regions 16 and 18 are structured to be in direct, securing contact when the mold is assembled, as shown in Figure 1.22.

The first and second mold members 12 and 14 can be securely joined or coupled together simply by moving one or both of the mold members toward each other until the peripheral regions 16 and 18 come into direct, securing contact. When it is desired to separate the first and second mold members 12 and 14, the mold members can be pulled apart or a tool can be used to overcome the direct, securing contact at the peripheral regions 16 and 18, preferably without causing substantial damage to at least one of the first and second mold members and to the ophthalmic lens product formed in the lens-shaped cavity.

The contact lens precursor composition 17 within the lens-shaped cavity often includes one or more monomers, macromers, polymers, or other reactive agents, and combinations thereof, which are polymerized, such as by exposure to UV light and/or heat, to form a contact lens product. Other processing steps may include, without limitation, disassembling the mold assembly or demolding the mold assembly, removing the contact lens product from the first mold member or second mold member or delensing the contact lens product from a mold member, extracting extractable materials from the contact lens product, for example, extracting extractable materials from a silicone hydrogel contact lens product, hydrating the extracted contact lens product, inspecting the contact lens, packaging the contact lens, and sterilizing the contact lens. In certain lenses, a separate extraction step may not be necessary. The resulting contact lens is a cast-molded contact lens (31).

1.4.1.6 Carboxy Betaine Ester

A hydrogel contact lens has been described from a polymer composition that can be obtained by polymerizing a monomer mixture

of a betaine ester (37). Betaine is also known as trimethylglycine or (trimethylammonio)acetate.

The synthesis of the carboxy betaine ester *N*-carbomethoxymethyl-*N*-methacryloylamidopropyl-*N*,*N*-dimethyl ammonium chloride is performed under a dry nitrogen atmosphere in dry acetone. Under these circumstances the carboxy betaine ester, which is a salt, precipitates from the solution. Being salts, the carboxy betaine esters are very hygroscopic since they absorb water rather quickly and thus must be stored under dry conditions to retain their quality.

In detail the synthesis runs as follows (37):

Preparation 1–6: First, 42.566 *g* (0.250 *mol*) *N*-[3-(dimethylamino)propyl]-methacrylamide in 100 *ml* of dry acetone was added to a three-necked flask and stirred. Then, 29.848 *g* (0.275 *mol*) methylchloro acetate in 30 *ml* dry acetone was added into a dropping funnel attached to the three-necked flask. The reaction commenced under a continuous slight dry nitrogen overpressure while the tip of the reaction flask touched the ice/water mixture, thus setting the initial temperature of the reaction solution at 15°C.

Now, methylchloro acetate was slowly added in about 30 *min*, while maintaining the reaction temperature just below 15°C by varying the immersion depth of the reaction flask in the ice/water mixture. During the addition of methylchloro acetate only a slight whitish haze developed in the reaction solution. After the addition of all methylchloro acetate, the reaction flask was lifted from the ice/water bath, and the reaction solution was allowed to warm to ambient temperature while still being stirred. Then the temperature slowly rose to about 30°C, slightly over ambient temperature, while more and more white crystals were formed. The temperature was controlled to avoid an increase above 30°C in order to prevent too much acetone being evaporated from the reaction solution. After one night of continuous stirring, a dense crust of white crystalline material had precipitated on the inside of the reaction flask, while a slurry of crystals had formed in the reaction solution. The crystals were isolated by filtration and washed with dry acetone under a flow of dry nitrogen gas to avoid water uptake. The crystals were dried in a vacuum oven at 50°C for one night. The yield was 60.215 *g* (79%).

The synthesis is also shown in Figure 1.23.

1.4.1.7 Silver Nanoparticles

The effect of the monomer composition on the binding capacity of hydrogels with silver nanoparticles was investigated and its antibacterial efficacy was evaluated (38).

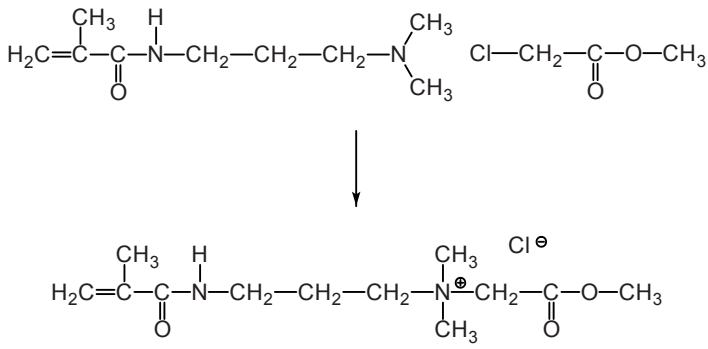


Figure 1.23 Synthesis of *N*-carbomethoxymethyl-*N*-methacryloylamidopropyl-*N*,*N*-dimethyl ammonium chloride.

Three series of poly(2-hydroxyethyl methacrylate) hydrogels were prepared using MA, methacrylamide, and 4-vinylpyridine as comonomers, and ethylene glycol dimethacrylate (EGDMA) as crosslinking agent (38).

The binding capacity of the hydrogels with the silver nanoparticles was evaluated in different concentrations of 2 *ppm*, 10 *ppm*, and 20 *ppm*. The *in-vitro* antibacterial activity of the silver nanoparticles-loaded hydrogels was studied against *Pseudomonas aeruginosa* (*P. aeruginosa*) isolated from the eyes of some patients. Then, the inhibitory effect of hydrogels in biofilm formation was evaluated in the presence of *Staphylococcus epidermidis* (*S. epidermidis*) (DSMZ 3270).

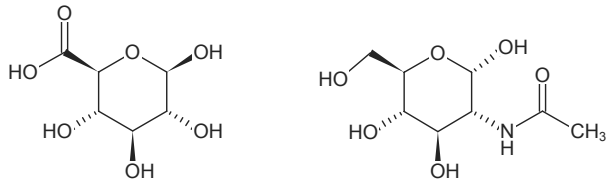
The obtained data indicated that poly(HEMA-*co*-MAA-*co*-EGDMA) showed a superior binding affinity for the silver nanoparticles in comparison to other hydrogels. All silver nanoparticle-loaded hydrogels showed excellent antimicrobial effects against *P. aeruginosa* and *S. epidermidis* after soaking in 10 *ppm* and 20 *ppm* silver nanoparticle suspensions (38).

1.4.1.8 Transparent Hydrogel Membrane

A method for preparing a transparent hydrogel membrane has been described. The method includes the following steps (39):

1. Preparing 6 to 10% of a hyaluronic acid solution based on a total weight of a mixture by dissolving a hyaluronic acid in a basic aqueous solution,
2. Mixing the hyaluronic acid solution with 0.01% to 0.05% of a crosslinking agent based on the total weight of the mixture, and
3. Shaping the transparent hydrogel membrane by pouring the mixture into a mold.

Hyaluronic acid (HA), cf. Figure 4.41, is one of the most widely used biocompatible polymers for medical use. It is a polymer consisting of two sugars, glucuronic acid and *N*-acetylglucosamine. These sugars are shown in Figure 1.24.



Glucuronic acid *N*-Acetylglucosamine

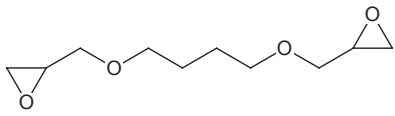
Figure 1.24 Sugars in hyaluronic acid.

Hyaluronic acid is a natural mucopolysaccharide that is widely distributed in the interstices of tissues, is present in a large amount in the synovial fluid, cartilage, skin, eyeballs, and the like of a human, serves as a three-dimensional crosslinker of intercellular molecules, and protects cartilages between the cartilages due to its high viscosity. Furthermore, hyaluronic acid contains a large amount of carboxyl groups, which is a hydrophilic group, and thus has a feature by which its mechanical strength is reduced when it comes into contact with moisture.

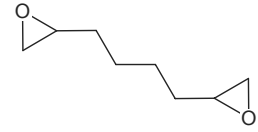
The crosslinking agent serves to link and copolymerize hyaluronic acid monomers, and an internal structure of the transparent hydrogel membrane may form a network structure by the copolymerization. Suitable crosslinking agents are listed in Table 1.15 and shown in Figure 1.25.

Table 1.15 Crosslinking agents (39).

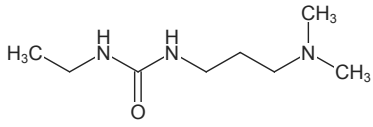
Compound
1,4-Butanediol diglycidyl ether
1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Diepoxyoctane
1,2-Bis-(2,3-epoxypropyl)-2,3-ethylene



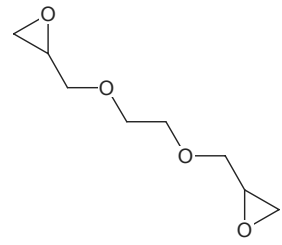
1,4-Butanediol diglycidyl ether



Diepoxyoctane



1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide



1,2-Bis-(2,3-epoxypropyl)-2,3-ethane

Figure 1.25 Crosslinking agents.

The preparation of a hyaluronic acid contact lens can be done as follows (39):

Preparation 1–7: A uniform hyaluronic acid mixture was prepared by dissolving a non-crosslinked hyaluronic acid in an amount of 8% in an aqueous sodium hydroxide solution with a pH of 8 and adding 0.01% of 1,4-butanediol diglycidyl ether thereto. The hyaluronic acid mixture was poured into a poly(carbonate) mold and dried in an oven at 40°C for 30 *h*. The hyaluronic acid contact lenses of a predetermined size prepared by drying the hyaluronic acid mixture were washed three times in total with distilled water every 24 *h*, and after a washing process of 72 *h* was performed, a hyaluronic acid hydrogel film was obtained. The hyaluronic acid hydrogel membrane had a diameter of 9 *mm* and a thickness of 20 μm.

1.4.2 PVA Hydrogel

A highly transparent poly(vinyl alcohol) (PVA) hydrogel can be obtained by freeze-thawing aqueous PVA solutions repeatedly at a relatively higher temperature. There is no need to use a chemical crosslinking agent. It is believed that these materials could be superior for use in contact lenses compared to the conventionally used 2-hydroxyethyl methacrylate (HEMA) (40).

Aqueous solutions of PVA are obtained by dissolving PVA in water at 80°C. The concentration of the polymers is around 5–20%. The solutions are then stored at room temperature for two weeks. Repeated freeze-thawing cycles are then performed. This procedure consists of 8 *h* freezing at 0°C. The thawing lasts 16 *h* at 37°C. A total of 15 cycles is appropriate (41).

1.4.3 Clear Contact Lenses

The materials for contact lenses have undergone significant changes over the past 20 years, in particular due to the introduction of silicone hydrogel materials (42).

The wettability of contact lenses is still an important part of biocompatibility. Contact lenses can be made more wettable by incorporation of surfactants into blister packs, internal wetting agents, surface treatments or care solutions (42). However, there is no clear association between contact lens wettability and comfort. This makes it challenging to predict these properties.

Most contact lenses are used on a daily wear, reusable basis, which requires them to be disinfected when not worn. The ideal disinfecting solution would also improve comfort during wear. However, balancing these requirements with other factors, including biocompatibility, remains a challenge.

Contact lens materials can sorb components of the tear film. These interactions are complex and may change the biochemistry of the tear film, which in turn may affect their comfort.

So, the interaction between lens materials, tear film and disinfection solution plays an important role in the biocompatibility of lenses.

The best available evidence to examine such complex relationships and the opportunities for practitioners to enhance the in-eye comfort of lenses have been reported (42).

1.5 Water Absorbable Formulations

It has been discovered that when a soft contact lens absorbs water and is hydrophilic, the lens will move on the eye sufficiently so that no physical damage will occur to the cornea and sufficient tear exchange will occur so that corneal metabolism will proceed normally.

It was found that poly(siloxane) soft contact showed some adhering to the eye. This problem has been a major obstacle in preventing the use of poly(siloxane)s as a soft contact lens material.

This major obstacle has now been overcome. Most unexpectedly, the instant poly(siloxane) copolymers are not only hydrophilic but are also water-absorbing. Therefore, the instant copolymers make excellent material for manufacturing contact lenses which not only do not stick to the eye but move sufficiently during normal wear so that corneal metabolism will proceed normally.

The contact lenses are made from a copolymer containing poly(siloxane) monomers copolymerized with acrylic acid.

The monomers that may be used are collected in Table 1.16. Some of these monomers are shown in Figure 1.26.

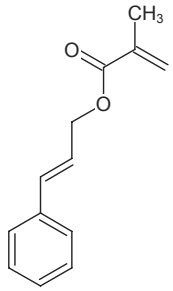
The monomers shown in Table 1.16 may be copolymerized in solution. A particularly preferred solvent is *p*-xylene. Poly(siloxane) monomers are collected in Table 1.17 and shown in Figure 1.27.

Table 1.16 Monomers (43).

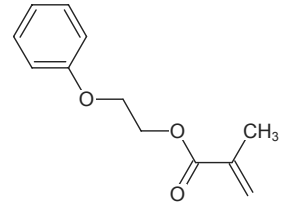
Compound	
Cyclohexyl acrylate	Cinnamyl methacrylate
Cinnamyl acrylate	Cyclohexyl methacrylate
Phenoxyethyl methacrylate	Phenoxyethyl acrylate
tert-butyl-styrene	Vinyl toluene
Methacrylic acid	Acrylonitrile
Allyl methacrylate	Allyl acrylate
N-Vinyl pyrrolidone	Isopropyl acrylate
Isoamyl acrylate	2-Chloroethyl methacrylate
Cyclopentyl acrylate	*n*-Decyl acrylate
Phenyl acrylate	Tetrahydrofurfuryl acrylate
Benzyl acrylate	Hexafluoroisopropyl acrylate
Naphthyl acrylate	

Table 1.17 Poly(siloxane) monomers (43).

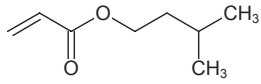
Compound
1,1,3,3-Tetramethyl-1,3-disila-2-oxacyclohexane
Octamethylcyclotetrasiloxane
1,3-Bis(4-methacryloxybutyl) tetramethyl disiloxane



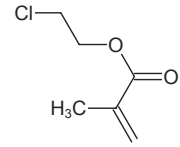
Cinnamyl methacrylate



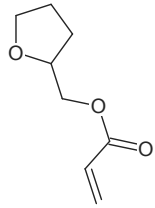
Phenoxyethyl methacrylate



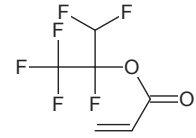
Isoamyl acrylate



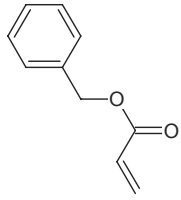
2-Chloroethyl methacrylate



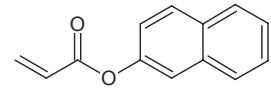
Tetrahydrofurfuryl acrylate



Hexafluoroisopropyl acrylate

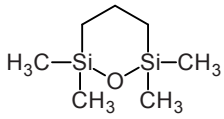


Benzyl acrylate

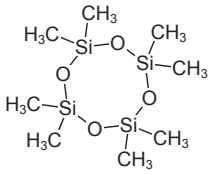


Naphthyl acrylate

Figure 1.26 Monomers.



1,1,3,3,-Tetramethyl-1,3-disila-2-oxacyclohexane



Octamethylcyclotetrasiloxane

Figure 1.27 Poly(siloxane) monomers.

The copolymerization of cyclic siloxanes was first presented in 1960 (44). These materials are copolymerized with silethylene siloxane, $-Si-O-Si-CH_2-CH_2-O-Si-$, and then the rates of polymerization are determined. The silethylene siloxane is used because it does not equilibrate between the ring form and the linear form. Once the ring form is broken the ring stays open, i.e., the reaction is kept going in one direction. The preparation of the materials can be done as follows (43):

Preparation 1–8: First, 96.9 *g* 1,1,3,3-tetramethyl-1,3-disila-2-oxacyclohexane and 3.1 *g* of 1,3-bis(4-methacryloxybutyl) tetramethyl disiloxane are charged in a 200 *ml* round-bottom polymerization flask. Then, 1.3 *ml* of trifluoromethanesulfonic acid, cf. Figure 1.28, are added to the polymerization flask and the flask is stoppered. An increase in the viscosity of the flask's contents and the evolution of heat are observed 2 *min* to 3 *min* after the addition of the acid to the flask. The contents of the flask are agitated on a shaker overnight.

Then, the polymerization is quenched by the addition of 10 *g* Na_2CO_3. Hexane is added to the viscous product and the solution filtered to remove the insoluble salts. The hexane solution of the product is then washed three times with water and dried over $MgSO_4$. The hexane is removed from the product at a reduced pressure. The viscosity of the product as measured with Gardner viscosity tubes is 910 *Stokes*. The number average and weight average molecular weights as measured by gel permeation chromatography (GPC) are 12.3 *k Dalton* and 31.7 *k Dalton* respectively.

Also, several other examples of preparation have been reported (43).

The oxygen transportability of poly(siloxane)s is substantially greater in comparison to the conventional contact lens polymers

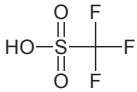


Figure 1.28 Trifluoromethanesulfonic acid.

such as PMMA or poly(2-hydroxyethyl methacrylate). The oxygen transportability of these materials can be varied by altering the percentage of siloxane units in the poly(siloxane) monomer. A high percentage of siloxane units results in a product that is more capable of transporting oxygen as compared with a lower percentage of siloxane units which results in a material with less ability to transport oxygen (43).

1.6 Bandage Contact Lenses

A bandage contact lens is used to protect an injured or diseased cornea from the mechanical rubbing of the blinking eyelids, therefore allowing it to heal (45). The bandage lens often makes the eye feel more comfortable, but has no focusing power. Usually a bandage contact lens is made from a soft lens material.

The materials employed as bandage contact lenses are basically those designed for use in the uncompromised eye for refractive contact lens purposes (46). Thus, there is an unmet challenge for therapeutic bandage lenses that are specifically designed for the injured (accident or surgery) or diseased cornea to aid healing.

1.6.1 Antimicrobial Bandage Contact Lens

Microbial adhesion to contact lenses is governed by many factors, including surface wettability, surface roughness and surface adhesion energy (47), and these factors differ substantially between silicone hydrogel contact lenses and conventional hydrogel contact lenses (48–50).

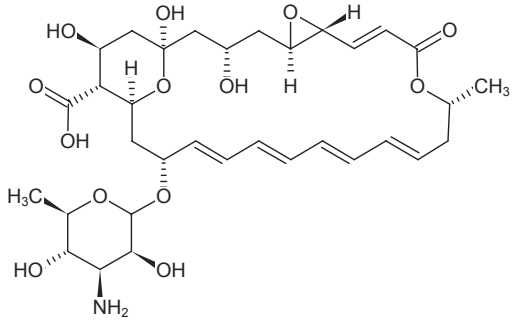
An antimicrobial bandage contact lens has been described wherein the antimicrobial bandage contact lens shields the eye from the environment while providing continuous long-term treatment (51).

The antimicrobial bandage contact lens can act as a prophylactic device that prevents microbial infections in an eye using inherently antimicrobial biomaterials with nanotopography. Furthermore, the antimicrobial bandage contact lens treats existing infection by dispensing antimicrobial medication at controlled rates over a period of up to 10 *d*. The antimicrobial bandage contact lens diminishes the risk of infection while simultaneously allowing damaged tissues to heal. The device allows the user to maintain vision to the extent allowed by the nature of the injury (51).

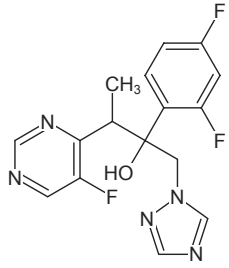
The antibacterial and antifungal surface is designed to be placed over the ocular lens to prevent ocular microbial infections while simultaneously delivering a drug at a controlled release rate that aids in healing of an injured or infected eye.

A transparent, therapeutic bandage material was designed that harnesses advanced nanotechnology to combine inherently antimicrobial biomaterials, antimicrobial nanoarchitectures, and an innovative biocomposite modality for antimicrobial drug delivery (51). The architecture of the antifungal bandage device contains three layers: A drug-eluting hydrogel-composite core layer sandwiched between two surface layers of lubricating hydrogel with antimicrobial nanopillars. The functions of the three layers are: The central layer of hydrogel-chitin composite provides structural and shape stability and strength, and acts as a reservoir for the long-term release of the antifungal and antibacterial drugs, and the outer layers provide wearability and antimicrobial shielding.

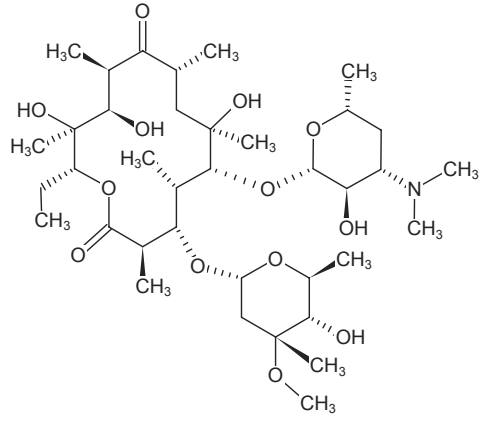
The ophthalmologic bandage must deliver antimicrobial drugs to the injured cornea. The current treatment for fungal keratitis involves hourly applications of topical agents such as natamycin that penetrate the posterior stroma to kill the hyphae. A mixture of drugs can also be coformulated for simultaneous delivery with natamycin, such as Voriconazole (2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H-1,2,4-triazol-1-yl)-2-butanol) or erythromycin (51). These compounds are shown in Figure 1.29.



Natamycin



Voriconazole



Erythromycin

Figure 1.29 Drugs.

1.7 Functional Contact Lenses

1.7.1 Remote Health Monitoring

The surface of the eye is an interface on which information may be gathered to determine the health status of patients (52). Tears are a source of biomarkers for ocular and systemic diseases (53–55).

The tear fluid contains a variety of biomarkers whose concentrations can be correlated to biologically important health markers, such as blood composition (52). Therefore, the detection of these biomarkers may provide a route towards noninvasive analysis of human health, with the help of a functional contact lens. Functional contact lenses are an emerging technology which provide a platform for the detection and analysis of biomarkers in the human tear (52).

Target biomarkers or target analytes that may be sensed by the biosensors used in the functional contact lenses described herein may be molecules that are within the precorneal tear, such as acids, ions, carbohydrates, proteins, enzymes, lipids, antigens, hormones, nucleic acids, small molecules, medications, or recreational drugs. Examples of such compounds are shown in Table 1.18 and in Figure 1.30.

In the functional contact lens at least one sensing element is disposed on the substrate for sensing a target analyte and undergoing a physical change representing a sensed signal. An antenna coupled to the sensing element is disposed on the substrate for transmitting the sensed signal to an external device (52).

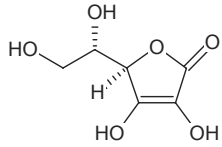
The opportunities afforded by using a functional contact lens for remote wireless health status monitoring were discussed and the progress to date in the development of this technology platform was detailed (56).

A functional contact lens complete with sensors and embedded circuitry can be used to monitor the composition of the tear fluid and, by extension, a number of health-status-related parameters in the body in a noninvasive and continuous fashion. The data collected by a disposable contact lens may be sent wirelessly to a mobile phone that, in turn, can relay the information to a medical practitioner via the cellular phone network.

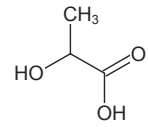
If successfully developed and deployed, such a system can be used for monitoring a variety of health indicators over a large geo-

Table 1.18 Target biomarkers (52).

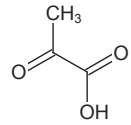
Compound	Compound
Ascorbic acid	Lactic acid
Pyruvic acid	Fructose
Glucose	Sucrose
Galactose	Maltose
Lactose	Lysozyme
Lipocalin	Cytokine
Albumin	Interleukins
Glycoproteins	Orosomucoid
Transferrin	Lactoferrin
Ceruloplasmin	Ferritin
Procalcitonin	Hexokinase
Aldolase	Triose phosphate isomerase
Phosphoglucose isomerase	Pyruvate kinase
Enolase	Lactic dehydrogenase
Citrate synthase	Aconitase
Phosphofructokinase	Phosphoglyceratemutase
Pyruvate dehydrogenase	Isocitric dehydrogenase
Succinate dehydrogenase	Fumarase
Matalate dehydrogenase	Peroxidase
Wax esters	Cholesterol
Cortisol	Catecholamines
Endorphins	Insulin
Ibuprofen	Acetaminophen
Alrex	Betaxon
Besivance	Cosopt
Lucentis	Metformin
Adriamycin	Adrucil
Cytoxan	Ethyol
Psychedelics	Barbiturates
Benzodiazepines	Amphetamines



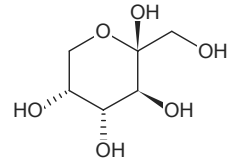
Ascorbic acid



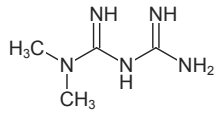
Lactic acid



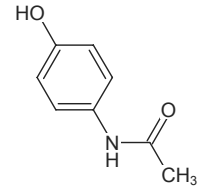
Pyruvic acid



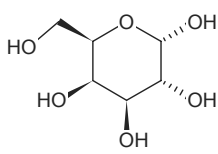
Fructose



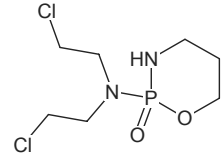
Metformin



Acetaminophen

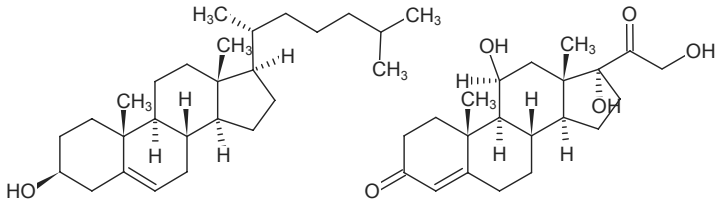


Galactose

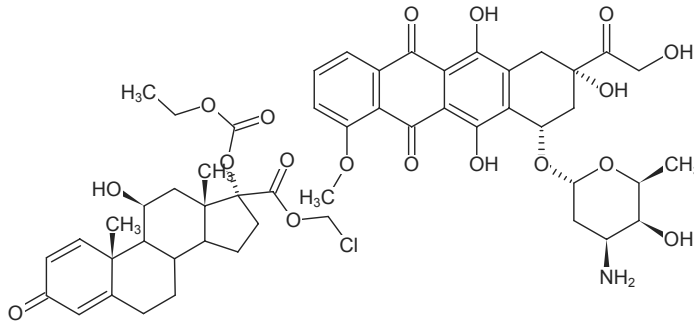


Cytoxan

Figure 1.30 Target biomarkers.

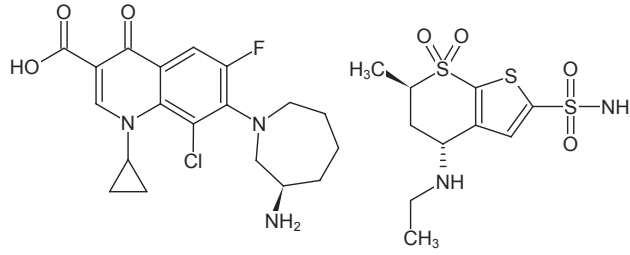


Cholesterol Cortisol

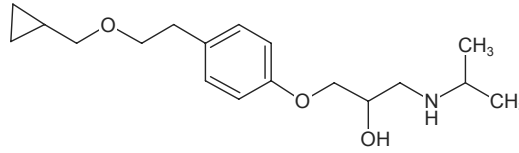


Alrex Adriamycin

HCl



Besivance Cosopt



Betaxon

Figure 1.30 (cont) Target biomarkers.

graphic area and population distribution with a minimal need for the physical presence of healthcare providers (56).

1.7.2 Graphene Oxide Nanocolloids

The physical properties of contact lenses made by adding hydrophilic HA and MA as additives, and graphene oxide nanocolloids were evaluated (57).

For the synthesis of a contact lens, 2,2´-azobisisobutyronitrile was used as an initiator with HEMA and EGDMA as crosslinking agent. HA and MA were both added at 5%. Graphene oxide nanocolloids were added at 0.1%, 0.3% and 0.5%, respectively. Each prepared contact lens was hydrated in 99% NaCl saline solution for 24 *h* (57).

The basic physical properties of these contact lenses were evaluated and compared. The refractive index of the sample with HA and MA added was 1.4390, which was not significantly different from that of the basic combination contact lens sample. When graphene oxide nanocolloids, a nanomaterial, were added, the refractive index decreased with increasing amount of graphene oxide nanocolloids from 1.4209 to 13959. In the case of water content, the sample with 5% HA and MA added slightly increased to 41.01%. In the case of graphene oxide nanocolloids added, 48.76% to 53.56% of graphene oxide nanocolloids were added.

Especially, it was observed that the water content increased sharply in the 0.1% sample of graphene oxide nanocolloids. When the amount of graphene oxide nanocolloids added to the contact lens material was increased, the refractive index, which is a basic physical property, gradually decreased as the contact lens material was added together with HA, MA, and graphene oxide nanocolloids added as a nanomaterial. The water content tended to increase gradually.

Therefore, the combination of graphene oxide and hydrophilic materials shows a synergistic effect of physical properties, which is considered to be suitable as a material for contact lenses (57).

1.7.3 Diabetic Diagnosis

1.7.3.1 Tear Glucose Analysis

A contact lens is an ideal vehicle for continuous tear glucose monitoring of glucose concentration in the tear film (58).

An approach for noninvasive monitoring of the concentration of blood glucose is to monitor the glucose concentrations in the human tear fluid. The understanding of the physiology of glucose transport in tears has been assessed, in addition to the regulation of the aqueous tear fraction (53).

The various tear collection methods employed greatly influence the measured tear glucose concentrations. Studies that involve mechanical irritation of the conjunctiva during sampling measure the highest tear glucose concentrations, while studies that avoid tear stimulation measure the lowest concentrations.

Attempts to monitor tear glucose concentration *in situ* by using contact lens-based sensing devices were discussed. These studies indicate the importance of the sampling method in determining tear glucose concentrations (53).

A methodology has been reported for possible tear glucose monitoring using glucose-sensitive silicone hydrogel contact lenses. An interpenetrating polymer network was assessed, with nearly pure silicone and water regions existing in the silicone hydrogels, using the polarity-sensitive probe Prodan, cf. Figure 1.31.

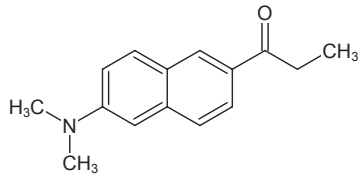


Figure 1.31 Prodan (1-(6-(Dimethylamino)naphthalen-2-yl)propan-1-one).

Then, a glucose-sensitive fluorophore Quin-C18 was synthesized with a hydrophobic side chain for localization of probe at the interfacial region. The synthesis of Quin-C18 is shown in Figure 1.32.

Here, glucose is bound to the boric acid moieties of Quin-C18.

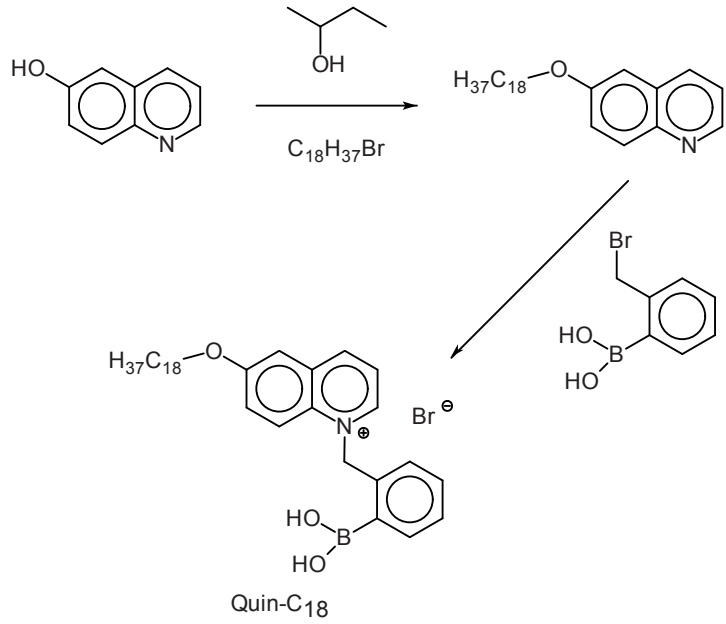


Figure 1.32 Synthesis of Quin-C18.

Using the glucose-sensing contact lens, it was possible to measure varying concentrations of glucose in an *in-vitro* system. The Quin-C18 strongly bound to the lenses with insignificant leaching even after multiple rinses. The lenses displayed a similar response to glucose after three months of storage in water. So the study demonstrated that it may be possible to develop a contact lens for continuous glucose monitoring in the near term, using the concept of fluorophore binding at the silicone-water interface.

1.7.3.2 Wireless Smart Contact Lenses

A smart contact lens can be used as an excellent interface between the human body and an electronic device for wearable healthcare applications (59). Despite wide investigations of smart contact lenses for diagnostic applications, hitherto there has been no report on electrically controlled drug delivery in combination with real-time biometric analysis.

Smart contact lenses were developed for both continuous glucose monitoring and the treatment of diabetic retinopathy. The smart contact lens device, built on a biocompatible polymer, contains ultrathin, flexible electrical circuits and a microcontroller chip for real-time electrochemical biosensing, on-demand controlled drug delivery, wireless power management, and data communication.

In diabetic rabbit models, tear glucose levels could be measured and compared by the conventional invasive blood glucose tests. So the feasibility of smart contact lenses for noninvasive and continuous diabetic diagnosis and diabetic retinopathy therapy was confirmed (59).

1.7.3.3 Capacitive Sensing

Certain medical conditions or states can be characterized by slow changes of a physiological property, e.g., a blood glucose concentration, over long periods of time by infrequent, short time scale events (60). Such physiological properties can be measured periodically.

An implanted or wearable device can be employed to provide a continuous or near-continuous measurement of such physiological properties. Such implantable or wearable devices can be battery

powered or powered by radio frequency energy or other wireless energy sources. Furthermore, such devices can be configured to indicate measured physiological properties wirelessly, e.g., by using an RFID antenna and transmitter or a Bluetooth antenna and transmitter (60).

An eye-mountable device has been described (60). The eye-mountable device includes a substrate, a capacitance sensor disposed proximate to the substrate, and a controller disposed proximate to the substrate. The substrate is at least partially embedded within a shaped polymeric material.

The capacitance sensor includes at least two sensor electrodes. At least one sensor electrode of the two sensor electrodes is operable to carry out an additional function. The controller is communicatively coupled to at least two of the sensor electrodes. The controller is configured to receive data indicative of a change in mutual capacitance between the two sensor electrodes. The controller is further configured to detect an eye-related movement based on the change in mutual capacitance being greater than a threshold capacitance. The controller is also configured to produce a signal in response to detecting the eye-related movement.

The method of measuring includes receiving data indicative of a change in mutual capacitance between at least two sensor electrodes of a capacitance sensor (60). At least one sensor electrode of these two sensor electrodes is operable to carry out an additional function. The capacitance sensor is disposed proximate to a substrate. The substrate is at least partially embedded within a shaped polymeric material. The shaped polymeric material is configured to be mounted proximate to an eye.

Such a sensor may be operable to measure a level of glucose in the tear fluid.

The method also includes detecting an eye-related movement based on the change in mutual capacitance being greater than a threshold capacitance. The method further includes producing a signal in response to detecting the eye-related movement.

The detection of the eye-related movement may be useful to trigger an electrochemical sensor reading of a glucose level or another type of sensor reading or action. For example, a detected eye-related movement may cause a display to indicate a measured value, which

may relate to a value of the analyte measured by the electrochemical sensor. Alternatively, the detection of an eye-related movement may trigger a communication signal to other components of the eye-mountable device or another device.

A block diagram of such a sensor is shown in Figure 1.33.

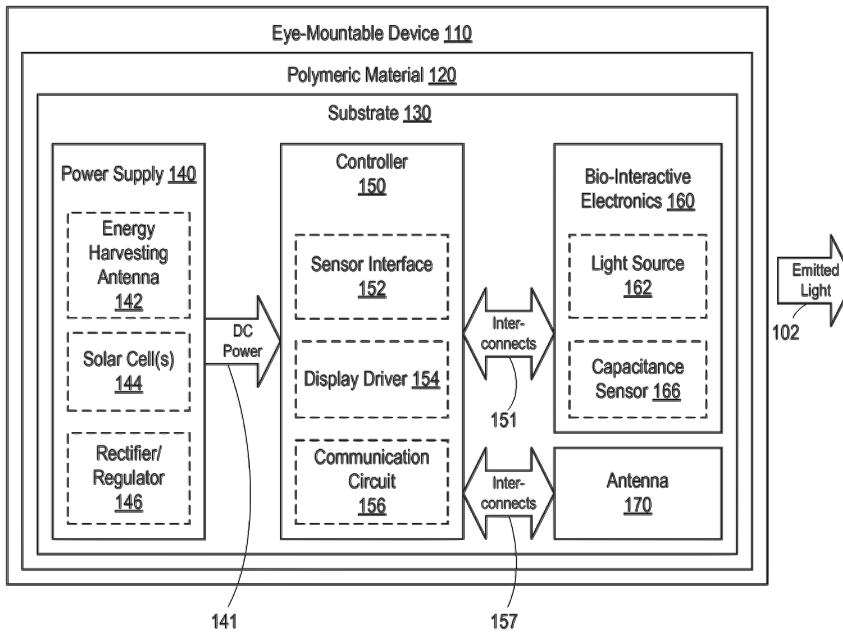


Figure 1.33 Block diagram of sensor (60).

The exposed regions of the eye-mountable device 110 are made of a polymeric material 120 formed to be contact-mounted to a corneal surface of an eye. A substrate 130 is embedded in the polymeric material 120 to provide a mounting surface for a power supply 140, a controller 150, bio-interactive electronics 160, and an antenna 170. The bio-interactive electronics 160 are operated by the controller 150. The power supply 140 supplies operating voltages to the controller 150 and/or the bio-interactive electronics 160. The antenna 170 is operated by the controller 150 to communicate information to and/or from the eye-mountable device 110, e.g., to communicate with an external device. The antenna 170, the controller 150, the power supply 140, and the bio-interactive electronics 160 can all be situated on the embedded substrate 130. Alternatively, one or more of the

elements of the eye-mountable device 110 may be situated on a plurality of substrates 130 embedded within the polymeric material 120. Because the eye-mountable device 110 includes electronics and is configured to be contact-mounted to an eye, it is also referred to herein as an ophthalmic electronics platform.

The power supply 140 is configured to harvest energy to power the controller 150 and bio-interactive electronics 160. For example, a radio frequency energy harvesting antenna 142 can capture energy from incident radio radiation, for example, from an external device. Additionally or alternatively, solar cells 144 (*photovoltaic cells*) can capture energy from incoming ultraviolet, visible, and/or infrared radiation. Furthermore, an inertial power scavenging system can be included to capture energy from ambient vibrations. The energy-harvesting antenna 142 can optionally be a dual-purpose antenna that is also used to communicate with an external device. That is, the functions of the communication antenna 170 and the energy-harvesting antenna 142 can be accomplished with the same physical antenna.

The controller 150 includes a sensor interface module 152 that is configured to receive data from the capacitance sensor 166. Based on the data received by the sensor interface module 152, the display driver 154 may cause the light source 162 to generate an indication related to information received from the capacitance sensor 166 (60).

1.7.4 Target Analyte Sensing

Functional contact lenses for detecting at least one target analyte contain a substrate for supporting electronic components and provide a structural support for the functional contact lens (61). At least one sensing element is disposed on the substrate for sensing at least one target analyte and undergoes a physical change representing a sensed signal. Furthermore, an antenna is disposed on the substrate for transmitting the sensed signal to an external device, the antenna being coupled to the sensing element.

Target biomarkers or target analytes that may be sensed by the biosensors used in the functional contact lenses may be molecules that are within the precorneal tear, such as acids, ions, carbohydrates, proteins, enzymes, lipids, antigens, hormones, nucleic acids, small molecules, medications, and recreational drugs.

Specific compounds are collected in Table 1.19 and some hormones are shown in Figure 1.34.

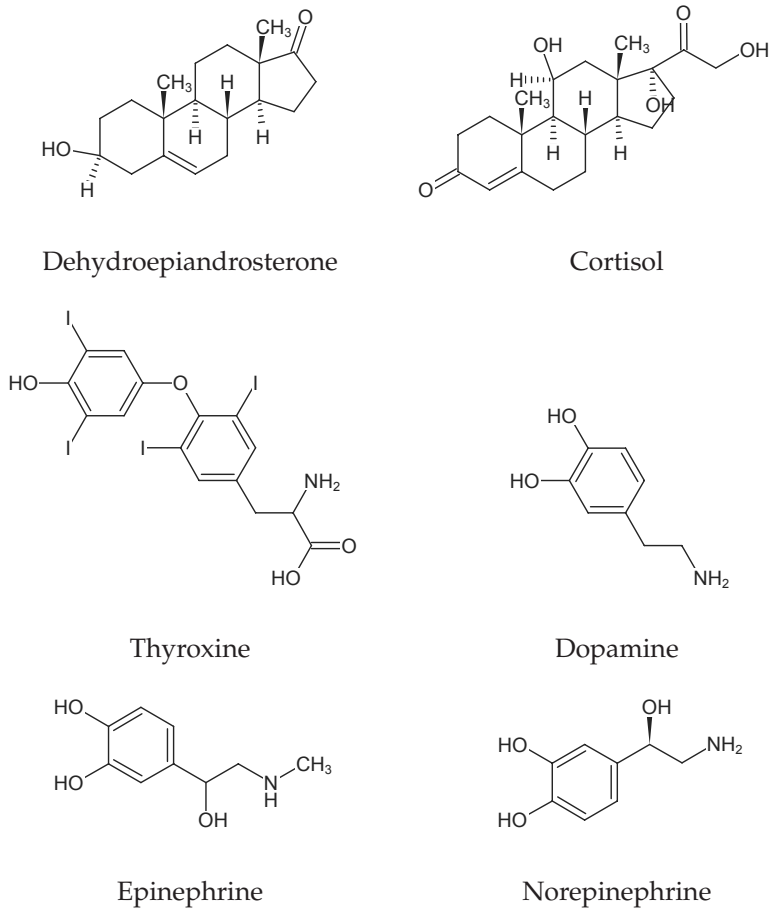


Figure 1.34 Hormones.

A schematic view of a chipless functional contact lens is shown in Figure 1.35.

Here, the functional contact lens does not have any integrated circuits or devices for processing, sensing, communication, or power. Instead, the sensing element is coupled with the antenna. The sensing element is a one-electrode system that uses a working electrode. The antenna may have one or more loops. When the antenna is

Table 1.19 Examples of target analytes (61).

Acids	Ions
Ascorbic acid	Calcium
Lactic acid	Potassium
Pyruvic acid	Sodium
Uric acid	Magnesium
Carbohydrates	**Proteins**
Fructose	Lysozyme
Glucose	Lipocalin
Sucrose	Cytokine
Galactose	Lipocalin
Maltose	Albumin
Lactose	Orosomucoid
Enzymes	**Lipids**
Hexokinase	Wax esters
Aldolase	Sterol esters
Pyruvate kinase	Polar lipids
Enolase	Hydrocarbons
Citrate synthase	Diesters
Aconitase	Triglycerides
Phosphofructokinase	Free sterols
Phosphoglyceratemutase	Free fatty acids
Pyruvate dehydrogenase	
Isocitric dehydrogenase	
Succinate dehydrogenase	
Fumarase	
Matalate dehydrogenase	
Transketolase	
Transaldolase	
Antigens	**Hormones**
Adenoviruses	Cortisol
Staphylococcus bacteria	Catecholamines
Streptococcus bacteria	Endorphins
Hemophilus influenza bacteria	Insulin
Chlamydia	Dehydroepiandrosterone
Gonorrhea	Thyroxine
	Epinephrine
	Dopamine

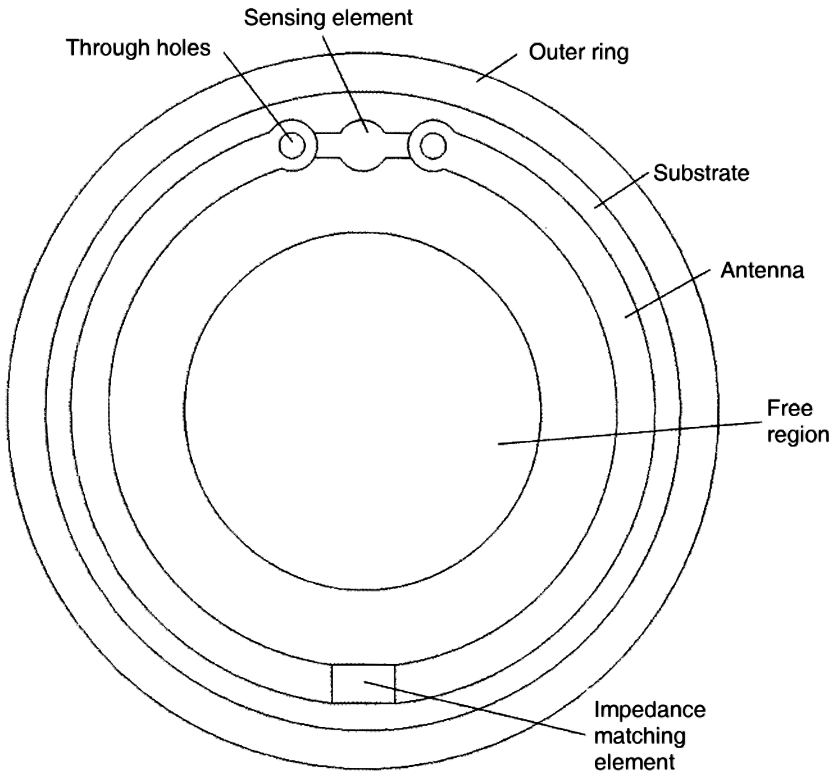


Figure 1.35 Chipless functional contact lens (61).

multilayered, then vias or through-holes may be used to vertically physically couple portions of the antenna that are on different layers of the substrate.

The sensing structure may be a biosensor, which may be an artificial enzymatic biosensor or an artificial non-enzymatic biosensor. Other types of sensors that may be used include label-free electrochemical immunoassay.

The thickness of the functional contact lens may be about 300 μm in order to reside inside the basal tear film of the user's eye for comfort. The periphery of the functional contact lens may be made of soft hydrogel material to maximize the wearing comfort for the user.

The tear film is a complex functional layer which protects the eye from infection and provides nutrition to the cornea. The tear film is about 7 μm thick and consists of three layers (62):

1. A thin mucin layer,
2. A thick middle aqueous layer, and
3. A thin lipid surface layer [1].

Tears have been shown to contain lipids, mucins, ions, proteases, immunoglobulins, catecholamines, endorphins, and multiple other small molecules (62).

The close compositional similarity, cf. Table 1.20, between blood and tears enables the detection and the management of multiple medical conditions.

Table 1.20 Common species in tears and blood (61).

Marker	Tear/[mM]			Blood/[mM]		
Na^+	120	–	165	130	–	145
K^+	20	–	42	3.5	–	-5
Ca^{2+}	0.4	–	1.1	2.0	–	2.6
Mg^{2+}	0.5	–	0.9	0.7	–	1.1
Cl^-	118	–	135	95	–	125
HCO^{3-}	20	–	26	24	–	30
Glucose	0.1	–	0.6	4	–	6
Urea	3.0	–	6.0	3.3	–	6.5
Lactate	2	–	5	0.5	–	0.8
Pyruvate	0.05	–	0.35	0.1	–	0.2
Ascorbate	0.008	–	0.04	0.04	–	0.06

A cortisol sensor has been formed using a graphene field-effect transistor that can measure cortisol concentration with a detection limit of 10 $pg\,ml^{-1}$, which is low enough to detect the cortisol concentration in human tears (63).

This soft contact lens only requires the integration of the cortisol sensor with transparent antennas and wireless communication circuits to make a smartphone the only device needed to operate the lens remotely without obstructing the wearer's view. *In-vivo* tests using live rabbits and the human pilot experiment confirmed the good biocompatibility and reliability of this lens as a noninvasive, mobile healthcare solution (63).

1.7.5 Adaptive Tuning

An augmented reality system including a source and a contact lens display can be used to project information from the contact lens display onto the retina of the wearer's eye (64). The source provides energy to the contact lens display and operates at a source frequency.

The source includes a source circuit including a conductive coil. The contact lens display includes a resonant circuit including another conductive coil and a capacitive circuit. The resonant circuit receives energy from the conductive coil of the source via a magnetic field, inductively coupling the conductive coils. The contact lens display additionally includes a feedback circuit to adjust the capacitance of the capacitive circuit to control a resonant frequency of the resonant circuit. The feedback circuit can control the capacitive circuit to maintain the resonant frequency of the resonant circuit near the source frequency as the wearer's eye blinks. The contact lens contains (64):

1. A resonant circuit including:
   (a) A first conductive coil to receive energy from an external source via inductive coupling, and
   (b) A capacitive circuit coupled parallel with the first conductive coil, the capacitive circuit having a capacitance that is adjustable to control a resonant frequency of the resonant circuit of the contact lens.
2. A contact lens display, and
3. A load coupled parallel with the first conductive coil and the capacitive circuit, the load consisting of:

(a) A projector to project images from the contact lens display towards a human retina based on data received wirelessly by the contact lens display, and
(b) An energy recovery circuit to recover energy from the resonant circuit and provide power for the projector.

A time-varying magnetic field is generated from a necklace, i.e., a source, worn about the neck of the wearer of the augmented reality system (64). The necklace includes a conductive coil and a time-varying current source, which generates a time-varying magnetic field.

The source provides energy to the contact lens display via the time-varying magnetic field, thereby resulting in wireless power transfer between the source and the contact lens displays. The contact lens display includes a resonant circuit with a conductive coil inductively coupled to the conductive coil of the necklace via the time-varying magnetic field.

The inductive coupling between the source and the resonant circuit allows energy generated by the source to be transferred to the contact lens display. The contact lens display recovers energy from the inductively coupled source and resonant circuit.

However, as the environment of the eye changes, e.g., the wearer's eye blinks, the eyeball rotates, the temperature changes, or the eyeball generates tears, the efficiency of the power transfer between the source and the resonant circuit fluctuates. Accordingly, the resonant circuit of the augmented reality system can include a tunable capacitance that can be adjusted to increase the efficiency of the power transfer.

Generally, constantly tuning the resonant circuit works to maximize the voltage across the resonant circuit and increase the efficiency of power transfer between the source and the resonant circuit. However, at times, the efficiency of power transfer is not maintained at maximum levels for any number of reasons, i.e., misalignment between the source and the contact lens display (64).

1.7.6 Wireless Communication

Developments in mobile communications combined with the increasing computing power have enabled significant processing and

rich real-time feedback to be employed within wearable device systems (65). Advances in miniaturization have further enhanced wearables by allowing electronic devices and sensors to be located on a human in a continually shrinking footprint. For example, a wearable miniaturized device may be implemented within a contact lens to provide a variety of functions, including the ability to communicate with other peripheral accessory devices proximate to the contact lens.

A device for communicating data with a contact lens through a communication interface has been presented (65). Here, an accessory device identifies one or more wireless channels to communicate with a contact lens. The scheduling of this wireless communication is performed such that a preferred channel is selected based on noise and/or interference. A centralized scheduler, such as a Wi-Fi access point, can be used to reserve the preferred channel within the associated wireless network so that clients within the network do not use this channel.

A general illustration of a secure electronic contact lens system is shown in Figure 1.36.

The electronic contact lens contains a contact lens material, a projector and one or more electronic modules (65). The contact lens material may be made from relatively rigid material that provides sufficient structural support for mounting the electronic modules on the contact lens. The projector may be a femtoprojector, which is a miniaturized video or image projector, and may couple with the modules that are electronic circuits and devices, such as a transceiver circuit, sensors, and data processing devices. The modules may perform a variety of functions, some or all of which may require the wireless communication of data between an accessory device and the contact lens.

A schematic diagram of an accessory device is shown in Figure 1.37.

The accessory device may remain in a sleep mode to reduce the energy consumption and wake up to start communication with the contact lens via a communication interface. When the accessory device wakes up, the interference determination unit may scan the communication environment to map the noise and interference within its environment.

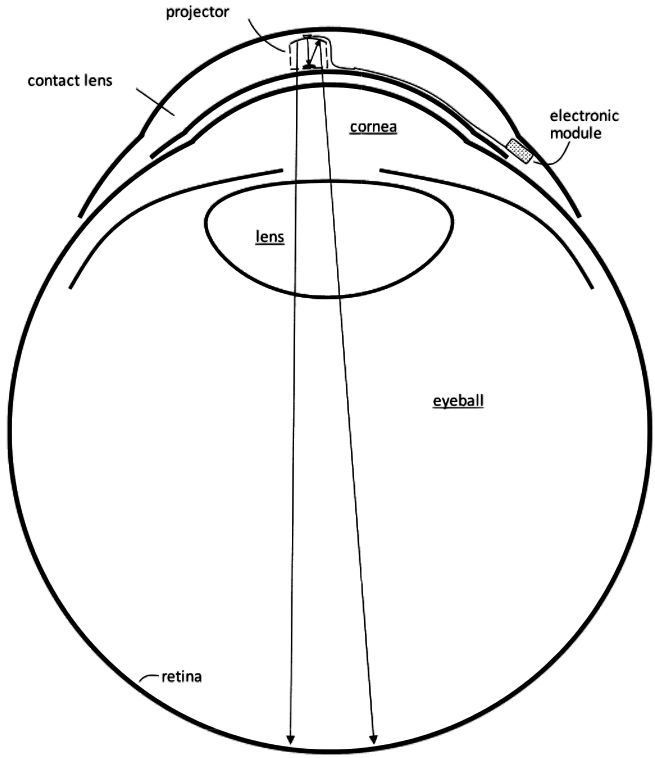


Figure 1.36 Electronic contact lens system (65).

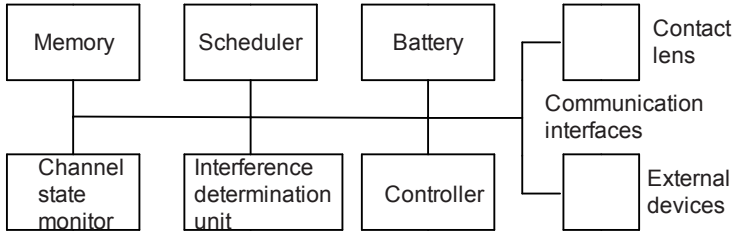


Figure 1.37 Accessory device (65).

Also, the interference determination unit may check for each Wi-Fi channel, whether the channel is not being used using signals received through a communication interface, and, if the channel is used, the interference determination unit may determine the level of interference in the channel.

The scheduler within the accessory device schedules the transmission of data on both the uplink and downlink of the wireless channel. This scheduling will depend on various factors, including the interference pattern within the channel and the sensitivity of the data to be transmitted. In performing this scheduling operation, a coordinator may communicate with other external device(s) that are also transmitting wireless signals within the area (65).

The accessory device may have multiple antennas to do the signal transmission.

The scheduler may select a channel and send the data to the contact lens in two steps:

1. The Wi-Fi manager 320 may send a control signal through the control channel, where the control data may notify the contact lens of the time slot during which the contact lens can anticipate data from the accessory device, and
2. The Wi-Fi manager may transmit data to the contact lens through the data channel during the notified time slot. In embodiments, the control channel may be the same as the data channel.

Figure 1.38 shows a schematic diagram of a beam pattern generated by an accessory device.

The accessory device may have multiple transmission antennas and use the antennas in such a way that the transmission signals from the antennas experience constructive interference at particular angles.

The left lobe shows the power distribution of the left downlink signal over an azimuthal angle, where the lobe is directed toward the left contact lens. Using the beamforming technique, the accessory device may use less power to deliver the signal compared to a omnidirectional transmission. The same is true for the right eye. Alternatively, the accessory device may generate one lobe for each contact lens at a point in time if both contact lenses cannot be cov-

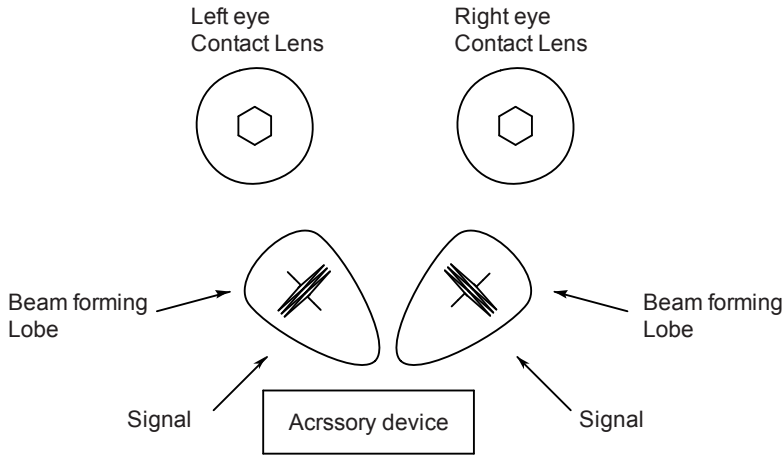


Figure 1.38 Beam pattern generated by an accessory device (65).

ered by one lobe. Otherwise, the accessory device may generate a single lobe to transmit a signal to both contact lenses (65).

1.7.7 Glucose Biosensors

Glucose detection using a biosensor can be categorized into either optical or electrochemical methods (66). Examples are shown in Table 1.21.

Table 1.21 Glucose biosensors developed for contact lenses (66).

Mode of detection	Glucose sensor	Reader	Reference
Fluorescence	Boronic acid, Concanavalin A	External detector	(67)
Colorimetric	Boronic acid	Color chart	(68)
Fluorescence	Boronic acid	Photodetector	(69)
Fluorescence, colorimetric	Boronic acid, Concanavalin A	External detector	(70)
Fluorescence, colorimetric	Boronic acid, Concanavalin A	Photodetector	(71)
Fluorescence	Boronic acid, Concanavalin A	External detector	(72)
Light emitted	Boronic acid	Photodetector	(73)
Electrochemical	Boronic acid	Electrode	(74)
Fluorescence, luminescence	Boronic acid	External reader	(75)
Light emitted	Boronic acid	Smartphone	(76)
Optical	Boronic acid	External reader	(77)
Absorbance	Concanavalin A	Spectrophotomer	(78)
Fluorescence	Concanavalin A	Handheld photofluorometer	(79)
Fluorescence	Concanavalin A	Handheld photofluorometer	(80)
Electrochemical	Glucose oxidase	Electrode	(81)
Electrochemical	Glucose oxidase	Handheld reader or smartphone	(82)
Electrochemical	Glucose oxidase	External receiver	(83)
Electrochemical	Glucose oxidase	On lens display	(84)
Electrochemical	Metal oxides	External receiver	(61)

Boronic acids are reversibly binding to carbohydrates. They show unique optical properties when bound to glucose, resulting in a colorimetric change or a change of fluorescence.

Concanavalin A is a lectin or carbohydrate binding protein. It is originally extracted from the jack bean (*Canavalia ensiformis*). In the absence of glucose, concanavalin is bound to a ligand, such as fluorescein-labeled dextran, and so shows a minimal fluorescence. In the presence of glucose, the ligand is displaced and instead glucose binds to concanavalin, resulting in an increase of the fluorescence.

1.7.8 Cancer Detection

It was found that the tear film is well suited to the detection of cancer biomarkers since it is less biologically complex than blood (85, 86). In addition, tear sampling is a relatively noninvasive method in comparison to the collection of blood samples (66).

In the early work in the detection of cancer in a tear film, the presence of a tear film protein called lacryglobin was detected (87).

Lacryglobin has similarities to mammaglobins upregulated in breast cancer (88). Lacryglobin is present in the tear film of patients with colon, lung, breast and prostate cancer, as well as patients with a family history of cancer (89).

Time-of-flight mass spectroscopy was used to compare the tear film of cancer patients and healthy controls, identifying differences in 20 tear film biomarkers (90–92).

1.8 Scleral Contact Lenses

Modern scleral lenses are a potentially life-changing technology (93). The growth in the scleral lens market and in the number of speciality contact lens practitioners in recent years (94) demonstrates their utility in the therapeutic treatment of ocular surface disease, the visual restoration of the irregular cornea, and the correction of simple refractive errors in patients who have normal corneas.

A theoretical model based on the Harvitt-Bonanno criteria was first developed in 2012 (95) and was soon followed by another model using a mathematical approach (96).

Both models suggested that scleral lenses may generate hypoxia-related stress in the central cornea if the lens material has limited

oxygen permeability and if the lens is designed such that it has increased thickness and results in increased tear fluid reservoir thickness. Consequently, both authors recommended that scleral lenses should be manufactured in high oxygen permeable materials (D_k greater than 150), with a maximum thickness of 250 μm and fitted with a central tear reservoir of 200 μm or less.

For these models some questions were raised about their clinical significance (97), in particular in light of the favorable outcomes regularly encountered in clinical practice under adverse conditions (98, 99).

It was also suggested that in the absence of obvious clinical signs, any hypoxia-related ocular sequelae would be minimal. However, clinical studies were needed to determine a correct approach (93). Hypoxia is a condition in which the body or a region of the body is deprived of adequate oxygen supply at the tissue level (100).

Any scleral lens can and should be fitted to minimize a hypoxia-related stress. This means limiting lens thickness, increasing material oxygen permeability, limiting the tear reservoir depth, and, for certain patients, limiting the wearing time (93).

It was suggested that the lens thickness, and not the tear reservoir depth, was the significant factor leading to hypoxia-related stress (101).

However, this is contrary to current theoretical modeling derived from the understanding of the permeability of fluids and solutions (102). However, if true, it is imperative to collaborate with manufacturers to produce thinner lens designs (93).

1.8.1 Fabrication of Scleral Lenses

Soft contact lenses have been limited in their ability to correct irregular refractive errors because the soft lens material is deforming and takes the irregular shape of the underlying eye (103).

Furthermore, rigid contact lenses have been limited in their use due to the complexity of fitting the lenses, the difficulty in reducing or eliminating the pressure of the rigid lens material on the underlying eye, and the problems relating to stagnation of the post-lens tear environment.

Hybrid bimodulus contact lenses with a rigid gas-permeable material surrounded by a soft flexible material have solved some of the

problems associated with rigid and soft contact lenses. However, lens flexure and the need to fit the lenses with a curvature that is substantially shorter in radius of curvature than the underlying eye are challenges to hybrid lens success. Furthermore, in some cases the soft peripheral skirt of hybrid lenses fails to elevate the rigid central zone above the cornea and the resultant bearing of the rigid gas-permeable material on the cornea is reported to cause discomfort and lens intolerance.

Because of the uncurving nature of the sclera near the limbus, often neither a concave downward curve nor an uncurved landing zone can contact the sclera at just inside the lens edge to accomplish appropriate edge lift without impinging on the more peripheral sclera to the point of penetration. Such landing zone curves may cause the entire lens to be supported further above the cornea and contact the sclera with a very narrow support zone.

To solve the abovementioned problems, scleral lenses have been designed. These lenses have a central zone and at least one peripheral zone defined by an angle (103).

Here, a peripheral zone is curved in either a concave or convex direction or is uncurved. In an exemplary embodiment, the angle for a plurality of semi-meridians or transverse sections can be varied to create a transverse undulation of a peripheral zone. These scleral lenses do not demonstrate excessive pressure on the sclera and allow for post-lens tear exchange.

The lens can be made from fluorosilicon acrylate, silicon acrylate, polymethylmethacrylate, a silicon hydrogel, or other suitable materials. In general, any gas-permeable, biocompatible material is suitable for use herein (103).

An illustration of a lens manufacturing system is shown in Figure 1.39.

The lens manufacturing system includes a controller, a lathe, and a scleral lens (103). The controller is a computer system, such as a data processing system. The controller causes the lathe to apply a modification to the scleral lens.

The tool is an object that removes material from the scleral lens when the lathe is rotating the scleral lens and the tool is in contact with the posterior surface of the scleral lens. The controller also causes the tool to move in some directions according to instructions

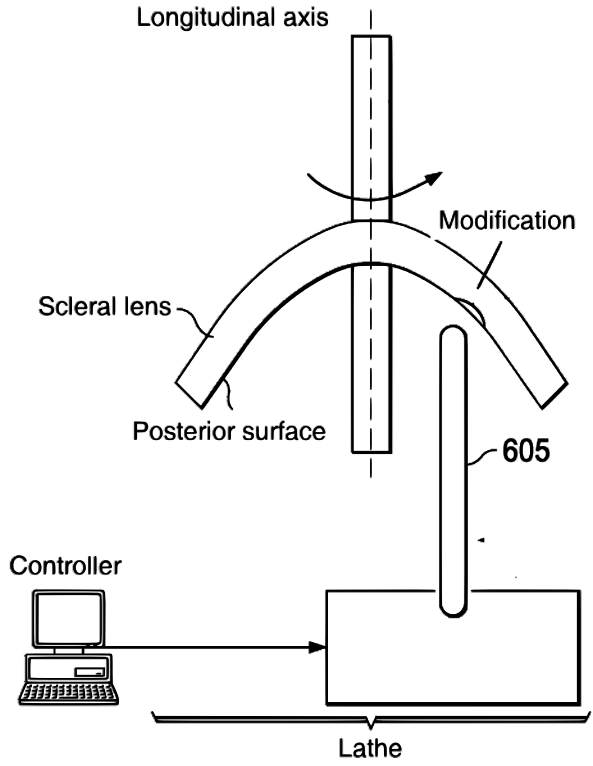


Figure 1.39 Lens manufacturing system (103).

received by the controller. For example, the controller may receive a plurality of computer numeric control codes.

The process of fabrication starts by generating an optical coherence tomography scan of an eye to identify the shape of the eye. The process then generates dimensions for the scleral portion of the scleral lens that correspond to the shape of the eye. Then the process performs wavefront aberrometry on the eye to identify alterations to wavefronts of light traveling through the areas of the pupil of the eye to generate measurements (103).

The process then identifies the differences in optical paths traveled by wavefronts of light entering the pupil at different points using the measurements and Zernike polynomials (104). The differences in optical paths are differences in optical path lengths (103). The process then identifies the differences in optical paths for additional areas of the pupil using the differences identified for the points. The process then generates modifications to the thickness of the posterior surface of a scleral lens that equalize the differences in optical paths. Next, the process generates computer numeric controlled instructions corresponding to the dimensions and the modifications. The process then applies the modifications to the scleral lens using a computer numeric controlled lathe. Thereafter, the process terminates (103).

1.8.2 Scleral Lens Fitting

A recent study evaluated the practitioner learning curve when fitting scleral lenses in 85 subjects using a diagnostic lens fitting (105).

Here, scleral lenses were fit by a single licensed optometrist who did not have a history of clinical experience fitting scleral lenses. In this study, the initial trial lens was selected based on the manufacturer's guidelines, severity of the corneal condition and clinical evaluation of the ocular surface.

Corneal topography, simulated keratometry measurements and corneal asphericity of the flat and steep corneal meridians were analyzed for each group. Objective measurements, such as scleral topography and ocular coherence tomography, were not utilized (106).

1.8.3 Ocular Drug Delivery Systems

Eyedrops are the standard method for delivering medications to the front of the eye. Eyedrops for long-term use have the same risk of any chronic patient-administered medication, requiring treatment adherence (107).

Scleral lenses provide a protected environment in which the corneal surface is continuously bathed in preservative-free fluid. These lenses are inherently stable to provide lasting ocular penetration of a drug. The main detriments of scleral lenses include handling and cost, along with a variety of other complications (108).

Various publications have reported the use of scleral lenses as ocular drug delivery systems. Treatment of corneal infiltrates with topical fortified non-preserved antibiotics in the bowl of the lens has been described (109).

Also, preservative-free antibiotics in the bowl of the scleral lens worn continuously to treat persistent epithelial defects has been reported (110).

Anti-VEGF agents have been used in the bowl of a scleral lens to treat corneal neovascularization (111, 112). The use of stem cells on a scleral lens carrier for management of a chemical burn in an animal model has also been described (113).

1.9 Multifocal Contact Lenses

The state of scientific publications concerning the multifocal contact lenses field was analyzed with a bibliometric study (114). A total of 346 articles were published between 1960 and 2019. The growth in the number of publications matches the exponential adjustment slightly better. The duplication time was found to be 13.2 years.

So, the research on multifocal contact lenses is seeing exponential growth, without evidence of having reached a saturation point. The main countries for scientific production in this field are the United States and Australia (114).

1.9.1 Bifocal Contact Lenses

Bifocal lenses contain two or more areas or zones, with different optical powers, typically including a far-power optic zone for distance

vision, and a near-power optic zone for near or close-up vision (115). The two zones may be subdivided into additional power zones, in which case a lens may be called a multifocal lens. Previously known multifocal lenses have been limited by known manufacturing apparatus, such as, for example, cast-molding, standard lathing or tooling technology, and injection molding technology.

The retinal image and the visual percept that results from it are dependent upon the light that enters an eye through the entrance pupil. In order for a bifocal contact lens to function properly, the entrance pupil must be covered at least partly or, more effectively, completely by the distance-power zone of a lens when an eye observes a distant object, and covered at least partly or, more effectively, completely by a near-power zone of a lens when an eye observes a near object. This function may be accomplished by the principle of alternating vision in which a shifting action or translation of a contact lens is made to occur in order to place one or the other zones in front of the entrance pupil as an eye alternates between viewing distant and near objects (115).

Alternatively, a principle known as simultaneous vision may be utilized whereby a lens is designed and fitted in such a way as to position part or all of both the far- and near-power zones in front of the entrance pupil at the same time so that each contributes to the retinal image simultaneously. There is little or no translation required with this type of lens; however, as a consequence two images are seen simultaneously, compromising vision.

Generally, the two types of conventional bifocal contact lenses are segmented and concentric. Segmented bifocal contact lenses or translating contact lenses, generally have two or more divided optical power zones. A far-power zone is usually the upper zone and a near-power zone is usually the lower zone. With such a translating lens, a far-power zone of a lens is in front of the entrance pupil of an eye in straight-ahead gaze, while in downward gaze, the add power or near-power zone of a lens is over the entrance pupil. Concentric bifocal contact lenses generally have a central power zone and one or more annular power zones that function usually, but not always, by the simultaneous vision principle. It is recognized that these lenses do not provide good vision for both distance and near viewing, and are only worn successfully by those who are willing to accept less than optimal vision (115).

The effective use of a bifocal contact lens requires the translation of an ocular system between vision surfaces when an eye changes from gazing at an object at a distance to gazing at a nearby object. Alternatively, there may be a desire to have a translating multifocal contact lens that may have one or more intermediate-power zones in addition to far-power and near-power optic zones. Such a translating contact lens may have to have an ability to control and optimize the amount of movement of a lens when the pupil translates from distance vision, to intermediate vision, to near vision, or any combination thereof (115).

1.9.2 Silicone Hydrogels

A contact lens product has been described that includes a multifocal contact lens and a buffer solution (21). The multifocal contact lens is immersed in the buffer solution. The buffer solution is a cycloplegic agent. The cycloplegic agent is favorable to relax the ciliary muscle and reduce the probability of drug side effects.

The multifocal contact lens includes a central region and at least one annular region. The annular region concentrically surrounds the central region, wherein a diopter of the annular region is different from a diopter of the central region.

Also, the multifocal contact lens can include a blue-light blocking agent. Therefore, the multifocal contact lens can block high--energy blue lights, and the probability that the retina hurt by the blue lights can be reduced. The blue-light blocking agent can be 4-(phenyldiazenyl) phenyl methacrylate. 4-(Phenyldiazenyl) phenyl methacrylate is shown in Figure 1.40.

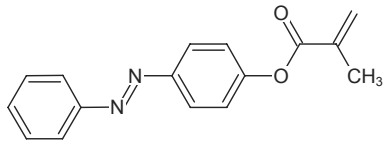


Figure 1.40 4-(Phenyldiazenyl) phenyl methacrylate.

However, the composition may contain a UV-blocking agent. Therefore, the multifocal contact lens can block high-energy UV

lights, and the probability that the retina hurt by the UV lights can be reduced. UV-blocking agents are collected in Table 1.22 and shown in Figure 1.41.

Table 1.22 UV-blocking agents (21).

Compound
4-Methacryloxy-2-hydroxybenzophenone
2-Phenylethyl acrylate
2-Phenylethyl methacrylate
2-(2′-Hydroxy-5′-methacryloxyethylphenyl)-2*H*-benzotriazole
2-(4-Benzoyl-3-hydroxyphenoxy)ethyl acrylate

The multifocal contact lens is made from a silicone hydrogel or hydrogel. The silicone hydrogel can be a contact lens material, classified as Group V by the U.S. Food and Drug Administration (116, 117), such as Balafilcon A, Comfilcon A, Efrofilcon A, Enfilcon A, Galyfilcon A, Lotrafilcon A, Lotrafilcon B, Narafilcon A, Narafilcon B, Senofilcon A, Delefilcon A and Somofilcon A.

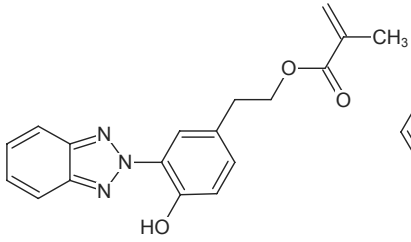
The monomers for a composition for manufacturing the silicone hydrogel are shown in Table 1.23 and in Figure 1.42.

Table 1.23 Silicone monomers (21).

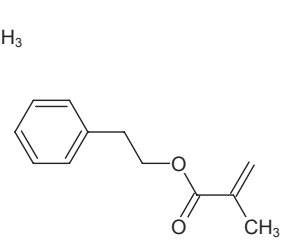
Compound
2-Hydroxyethyl methacrylate
3-Methacryloxypropyltris(trimethylsiloxy) silane
2-Hydroxy-2-methyl-propiophenone *N*-Vinyl-2-pyrrolidinone
N,*N*-Dimethyl acrylamide
Ethylene glycol dimethacrylate
3-(3-Methacryloxy-2-hydroxypropoxy)propyl-bis(trimethylsiloxy)methylsilane
Isopropyl alcohol
Methacrylic acid

A composition for manufacturing a hydrogel is listed in Table 1.24.

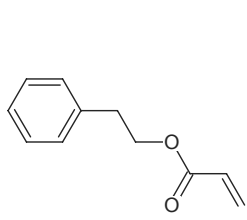
So, the multifocal contact lens can block UV lights by adding 2-(2′-hydroxy-5′-methacryloxyethylphenyl)-2*H*-benzotriazole.



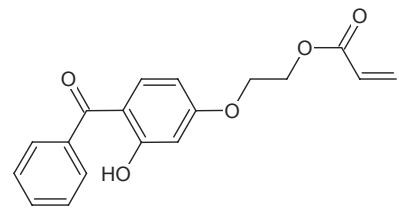
2-(2′-Hydroxy-5′-methacryloxy ethylphenyl)-2*H*-benzotriazole



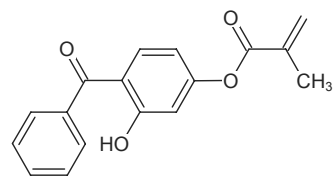
2-Phenylethyl methacrylate



2-Phenylethyl acrylate

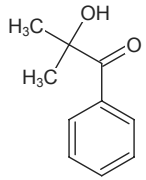


2-(4-Benzoyl-3-hydroxyphenoxy) ethyl acrylate

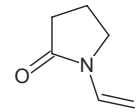


4-Methacryloxy-2-hydroxybenzophenone

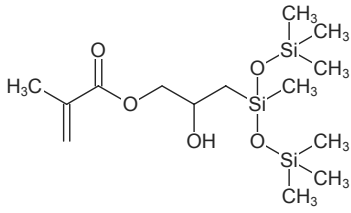
Figure 1.41 UV-blocking agents.



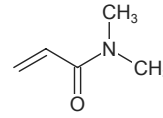
2-Hydroxy-2-methyl-propiophenone



N-Vinyl-2-pyrrolidinone



3-(3-Methacryloxy-2-hydroxypropoxy) propyl bis(trimethylsiloxy)methylsilane



N,*N*-Dimethyl acrylamide

Figure 1.42 Silicone monomers.

Table 1.24 Composition for a multifocal contact lens (21).

Ingredient	Content/[%]
2-Hydroxyethyl methacrylate	82.0
2-(2′-Hydroxy-5′-methacryloxyethylphenyl)-2H-benzo triazole	1.2
Ethylene glycol dimethacrylate	0.4
2-Hydroxy-2-methyl-propiophenone	0.5
Glycerol	13.5
Trimethylol propane trimethacrylate	0.2
Methacrylic acid	2.2

1.9.3 Non-Silicone Hydrogels

Non-silicon-containing hydrogel compositions contain monomers or monomer mixtures which are polymerized to form non-silicon-containing soft or hydrogel contact lens products in the mold assembly comprised of the two mold members or halves (31). Monomers for these types are collected in Table 1.25. Some of these compounds are also shown in Figure 1.43.

Table 1.25 Monomers for non-silicone hydrogels (31).

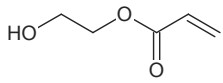
Monomer	Monomer
Methyl acrylate	2-Hydroxyethyl methacrylate
Methyl methacrylate	2-Hydroxyethyl acrylate
N-Vinyl pyrrolidone	*N*-vinyl acrylamide
2-Hydroxypropyl methacrylate	Isobutyl methacrylate
Styrene	Ethoxyethyl methacrylate
Dimethylamino ethyl acrylate	Glycidyl methacrylate
Diacetone acrylamide	Vinyl acetate
Acrylamide	Hydroxytrimethylene acrylate
Methoxyethyl methacrylate	Acrylic acid
Methacrylic acid	Glycerol methacrylate
Methoxy triethylene glycol methacrylate	

The non-silicon-containing precursor compositions preferably contain a small amount of a crosslinking agent, usually from 0.05% to 2% and most frequently from 0.05 to 1.0%, of a diester or triester. Examples of representative crosslinking agents are collected in Table 1.26 and shown in Figure 1.44.

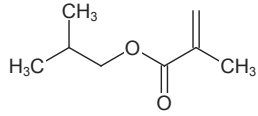
Typical crosslinking agents may have at least two ethylenically unsaturated double bonds.

The non-silicon-containing precursor compositions generally also include a catalyst, usually from about 0.05% to 1% of a free radical catalyst. Typical examples of such catalysts are shown in Table 1.27 and in Figure 1.45.

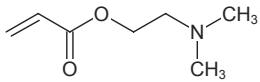
The polymerization of the monomer or monomer mixture in the mold assembly is preferably carried out by exposing the composition to polymerization-initiating conditions (31). The preferred technique is to include initiators in the composition which work upon exposure to thermal radiation, and exposing the composition to thermal radiation of an intensity and duration effective to initiate



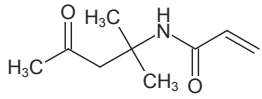
2-Hydroxyethyl acrylate



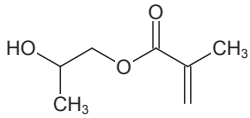
Isobutyl methacrylate



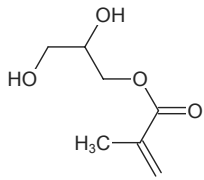
Dimethylamino ethyl acrylate



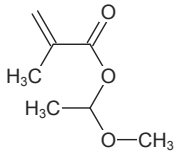
Diacetone acrylamide



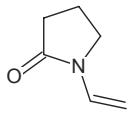
2-Hydroxypropyl methacrylate



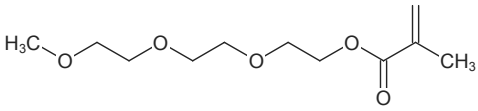
Glycerol methacrylate



Methoxyethyl methacrylate

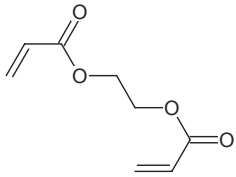


N-Vinyl pyrrolidone

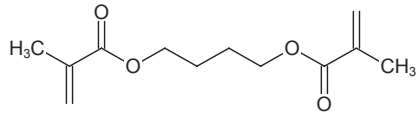


Methoxy triethylene glycol methacrylate

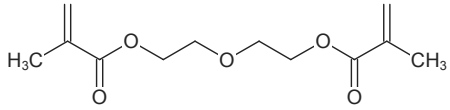
Figure 1.43 Monomers for non-silicone hydrogels.



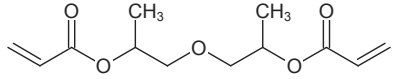
Ethylene glycol diacrylate



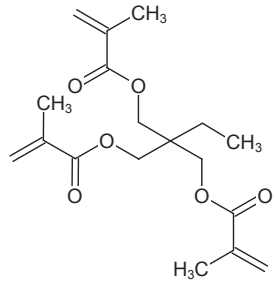
1,4-Butylene dimethacrylate



Diethylene glycol dimethacrylate

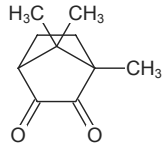


Dipropylene glycol diacrylate

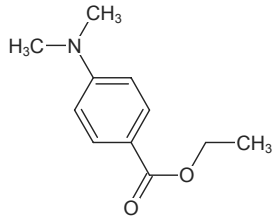


Trimethylol propane trimethacrylate

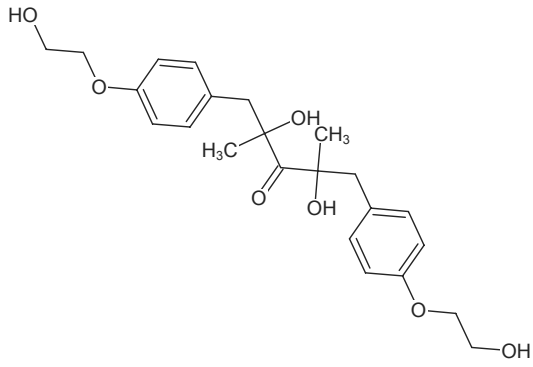
Figure 1.44 Crosslinking agents.



Camphorquinone



Ethyl-4-(*N*,*N*-dimethyl-amino)benzoate



4-(2-Hydroxyethoxy)phenyl-2-hydroxy-2-propyl-ketone

Figure 1.45 Catalysts.

Table 1.26 Crosslinking agents for non-silicone hydrogels (31).

Monomer	
Ethylene glycol diacrylate	1,2-Butylene dimethacrylate
1,3-Butylene dimethacrylate	1,4-Butylene dimethacrylate
Propylene glycol diacrylate	Propylene glycol dimethacrylate
Diethylene glycol dimethacrylate	Dipropylene glycol dimethacrylate
Diethylene glycol diacrylate	Dipropylene glycol diacrylate
Glycerine trimethacrylate	Trimethylol propane triacrylate
Ethylene glycol dimethacrylate	
Trimethylol propane trimethacrylate	

Table 1.27 Free radical catalysts and initiators (31).

Initiators	Catalysts
Lauroyl peroxide	Ethyl-4-(*N*,*N*-dimethyl-amino)benzoate
Isopropyl percarbonate	Camphorquinone
Benzoyl peroxide	4-(2-Hydroxyethoxy)phenyl-2-hydroxyl-2-propyl ketone

polymerization and to allow the polymerization of the composition to proceed to form a polymerized contact lens product.

After polymerization of the lens precursor composition, the mold assembly can be demolded, the polymerized contact lens product can be delensed from one of the mold members, either the female or male mold member, the delensed contact lens product can then be inspected and packaged in a packaging solution and sterilized. In certain embodiments, such as silicone-containing hydrogel contact lenses, the delensed contact lens product can be extracted and hydrated prior to packaging the lenses in a packaging solution (31).

1.9.4 Tilted-Wear Type Contact Lenses

For the purpose of correcting presbyopia, it is widely known to prescribe multifocal contact lenses, such as bifocal lenses having multiple diopter power regions, and specifically a distance region provided as a first diopter power regions and a near region provided as a second diopter power region having more positive additional diopter power than that of the distance region. A multifocal contact

lens has been described having a plurality of diopter power regions (118).

The tilted-wear type contact lens contains an optical zone situated in a lens center section, with a first diopter power region and a second diopter power region having a lens diopter power that is more positive than that of the first diopter power region (118).

Here, the contact lens has a lens profile that is axisymmetric with respect to a symmetrical meridian defined by one diametrical line of the optical zone; a superficial center of at least one of the first diopter power regions and the second diopter power region is decentered on the symmetrical meridian against a geometric center of the optical zone; a circumferential positioning member is provided to afford stable positions in a lens circumferential direction when worn in an eye, an orthogonal meridian that is orthogonal to the symmetrical meridian is tilted by a prescribed angle with respect to the vertical line of the eye. The circumferential positioning member is adapted to give rise to a first stable state in which, with the lens placed in a right eye, the orthogonal meridian is tilted by a first tilt angle in the circumferential direction relative to the vertical line of the eye, and to a second stable state in which, with the lens placed in a left eye with an orientation thereof flipped vertically from that when worn in the right eye, the orthogonal meridian is tilted relative to the vertical line of the eye by a second tilt angle to an opposite side in the circumferential direction from the first tilt angle; and a visible indicator mark is provided for identifying normal position and flipped position in relation to the orientation in a lens vertical direction (118).

1.9.5 Neutral Density Filters

The effect of wearing neutral density filters with different transmittance levels over multifocal contact lenses on pupil size, visual functions and the dynamic accommodative response under daylight conditions in early presbyopes was investigated (119).

There was no effect of the optical conditions on the accommodative response. However, there was a significant effect on the fixation distance.

So, the results of the study demonstrated that wearing neutral density filters over multifocal contact lenses was enough to induce a

pupil size variation. However, pupil size changes induced by tinted lenses may not improve distance vision while wearing multifocal contact lenses under brightly illuminated conditions.

In addition, neutral density filters with less than 50% of visible light transmittance have a negative effect on distance visual acuity. Anecdotal suggestions to improve distance by enlarging the pupil when wearing a center-near design of a multifocal contact lens were not supported by the findings of this study. Therefore, adjustment of the prescription should be considered first for improving near or distance visual acuity with multifocal contact lens wear (119).

1.10 Augmented Reality Contact Lens Systems

General information about augmented reality technology has been provided which acts as a resource for special education researchers and teachers who are interested in using augmented reality as a learning/teaching material (120). In addition, the research that used augmented reality as a learning material in the education of individuals with special needs was examined and the obtained results revealed. In the education of individuals with special needs, 19 articles published between 2013 and 2019, addressing the use of augmented reality as learning material and meeting the inclusion criteria, were analyzed using descriptive content analysis in terms of general characteristics.

Also, the properties of augmented reality contents and development environments were examined in detail. The findings of the research indicate that the use of augmented reality as a learning material gives positive results in the education of individuals with special needs (120). Augmented reality contents are mostly used to support effective teaching strategies.

Augmented reality adds computer-generated information to a person's view of the world around them (121, 122). When the augmented reality system is displaying images, reacting to speech or receiving messages, it provides functions like that of a smartphone but in a more natural way.

1.10.1 Electronic Contact Lenses

An augmented reality system has been described that includes an electronic contact lens and a plurality of conductive coils to be worn, e.g., around a neck, around an arm, or on the chest of a user (121).

The conductive coils can inductively couple to the electronic contact lens by producing magnetic fields that the electronic contact lens can convert into power. A direction of the resulting magnetic field at the electronic contact lens can rotate over time, enabling the electronic contact lens to periodically form a strong inductive coupling with the plurality of conductive coils despite the orientation of the electronic contact lens.

The electronic contact lens can also output a feedback signal representative of the power produced at the electronic contact lens or an orientation signal representative of the orientation of the eye, and the magnetic fields produced by the conductive coils can be altered based on the feedback signal or orientation signal (121).

1.10.2 Smart Contact Lenses

In another study, methods of manufacturing smart contact lenses were detailed (122). A method of manufacturing such a smart contact lens consists of the following steps:

1. Forming a display unit. This step uses:
   (a) Forming a transparent substrate layer on a curved surface of a mold layer,
   (b) Transferring a switch array layer to the transparent substrate layer,
   (c) Transferring a light emission layer to the switch array layer, and
   (d) Forming wires to connect the devices of the switch array layer with devices of the light emission layer.
2. Mounting the display unit in a center region of a first contact lens, the mounting includes forming a groove in the center region of the first contact lens, and disposing the display unit in the groove, a size of the groove corresponding to a size of the display unit,
3. Forming a peripheral device on the first contact lens around the display unit and in connection with the display unit,

forming the peripheral device, including forming wiring around the display unit, the wiring having a circular shape and connecting the display unit to components of the peripheral device that are around the wiring, the wiring being between the display unit and the components of the peripheral device. Formation of the peripheral device consists of:
   (a) Forming a device layer on a substrate,
   (b) Separating the device layer from the substrate,
   (c) Flattening the first contact lens by pulling the first contact lens in radial directions,
   (d) Transferring the device layer to the flattened first contact lens,
   (e) Forming the wiring to connect the device layer and the display unit, and
   (f) Returning the first contact lens to an original shape.
4. Forming a passivation layer to cover the display unit and the peripheral device, and
5. Forming a material layer on the first contact lens to cover the passivation layer, the material layer making hermetic contact with the first contact lens around the passivation layer wherein the material layer covers only a front surface of the first contact lens in the first contact lens.

The method of operating the smart contact lens consists of (122):

1. Receiving information,
2. Transmitting the information to a display unit, and
3. Projecting the light directly onto a retina using the display unit.

1.10.3 Wearable Smart Contact Lenses

Wearable smart contact lenses have attracted extensive interest because of their ability to monitor physiological information and ambient information directly from eyeball and body fluids (123).

However, conventional smart contact lens systems lack efficient sensor modalities, facile fabrication process, mechanical stability, or biocompatibility. A multifunctional, high-transparency and easy-access smart contact lens system was developed (123).

Here, the serpentine mesh sensor system can be directly mounted onto the lens substrate and maintain direct contact with tears, delivering high detection sensitivity, while being mechanically robust and not interfering with either blinking or vision. This integrated contact lens sensor system and fabrication strategy allows for easy incorporation of other functional components, such as an electrode array for electroretinography, antennas for wireless communication, and power modules for future *in-vivo* exploration (123).

In such a system, MoS_2 transistors were chosen as the core sensing material because of their large surface-to-volume ratio, layered dangling-bond-free surface, tunable bandgap and charge transfer properties, and good biocompatibility (123).

1.10.4 Collimated Light-Emitting Diodes

A design of a contact lens display has been presented, which features an array of collimated light-emitting diodes and a contact lens, for the augmented reality. By building the infrastructure directly on top of the eye, the eye is allowed to move or rotate freely without the need of exit pupil expansion nor eye tracking (124). The resolution of light-emitting diodes is foveated to match with the density of cones on the retina. In this manner, the total number of pixels as well as the latency of image processing can be significantly reduced.

The proposed contact lens display consists of two components, i.e., a contact lens and a collimated light-emitting diode (LED) array. For the sake of symmetry, the contact lens, LED array and eye are center-aligned. Adjacent to the cornea is a thin layer of contact lens for fixing the refractive errors. On top of the contact lens is an array of LEDs, each pixel of which is able to emit a collimated beam of light towards the center of the eye lens. In this regard, this contact lens display is analogous to the said virtual retinal display or retinal scanning display. The major difference is that in this contact lens display, the eye can rotate freely without losing the image, thanks to the surface tension of tears that tightly adheres the whole device to the eye (124).

The idea of contact lens display is validated through the numerical simulation on Code V (Synopsys). The design wavelength was 532 *nm*.

1.11 Siloxane Macromers

Because of the hydrophobic characteristic on the surface of silicone hydrogel contact lenses, it is apt to incur a bacteria breed and eye irritation. Therefore, a composition of contact lenses has been provided that does not show the above disadvantages (125). Such a composition contains a siloxane macromer, a hydrophilic monomer, a crosslinking agent and an initiator.

The preparation of such a siloxane macromer runs as follows (125):

Preparation 1–9: First, 4.44 *g* of isophorone diisocyanate, 0.0025 *g* of dibutyltin dilaurate as the catalyst, and 40 *ml* of methylene chloride were added to a flask, and the solution stirred under a stream of nitrogen. Then, 20 *g* of α-butyl-ω-[3-(2,2-(dihydroxyethyl)butoxy)propyl]poly(dimethyl siloxane) was accurately weighed and added dropwise to the solution over about 1 *h*. After the reaction at room temperature for 12 *h*, another 0.0025 *g* of dibutyltin dilaurate and 7.2 *g* of poly(ethylene glycol) mono methacrylate were accurately weighed and added dropwise to the solution over about 1 *h*. After the reaction is conducted at room temperature for another 12 *h*, the resulting reaction product was washed with a large amount of water, and then dehydrated and filtered to obtain the raw product. Then, the methylene chloride was evaporated to obtain a siloxane macromer.

According to the method presented above, a second similar macromer was synthesized.

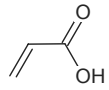
The hydrophilic monomer was selected from a group consisting of HEMA, *N*-vinyl-2-pyrrolidone (NVP), methacrylic acid, acrylic acid, glycidyl methacrylate, *N*-methyl acrylamide, *N*,*N*-dimethylacrylamide (DMA), vinyl carbamate and a combination thereof. Some of these monomers are shown in Figure 1.46

The initiator suitably used in conventional compositions for manufacturing contact lenses can be used in the corn position, such as materials shown in Table 1.28 and in Figure 1.47.

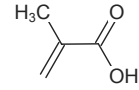
Preferably, the initiator for manufacturing contact lenses is 2,2′-azo-bis(isoheptonitrile).

For the preparation of contact lenses, both siloxane macromers, HEMA and NVP, 2,2′-Azo-bis(isoheptonitrile), and EGDMA were mixed and stirred about 1 *h*.

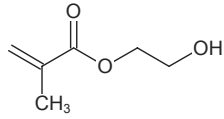
The contents of the contact lenses are shown in Table 1.29.



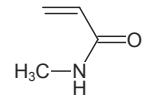
Acrylic acid



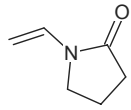
Methacrylic acid



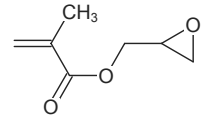
2-Hydroxyethyl methacrylate



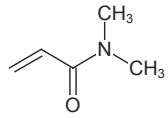
N-Methyl acrylamide



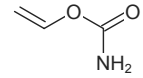
N-Vinyl-2-pyrrolidone



Glycidyl methacrylate



N,*N*-Dimethyl acrylamide

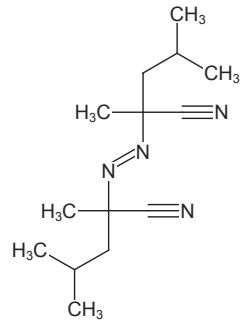


Vinyl carbamate

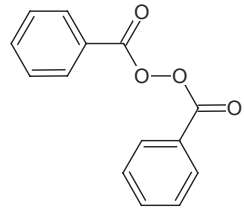
Figure 1.46 Hydrophilic monomers.

Table 1.28 Initiators.

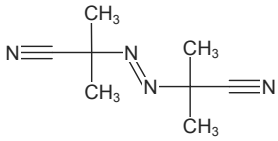
Initiator
2,2′-Azo-bis(isoheptonitrile)
2,2′-Azo-bis(2,4-dimethylvaleronitrile)
2,2′-Azo-bis(2-methyl-propanenitrile)
2,2′-Azo-bis(2-methyl-butanenitrile)
Benzoyl peroxide



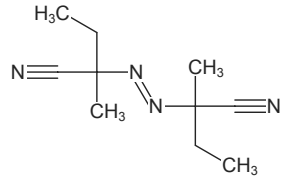
2,2′-Azo-bis(isoheptonitrile)



Benzoyl peroxide



2,2′-Azobis
(2-methyl-propanenitrile)



2,2′-Azobis
(2-methyl-butanenitrile)

Figure 1.47 Initiators.

Table 1.29 Contents of the contact lenses (125).

Compound	Amount/[%]
Siloxane macromer (A)	15 ~ 60
Siloxane macromer (B)	0 ~ 30
N-Vinyl-2-pyrrolidone	30 ~ 75
2-Hydroxyethyl methacrylate	0 ~ 10
Ethylene glycol dimethacrylate	0 ~ 10
2,2′-Azo-bis(isoheptonitrile)	0.1 ~ 1

Then the mixtures were injected into a mold of contact lens made of PP and heated to initiate the radical polymerization thereof at 60°C for 1 *h*, at 80°C for 2 *h*, and then at 135°C for 2 *h*. After the polymerization was completed, the mold was immersed in 80% alcohol solution for 1 *h* and the resulting molded lens was taken out of the mold. A hydration treatment was conducted on the resulting lens to obtain a contact lens with excellent oxygen permeability. Finally, a sterilizing treatment on the lens was conducted. The steps and the conditions of hydration treatment were as follows (125):

1. The mold was immersed in 80% alcohol solution for 1 *h* then the resulting molded lens was taken out of the mold.
2. The resulting polymer molded lens was then immersed in 90% alcohol solution for 1 *h*.
3. The alcohol-immersed contact lens was heated in water at 80°C for 1 *h*.
4. The contact lens was immersed in a buffer solution to obtain equilibrium.

The sterilizing treatment was done at 12°C for 30 *min* (125).

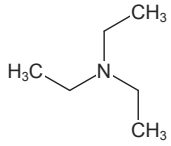
1.11.1 Silicone Urethane Polymers

It has been discovered that if polyfunctional high-molecular-weight poly(siloxane)s, whose equivalent weight is not greater than 5000 and which are connected to at least two terminal or pendant polymerizable vinyl groups through bisurethane linkages, are incorporated into a crosslinked vinyl copolymer, hard, stiff and clear products are obtained which have excellent oxygen permeability, which even at a siloxane content of greater than 50% are stiff enough to fulfill the requirements of a hard contact lens (126). Furthermore, it has been found that the siloxane-containing polymers can be made with better wettability than conventional PMMA hard lenses, despite their high poly(siloxane) content.

The poly(siloxane) macromers are obtained conveniently by a 2-step synthesis from the corresponding polyfunctional poly(siloxane)s.

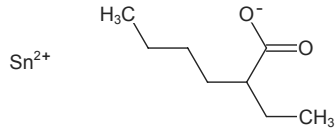
In the first step, the poly(siloxane) is reacted, either in bulk or in solution, with a given amount of a diisocyanate or triisocyanate

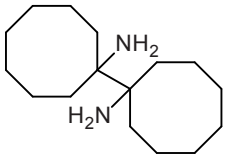
in the presence of any of the conventional catalysts. These catalysts may be tertiary amino groups containing compounds, such as triethylamine, pyridine or diaminobicyclooctane, or metal-based catalysts like dibutyltin dilaurate or stannous octoate. Some catalysts are shown in Figure 1.48. The reaction is carried out at either ambient or elevated temperatures under a dry nitrogen blanket.



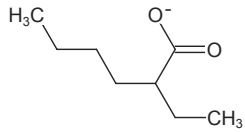
Triethylamine

Pyridine





Diaminobicyclooctane



Stannous octoate

Figure 1.48 Catalysts.

The second step of the reaction consists of end-capping this poly(isocyanate) with a hydroxy or amino-functional vinyl compound, most commonly with 2-hydroxyethyl methacrylate. It is advisable to use at least a small excess of the end-capping monomer. Since it is a preferred practice to incorporate a small amount of a water-soluble monomer into the final polymer in order to achieve good wetting characteristics, a greater excess of the hydroxy or amino-functional monomer is not detrimental. The reaction proceeds at ambient or elevated temperatures over a period of several hours with no additional catalyst necessary.

The transparent, hard and oxygen-permeable polymers are pro-

duced in a final synthesis step by free radical copolymerization, either in bulk or in the presence of small amounts of solvents. The polymerization is suitably carried out with a free radical generating initiator at a temperature in the range from about 50°C to about 100°. The here used initiators are preferably peroxides or azo catalysts having a half-life at the polymerization temperature of at least 20 *min*. Also, other free radical generating mechanisms can be employed, such as X-rays, electron-beams and UV radiation.

Typical useful free radical generating initiators are shown in Table 1.30 and in Figure 1.49.

In detail, the preparation runs as follows (126):

Preparation 1–10: A 1-*l* 3-necked flask fitted with a mechanical stirrer, thermometer, condenser and nitrogen inlet is charged with 186.6 *g* (0.03 *mol*) of poly(dimethyl siloxane)-triol (Dow Corning, 1248 fluid), which had been stripped free of volatiles by passing it through a wiped-film evaporator. Then, 21.0 *g* (0.0945 *mol*) 1-isocyanatomethyl-5-isocyanato-1,3,3-trimethylcyclohexane (isophorone diisocyanate) is added together with 0.025 *g* dibutyltin dilaurate as catalyst. The mixture is then stirred under nitrogen in a temperature controlled water bath at 50°C for 5 *h*. At that time the isocyanate content as determined by titration has fallen to 1.94% (2.00% theoretical).

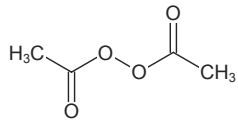
Then, 169.4 *g* of the poly(dimethyl siloxane triisocyanate) prepolymer is diluted with 10.2 *g* 2-hydroxyethyl methacrylate and stirred under nitrogen atmosphere at room temperature until all −N=C=O groups have been reacted as determined by the absence of the isocyanate band from the infrared spectrum. The resulting product consists of more than 99.9% methacrylate-terminated poly(siloxane) and a minor amount of HEMA-capped isophorone diisocyanate, indicating that some chain extension had taken place. This was also confirmed by GPC

Then, the preparation of the polymer samples is done as follows:

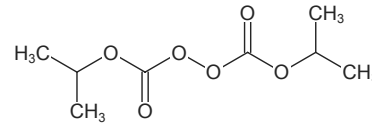
Preparation 1–11: First, 30 *g* each of the poly(siloxane) macromer prepared according to preparation 1–10 are mixed with various comonomers, as shown in Table 1.31. Then, 0.06 *g* (0.2%) 1-Hydroxycyclohexyl phenyl ketone, IRGACURE-184, (a Ciba-Geigy UV-initiator) is added and each mixture and is thoroughly degassed and then stored under nitrogen atmosphere. One portion of each mixture is used to prepare 0.1 *mm* thick films between silane-treated glass plates. A 0.1 *mm* thick Mylar film (polyester film from DuPont) is used as a spacer and the mold is held together by clamps. The molds are exposed to UV light from a black light blue lamp (Sylvania) for 3 *h*, after which time the polymer is removed from the mold to be used for oxygen permeability measurements.

Table 1.30 Free radical generating initiators (126).

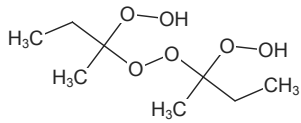
Peroxides
Isopropyl percarbonate
tert-Butyl peroctoate
Benzoyl peroxide
Lauroyl peroxide
Decanoyl peroxide
Acetyl peroxide
Succinic acid peroxide
Methyl ethyl ketone peroxide
tert-Butyl peroxyacetate
Propionyl peroxide
2,4-Dichlorobenzoyl peroxide
tert-Butyl peroxypivalate
Pelargonyl peroxide
2,5-Dimethyl-2,5-bis(2-ethylhexanoylperoxy)hexane
p-Chlorobenzoyl peroxide
tert-Butyl peroxybutyrate
tert-Butyl peroxymaleic acid
tert-Butyl-peroxyisopropyl carbonate
Bis(1-Hydroxycyclohexyl)peroxide
Azo compounds
2,2-Azo-bis-isobutyronitrile
2,2′-Azo-bis(2,4-dimethylvaleronitrile)
1,1′-Azo-bis(cyclohexane carbonitrile)
2,2′-Azo-bis(2,4-dimethyl-4-methoxyvaleronitrile)
Photoinitiators
Diethoxyacetophenone
1-Hydroxycyclohexyl phenyl ketone
2,2-Dimethoxy-2-phenylacetophenone
Phenothiazine
Diisopropylxanthogen disulfide
Benzoin



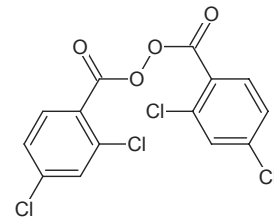
Acetyl peroxide



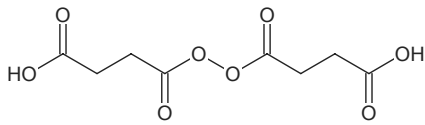
Isopropyl percarbonate



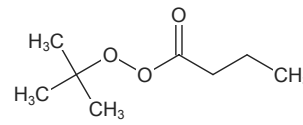
Methyl ethyl ketone peroxide



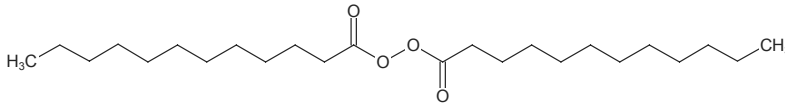
2,4-Dichlorobenzoyl peroxide



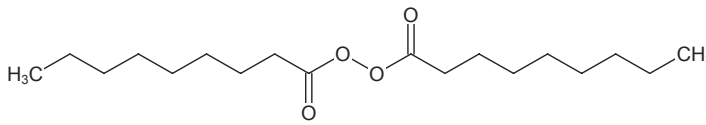
Succinic acid peroxide



tert-Butyl peroxybutyrate

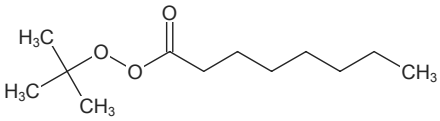


Lauroyl peroxide

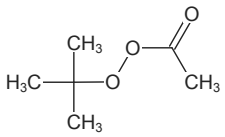


Pelargonyl peroxide

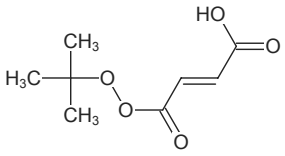
Figure 1.49 Peroxides.



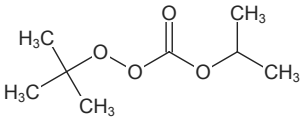
tert-Butyl peroctoate



tert-Butyl peroxyacetate



tert-Butyl peroxymaleic acid



tert-Butyl-peroxyisopropyl carbonate

Figure 1.49 (cont) Peroxides.

Furfuryl methacrylate and Dicyclopentenyl-oxy-ethyl methacrylate are shown in Figure 1.50.

The hardness and clarity of these polymers are a result of two features: first, in the case of the comb-like structure of a high--molecular-weight poly(siloxane), the actual linear chain length of $-SiO(CH_3)_2-$ between crosslinks is relatively short, despite an overall high molecular weight. This short effective chain length between crosslinks restricts the mobility of the poly(siloxane) chains.

Because of their good tissue compatibility and oxygen permeability and strength and elasticity, the polymers are particularly suitable for use as intramuscular and subcutaneous implants in warm-blooded animals and as contact lens material. For the same reasons, these materials may also be fashioned into substituted blood vessels or extracorporeal shunts (126).

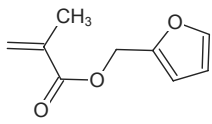
1.12 Oxygen-Permeable Lenses

1.12.1 Extended Wear Lenses

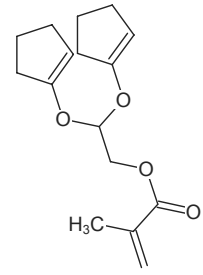
Contact lenses have been described that are useful as extended wear contact lenses. The lens is preferably formed by copolymerization

Table 1.31 Synthesis and properties of polymers.

Comonomer	Appearance	H_2O Content	Young's Modulus	Shore D /[*GPa*]	Hardness
Methyl methacrylate	clear	24.3	95	2.0	78
Cyclohexyl methacrylate	clear	31.0	120	1.5	79
Furfuryl methacrylate	opaque	36.3	131	–	65
Isobornyl methacrylate	clear	33.4	119	1.4	82
Methoxy-styrene	clear	30.7	118	–	79
Styrene	clear	33.2	109	1.6	75
Isobutyl methacrylate	clear	31.3	117	1.2	69



Furfuryl methacrylate



Dicyclopentenyl-oxy-ethyl methacrylate

Figure 1.50 Monomers.

Table 1.31 (cont) Synthesis and properties of polymers.

Comonomer	Appearance	H_2O Content	Young's Modulus	Shore D /[*GPa*]	Hardness
Benzyl methacrylate	clear	52.4	110	1.0	71
Methylene bornenyl methacrylate	clear	29.1	144	1.3	79
Dicyclopentenyl methacrylate	clear	33.8	123	1.6	79
Dicyclopentenyloxyethyl methacrylate	clear	37.7	114	1.0	69
Allyl methacrylate	clear	48.4	120	1.3	74
tert-Butyl methacrylate	clear	32.2	115	1.4	79
Methyl methacrylate:*tert*-Octyl methacrylate 1:1	clear	30.5	127	1.4	78
Isopropyl methacrylate	clear	41.0	112	1.2	77

of at least (127):

1. One oxyperm polymerizable material which is capable of polymerizing to form a polymer having a high oxygen permeability, and
2. One ionoperm polymerizable material which is capable of polymerizing to form a polymer having a high ion permeability.

Oxyperm polymerizable materials include a wide range of materials which may be polymerized to form a polymer displaying a relatively high oxygen diffusion rate therethrough. In addition, these materials must be relatively ophthalmically compatible. These oxyperm polymerizable materials include siloxane-containing macromers and monomers, fluorine-containing macromers and monomers, and carbon-carbon triple bond-containing macromers and monomers. The oxyperm macromer or monomer may also contain hydrophilic groups.

Ionoperm polymerizable materials include a wide range of materials which may be polymerized to form a polymer displaying a relatively high ion diffusion rate therethrough. In addition, these materials must be relatively ophthalmically compatible.

Oxyperm polymerizable materials and ionoperm polymerizable materials are listed in Table 1.32.

Table 1.32 Monomers (127).

Oxyperm monomers
Siloxane-containing macromers and monomers
Poly(dimethyl siloxane)s
Fluorine-containing macromers and monomers
Carbon-carbon triple bond-containing macromers
Ionoperm monomers
2-Hydroxyethyl methacrylate
Acrylamide
Methacrylamide
Dimethyl acrylamide
N-Vinyl-2-pyrrolidone

A preferred poly(siloxane) macromer segment is defined by the formula CP-PAO-DU-ALK-PDMS-ALK-DU-PAO-CP, where (127):

PDMS is a divalent poly(disubstituted siloxane),

CP is an isocyanatoalkyl acrylate or methacylate, preferably 2-isocyanatoethyl methacrylate, where the urethane group is bonded to the terminal carbon on the PAO group,

PAO is a divalent poly(oxyalkylene), which may be substituted, and is preferably a poly(ethylene oxide),

DU is a diurethane, preferably including a cyclic structure, where an oxygen of the urethane linkage is bonded to the PAO group and an oxygen of the urethane linkage is bonded to the ALK group, and

ALK is an alkylene or alkylenoxy group having at least 3 carbon atoms, preferably a branched alkylene group or an alkylenoxy group with 3 to 6 carbon atoms, and most preferably a *sec*-butyl group or an ethoxypropoxy group.

The diurethane (DU) group can be formed from a wide variety of diisocyanates or triisocyanates, including aliphatic, cycloaliphatic or aromatic poly(isocyanate)s. Examples are shown in Table 1.33 and in Figure 1.51.

The poly(siloxane) macromer may be synthesized by the following process (127):

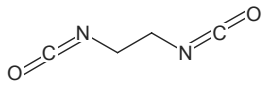
Preparation 1–12: At about 20°C–25°C, a poly(dimethyl siloxane) dialkanol having hydroxyalkyl (e.g., hydroxy-*sec*-butyl) or hydroxyalkoxy (e.g., hydroxyethylpropoxy) end groups and having a molecular weight of preferably about 2200 *Da*, i.e., having about 28 repeating siloxane groups, is reacted with isophorone diisocyanate at about a 1:2 molar ratio, using about 0.2% weight percent dibutyltin dilaurate added as a catalyst.

The reaction is carried out for about 36 *h* to 60 *h*. To this mixture poly(ethylene glycol) (PEG) is added having a molecular weight of preferably about 500 *Da* to 700 *Da* molar ratio of about a 2:1 or 2.1:1 molar ratio with respect to the poly(dimethyl siloxane), about 0.4 to 0.5 weight percent dibutyltin dilaurate (based on PEG weight), and chloroform sufficient to ensure substantial mixture homogeneity.

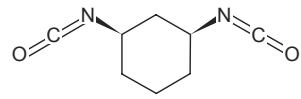
This mixture is agitated for about 12 *h* to 18 *h*, then held at a temperature of about 44°C to 48°C for about 6 *h* to 10 *h*. The excess chloroform is evaporated therefrom at about room temperature to produce a composition having about 50% solids. Then, 2-isocyanatoethyl methacrylate, cf. Figure 1.52, is added to the mixture in about a 2:1 to 2.3:1 molar ratio with respect

Table 1.33 Isocyanates (127).

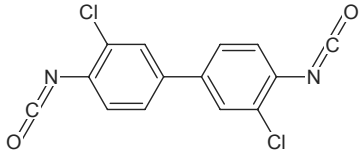
Diisocyanate Compounds
Ethylene diisocyanate
1,2-Diisocyanatopropane
1,3-Diisocyanatopropane
1,6-Diisocyanatohexane
1,2-Diisocyanatocyclohexane
1,3-Diisocyanatocyclohexane
1,4-Diisocyanatobenzene
Bis(4-isocyanatocyclohexyl)methane
Bis(4-isocyanatophenyl)methane
1,2-Toluene diisocyanate
1,4-Toluene diisocyanate
3,3-Dichloro-4,4′-diisocyanatobiphenyl
1,5-Diisocyanatonaphthalene
1-Isocyanatomethyl-5-isocyanato-1,3,3-trimethylcyclohexane
Isophorone diisocyanate
1,6-Diisocyanato-2,2,4-trimethylhexane
2,2′-Diisocyanatodiethyl fumarate
1,5-Diisocyanato-1-carboxypentane
Diisocyanatonaphthalenes
2,4-Diisocyanato-1-methylnaphthalene
2,7-Diisocyanato-1-methylnaphthalene
1,4-Diisocyanatomethylcyclohexane
1,3-Diisocyanato-6(7)-methylnaphthalene
Diisocyanato phenyl compounds
4,4′-Diisocyanatobiphenyl
4,4′-Diisocyanato-3,3′-dimethoxybisphenyl
3,3′-Diisocyanato-2,2′-dimethylbisphenyl
4,4′-Diisocyanato-2,2′-dimethylbisphenyl
Bis(4-isocyanatophenyl) ethane
Bis(4-isocyanatophenyl ether)
1,2-Toluene diisocyanate
1,4-Toluene diisocyanate
2,4-Toluene diisocyanate
Triisocyanate Compounds
Tris(4-isocyanatophenyl)methane
1,3,5-Tris(6-isocyanatohexyl) biuret



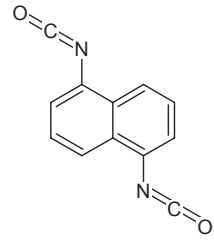
Ethylene diisocyanate



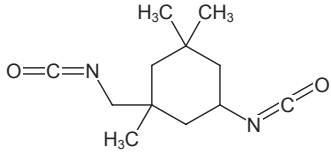
1,3-Diisocyanatocyclohexane



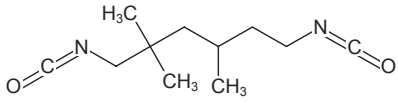
3,3-Dichloro-
4,4′-diisocyanatobiphenyl



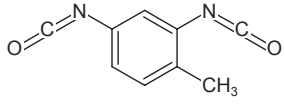
1,5-Diisocyanatonaphthalene



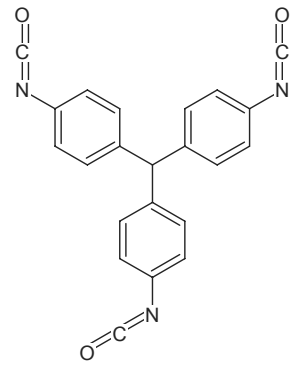
Isophorone
diisocyanate



1,6-Diisocyanato-
2,2,4-trimethylhexane



2,4-Toluene diisocyanate



Tris(4-isocyanatophenyl)methane

Figure 1.51 Isocyanates.

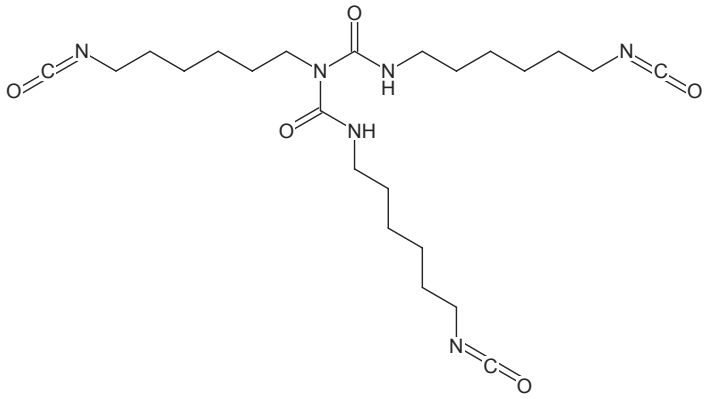


Figure 1.51 (cont) 1,3,5-Tris(6-isocyanatohexyl) biuret.

to the poly(dimethyl siloxane). The mixture is agitated at room temperature for about 15 *h* to 20 *h*. The resulting solution contains a poly(siloxane) macromer having a number average molecular weight preferably of about 3000 *Da* to 5000 *Da*.

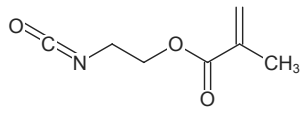


Figure 1.52 2-Isocyanatoethyl methacrylate.

From this macromer, a copolymer can be formed with an acrylated or methacrylated siloxane monomer, 3-(methacryloyloxy)propyltris(trimethylsiloxy)silane (TRIS) or HEMA, and a crosslinking agent such as EGDMA. The final copolymer composition preferably includes about 70% to 90% poly(siloxane) macromer; about 8% to 20% siloxane monomer,1% to 5% acrylate or methacrylate monomer, and preferably up to about 2% crosslinking agent, based on a total dry copolymer weight. A more preferred composition includes about 80% to 84% poly(siloxane) macromer, about 12% to 15% TRIS, about 3% to about 4% 2-hydroxyethyl methacrylate, and about 0.7% to about 1.2% EGDMA.

Then, contact lenses may be prepared from the monomer solution by applying the monomer solution to appropriate lens molds and applying sufficient UV radiation to initiate the polymerization. The UV light may be applied for a period of a few minutes to about 5 *h*, depending on the intensity of light applied. Subsequent to polymerization, the contact lens may be extracted with a solvent, e.g., isopropanol, to remove the unreacted monomers.

In summary, the preparation of the contact lenses runs as (127):

1. Contacting a poly(dialkylsiloxane) dialkanol with a diisocyanate compound in the presence of a first catalyst at conditions sufficient to cause reaction of said dialkanol with said diisocyanate, thereby forming a first mixture,
2. Contacting said first mixture with poly(alkylene glycol), a second catalyst, and sufficient solvent to ensure mixture homogeneity, thereby forming a second mixture,
3. Evaporating sufficient solvent from said second mixture to generate a third mixture having a solids content of about 40% to 60%,
4. Adding isocyanatoalkyl methacrylate to said third mixture, thereby forming a fourth mixture containing a poly(siloxane) macromer,
5. Adding to the said fourth mixture TRIS, a hydrophilic monomer, a crosslinking agent and a photoinitiator, thereby forming a fifth mixture,
6. Placing said fifth mixture into a mold, and
7. Applying sufficient radiation to copolymerize said monomers, thereby forming said polymeric material into a molded polymeric article.

1.12.2 Structures for Thick Payloads

Contact lenses that provide refractive vision correction are ubiquitous (128). In addition, therapeutic lenses may be used to treat eye diseases and injuries. For example, scleral contact lenses, which are supported at the periphery of the eye and form a tear-filled vault over the cornea, may be used to treat cornea disorders and severe dry eye syndrome, in addition to providing refractive vision correction.

Due to the lack of blood vessels within the human cornea, the tissue that makes up the cornea must receive oxygen through exposure to air. As such, in order to maintain corneal health, any contact lens disposed over the cornea requires at least a threshold amount of oxygen permeability to allow for a sufficient amount of oxygen from the air to reach the cornea.

Various contact lens structures may be used to perform different functions. In some cases, the contact lens structure may contain active devices, which will be referred to as active payloads. For example, an active contact lens structure may contain a sensor device for monitoring glucose concentration in tear fluid, or for measuring intraocular pressure (128). As another example, a very small projector or camera may be contained in the contact lens structure; for example, a femtoprojector as described by Deering (129, 130).

The projector may project images onto the wearer's retina, thus superimposing virtual objects onto the field of view of the wearer. Thus, when a person is wearing the contact lens display, he may see an augmented reality (128). Other active payloads may include other electronic, optical or micro-electromechanical devices.

In order to embed a payload within a contact lens, the contact lens structure may be made thicker. However, increasing the thickness reduces the oxygen transmission to the cornea. In addition, relatively impermeable materials may be used to provide a mechanical support for the payload, thus further reducing oxygen transmission to the cornea. Insufficient oxygen transmission to the cornea may quickly become intolerable for the wearer and may even lead to eye discomfort.

To avoid such problems, a contact lens structure is constructed using layers of materials with high oxygen transmissibility and low oxygen transmissibility. The low transmissibility layers have sufficient rigidity for providing an mechanical support for the active payloads, and the high transmissibility layers provide adequate oxygen transmission. The ratio of the thicknesses of the two layers changes abruptly at the boundaries between the payload and non-payload regions of the structure.

A contact lens structure is shown in Figure 1.53.

Here, the eye includes a cornea and a sclera. The scleral contact lens structure is designed to contact the sclera and to form a tear-filled vault over the cornea. The contact lens structure also includes

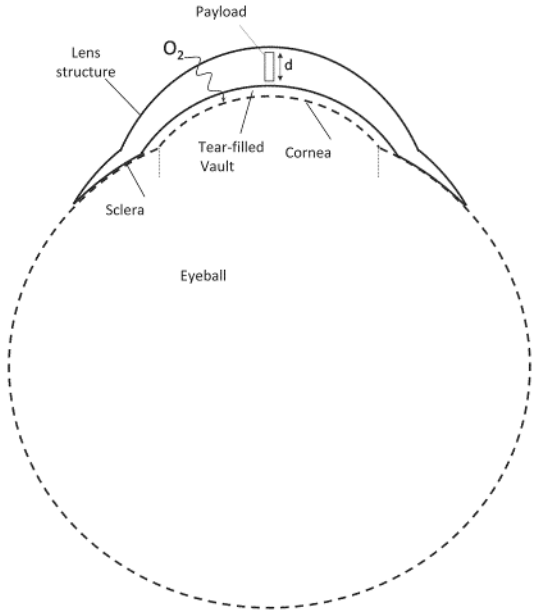


Figure 1.53 Contact lens structure (128).

a payload of thickness d, which may be a femtoprojector. Oxygen permeates through the lens structure to the cornea, based upon the oxygen transmissibility properties and thickness of the materials of the contact lens structure. In some embodiments, the contact lens structure may have a thickness of a few hundred microns above or below the payload in order to provide mechanical support for the payload.

In some designs, the low transmissibility material is the inner layer facing the eye. When rigid materials face the sclera, this can reduce potential slippage between the eye and the contact lens structure. Rigid gas-permeable materials may offer a good stiffness for mechanical support with some transmissibility. For example, a contact lens display with a femtoprojector may require some minimum stiffness in order to prevent the femtoprojector from shifting or moving relative to the wearer's eye, particularly if the femtoprojector is intended to always project images to the same part of the user's retina. However, rigid gas-permeable materials thicker than a few hundred microns typically do not transmit enough oxygen to maintain corneal health (128).

Poly(siloxane)s offer a high oxygen transmissibility (126). Plasma treatments may be used to promote the adhesion between the different materials (128).

1.13 Natural Protein Polymer Contact Lenses

A method has been presented for manufacturing a flexible contact lens from a biological protein material, wherein a hydrogel is made by hydrating the proteinous biological material (131). Then, a lens preform is made from the hydrogel at a temperature between ambient temperature and the temperature at which the material liquefies.

The preform is then placed in a mold made from a low-loss dielectric material and in at least two parts which, when locked together, define a three-dimensional shape and a finished lens surface state. The hydrogel is then liquefied by irradiating the mold by means of an electromagnetic field at a frequency between 10^8 and 10^{10} *Hz*. The parts of the mold are then locked together, the hydrogel is then gelified by cooling in the mold and the hydrogel is then crosslinked by contact with a crosslinking agent.

Gelatine hydrogels and collagen hydrogels can be used. A gelatine hydrogel can be prepared as follows (131):

Preparation 1–13: First, 100 *g* of powdered gelatine is swelled in 400 *ml* of deionized water for a period of 2 *h* to 11 *h*. The mixture is then heated to 60°C ± 5°C for 30 *min* to homogenize it. The so produced hydrogel showed a paste-like consistency, and was cast into preforms in the molds.

The liquefaction temperature was found to be around 70°C to 80°C. Two types of preforms were used during the tests.

Some had a central area substantially the same shape as the finished lens and an annular flange approximately 0.3 *mm* thick. They were made by injection molding, in a mold with a shape complementary to that of the preform, a quantity of hydrogel the weight of which exceeded that of the finished lens by 20 to 40%, averaging 30%.

The others were made in substantially the same shape as the finished lens. A quantity of hydrogel exceeding the weight of the finished lens by 2 to 4%, averaging 3%, was injected into a mold similar to the finished lens molds.

The prepared preforms were placed in the finished lens molds, and these molds were placed between the plates of a portable press. The press and the loaded molds were placed in a 2.45 *GHz* microwave oven. The oven was adjusted to deliver an electromagnetic power of 500 *W* and this power was applied to the molds for 30 *s*. After completion of the irradiation, the fluid under pressure was applied to the press to lock the molds. The latter were then removed from the oven and placed in an enclosure cooled to approximately 4°C.

1.14 Ultrathin Coating

Silicone rubber has great advantages as a contact lens material because of its very high oxygen permeability, softness, and excellent mechanical strength and durability (132). However, its practical application is hampered by inherent characteristics of elastomers, i.e., high tackiness and highly hydrophobic surface properties.

By applying a thin layer, e.g., 5 *nm*, of plasma polymer of methane, it was found that all these disadvantages can be eliminated without sacrificing high oxygen permeation rate, e.g., less than 15% reduction. It could be shown that the contact angle of methane plasma polymerized sheets, treated with wet oxygen plasma, decreased to 2.9 times less than that of the uncoated film.

Also, the optimization of the operational parameters to achieve this task has been investigated. It was found that under optimal conditions the coating withstood severe and repeated flexing of the contact lens (132).

The unique technique of glow discharge polymerization is capable of producing a highly crosslinked, pin-hole-free, thin film (10 *nm*) of an organic polymer. It can also be used to widely vary the properties of the polymer surface without changing the bulk properties of the substrate when the plasma polymer film is deposited.

As a cornea contact lens will inevitably be in contact with the corneal epithelium and tear fluid, the high wettability of the lens surface which can be achieved through the plasma technique plays an important role in eliminating irritation of eyes and preventing mucus material from accumulating on the surface of the lens. In addition, the thin, tightly grafted polymer film provides an effective

barrier for prohibiting lipids, large molecules, and water vapor from penetrating through the lens without offsetting the optical index and high permeabilities of oxygen and carbon dioxide.

A methane plasma polymer can be formed in an extremely tight network, which not only functions as a good barrier but also provides excellent surface durability (133, 134).

The composite parameter W/FM is used to represent the energy supply per unit mass of the monomer, where W is the discharge power to maintain glow, F is the flow rate of the gas given in cubic centimeters per minute introduced into the system, and M is the molecular weight of the monomer. W/FM represents the energy input per unit mass of monomer, and its SI units are Jkg^{-1} (132).

The contact angle of water of a silicone rubber sheet coated by a a methane plasma polymer versus W/FM is shown in Figure 1.54.

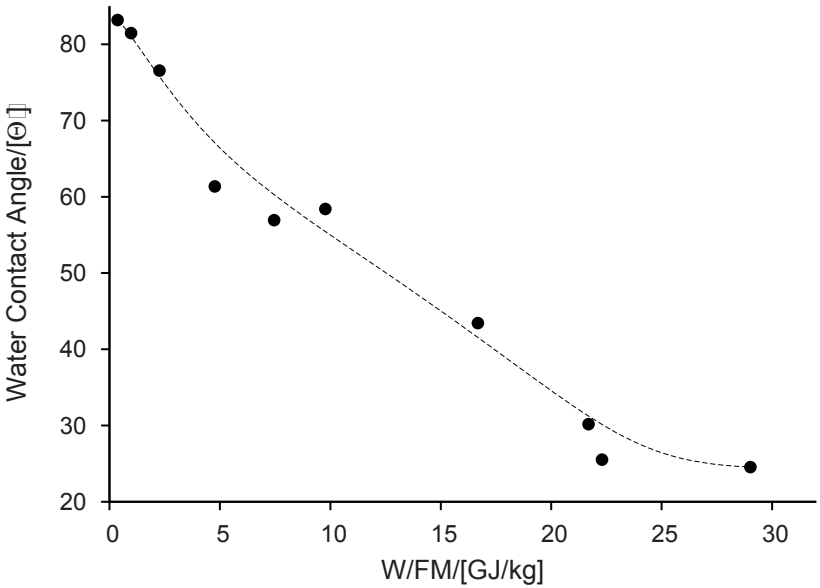


Figure 1.54 Contact angle of water of a silicone rubber sheet coated by a methane plasma polymer versus W/FM (132).

1.15 Anti-Biofouling Contact Lenses

1.15.1 Phosphorylcholine

Poly(3-trimethoxysilyl propyl methacrylate) and poly(2-methacryloyl oxyethyl phosphorylcholine) with various compositions were synthesized for the surface modification of current commercially available lenses (135).

The properties of these anti-biofouling contact lenses were investigated, which indicated that the modified contact lenses had a significant surface wettability improvement, superior antibacterial adhesion properties and resistance to protein adsorption.

The polymers can be immobilized on current commercially available lenses by a one-step modification while maintaining their excellent clinical performance and biocompatibility. The prepared anti-biofouling contact lenses may be realized in a more convenient and feasible way (135).

1.15.1.1 Improvement of Properties

2-Methacryloyloxyethyl phosphorylcholine (MPC) can enhance the adsorption of water molecules and is therefore used for contact lenses. The mechanical strength, anti-protein deposition, and anti-lipid adsorption effects of the addition of MPC to contact lenses was investigated (136). The contact lenses were produced by copolymerizing multiple ratios of MPC to HEMA.

Atomic force microscopy revealed that the addition of MPC increased the surface roughness. The anti-protein deposition and anti-lipid adsorption effects on poly(HEMA-MPC) polymers with various phosphorylcholine quantities were experimentally confirmed (136). Furthermore, the water content of the contact lenses was proportional to the MPC content in the polymer. The hydrated PC moiety of MPC drastically altered the network of the copolymer by inserting water molecules, which were trapped in the concave region of the surface. The addition of MPC had negative effects on all examined strength factors because of structural destabilization of the copolymer through water insertion. The anti-deposition effects of MPC were verified by examining the lysozyme and lipid adsorption abilities of the prepared contact lenses.

The results of the study revealed that MPC enhanced interactions of the poly(HEMA-MPC) copolymer with water molecules. These interactions weakened the mechanical strength of the copolymer but markedly improved the anti-adsorption property of the biomolecules. The optimal proportion of HEMA-MPC for contact lenses is in the range of 14.9% to 28.5% (136).

1.15.1.2 Surface Grafting

Biomimetic phospholipid polymers possess excellent anti-biofouling properties and biocompatibility and have the potential to play a valuable role in the surface modification of a silicone hydrogel (137). A representative phospholipid polymer containing a MPC unit can suppress nonspecific protein adsorption, can increase the cell compatibility and contributes to blood compatible biomaterials.

The synthesis of the monomers MPC and (2-methacryloyloxy)ethyl-[*N*-(2-methacryloyloxy)ethyl] phosphorylcholine is shown in Figure 1.55.

The phospholipid polymer coating on the silicone hydrogel improved its water wettability and biocompatibility, while maintaining high oxygen permeability, compared with the original silicone hydrogel. Furthermore, the prepared phospholipid-type intermolecular crosslinking agent made it possible to synthesize a 100% phospholipid polymer hydrogel that can enhance the anti-biofouling properties and biocompatibility (137).

A silicone hydrogel contact lens material has been designed for long-term ocular performance. An enhancement of this silicone hydrogel contact lens material was achieved through surface modification using a crosslinkable bioinspired 2-methacryloyloxyethyl phosphorylcholine polymer, which creates a soft surface gel layer on the silicone hydrogel base material (138).

The surface properties of this 2-methacryloyloxyethyl phosphorylcholine polymer-modified lens were characterized under hydrated condition revealing, inter alia, its unique polymer structure, excellent hydrophilicity, lubricity, and flexibility. The analysis of the 2-methacryloyloxyethyl phosphorylcholine polymer layer in a hydrated state was performed using a combination of a high-resolution environmental scanning electron microscopy and atomic force microscopy.

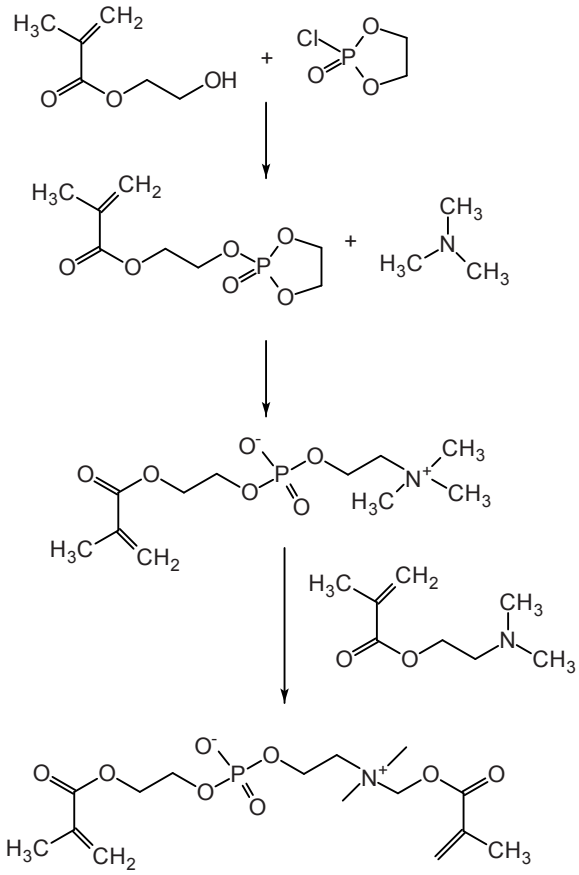


Figure 1.55 Synthesis of 2-methacryloyloxyethyl phosphorylcholine and (2-methacryloyloxy)ethyl-[*N*-(2-methacryloyloxy)ethyl] phosphorylcholine (137).

Compared to the silicone hydrogel base material, this surface had a higher captive bubble contact angle, which corresponds to higher hydrophilicity of the surface. In addition, the hydrated 2-methacryloyloxyethyl phosphorylcholine polymer layer exhibited an extremely soft surface and reduced the coefficient of friction by more than 80%. These characteristics were attributed to the hydration state of the 2-methacryloyloxyethyl phosphorylcholine polymer layer on the surface of the silicone hydrogel base material. Also, the interaction force of protein deposition was lowered on the surface (138).

1.15.1.3 Silicone Hydrogels

Silicone hydrogels from MPC and bis(trimethylsilyloxy) methylsilylpropyl glycerol methacrylate (SiMA) were synthesized using two methods (139):

1. Random copolymerization with a small amount of crosslinking agent, and
2. Construction of an interpenetrating network (IPN) structure composed of crosslinked poly(MPC) chains and crosslinked poly(SiMA) chains.

Bis(trimethylsilyloxy)methylsilylpropyl glycerol methacrylate is shown in Figure 1.56.

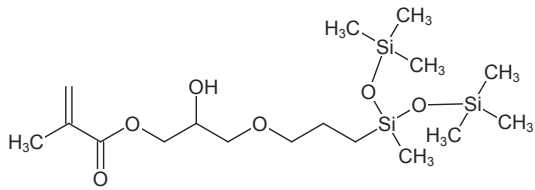


Figure 1.56 Bis(trimethylsilyloxy)methylsilylpropyl glycerol methacrylate.

The polymerization was carried out by photoreaction. The surface hydrophilicity and water absorbability of P(SiMA-co-MPC) increased with an increase in the MPC unit composition.

On the other hand, in the case of the IPN, a superhydrophilic surface was obtained by the surface enrichment of the MPC units.

The optical and mechanical properties of PSiMA-ipn-PMPC are suitable for use as a material for preparing contact lenses. In addition, the oxygen permeability remains high because of the Poly(SiMA) chains. The MPC units at the surface of the hydrogels reduce protein adsorption effectively (139).

1.15.1.4 Grafted Silicone Hydrogels

Silicone hydrogel contact lenses permit an increased oxygen permeability through their incorporation of siloxane functional groups (140). However, contact lens biofouling can be problematic with these materials. So, a surface modification to increase the lens compatibility is necessary for acceptable properties.

The creation of an antifouling contact lens surface was tested through a novel grafting method. A polymer incorporating MPC, cf. Figure 1.11, that is well known for its antifouling and biomimetic properties, was grafted onto the model lens surfaces using surface-initiated atom transfer radical polymerization (ATRP). This modification generated a unique double-grafted polymeric architecture designed to resist protein adsorption through the presence of a surrounding hydration layer due to the PC groups and steric repulsion due to the density of the grafted chains. The polymer was grafted from model silicone hydrogel contact lens using a four-step surface-initiated ATRP process (140).

1.15.2 2-Hydroxyethyl methacrylate

Hydrogels based on polymers from HEMA were examined for contact lenses (141).

A study was conducted on how to reduce the adsorption of protein components from tears and bacterial deposition by a surface modification of the hydrogel with different functional groups. These groups included carboxylic acid, primary amine, and quaternary ammonium.

The hydrogel was treated with a solution of sulfuric acid for partial hydrolysis of the poly(2-hydroxyethyl methacrylate) (PHEMA) ester groups to induce acid groups on the surface of the hydrogel. Carboxylic acid groups of the modified PHEMA were converted to

primary amine and quaternary ammonium groups via carbodiimide chemistry.

The surface physical and chemical properties of different samples were investigated by atomic force microscopy and X-ray photoelectron spectroscopy, respectively.

A bicinchoninic acid assay was used to evaluate protein deposition from artificial tear fluid on samples. Bicinchoninic acid is shown in Figure 1.57.

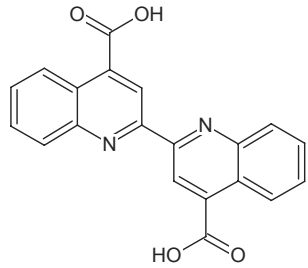


Figure 1.57 Bicinchoninic acid.

Also, the antibacterial properties of the modified hydrogels were investigated with a culture of *Staphylococcus aureus*, one of the major causes of eye infections.

The cytotoxicity test for the modified hydrogels was done by optical microscopy and immunofluorescent staining for corneal epithelial marker cytokeratin (red) and DAPI (blue) for the identification of the nuclei. Cytokeratins are keratin proteins. 4′,6-Diamidin-2-phenylindol (DAPI) is shown in Figure 1.58.

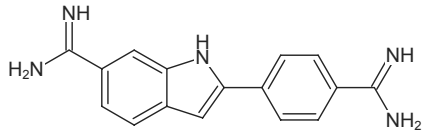


Figure 1.58 4′,6-Diamidin-2-phenylindol.

A biofouling evaluation of hydrogels is shown in Table 1.34.

The number of colony-forming units (CFUs) was determined to

Table 1.34 Protein absorption of artificial tear fluid on the surface of sample groups (141).

Modified hydrogel	Protein amount/[$\mu g\, cm^{-1}$]
Neat	26.5
Acid	22.0
Amine	12.1
Ammonium	7.2

quantify bacterial attachment to the samples. The results are shown in Table 1.35.

Table 1.35 Number of colony-forming units (141).

Modified hydrogel	Colony-forming units
Neat	264.3
Acid	354.8
Amine	57.1
Ammonium	78.6

The data of these tests showed that positively charged amine and ammonium groups efficiently resisted the protein adsorption and the bacterial deposition compared to alcohol and carboxylic acid groups (141).

1.15.3 Chitosan

Chitosan-conjugated PHEMA was used for contact lens application (142), with the aim of increasing the affinity of anionic drugs used in treatment of eye diseases. A part of a chitosan polymer is shown in Figure 1.59.

The delivery of the small molecule anionic drug, ascorbic acid, cf. Figure 1.30, from the chitosan-conjugated PHEMA was evaluated (142). The chitosan immobilization improves the drug loading efficiency and induces a sustained release of ascorbic acid. The chitosan-modified hydrogel also reduces the biofouling of tear fluid components.

The results of this study showed that surface modification by chitosan inhibits protein and bacterial deposition on the contact lens.

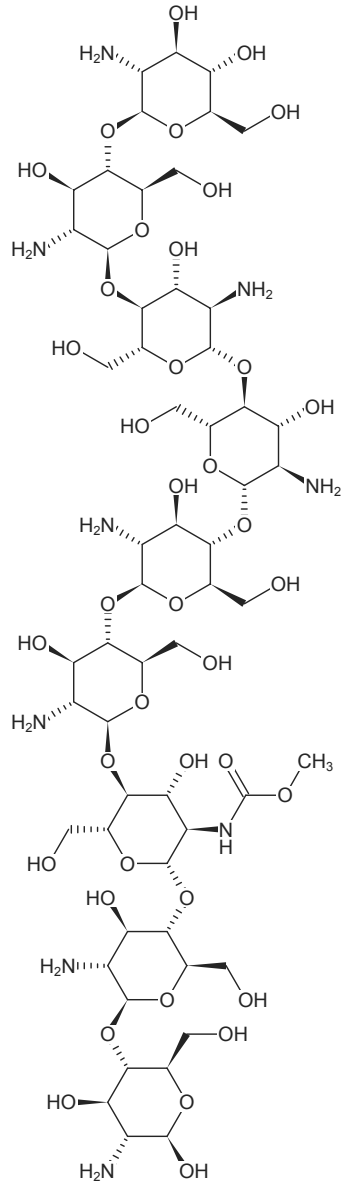


Figure 1.59 Chitosan structure.

Protein absorption analysis revealed that neat PHEMA adsorbed tear proteins at a density of 28.4±4.4 $\mu g\, cm^{-2}$, whereas the chitosan-conjugated hydrogel adsorbed tear proteins at a density of 18.5±1.8 $\mu g\, cm^{-2}$. Moreover, the neat PHEMA bacterial adhesion had a mean CFU value of 273±27. However, a significant decrease in the number of bacterial colonies was observed in the chitosan group with a CFU value of 9±6 (142).

1.16 Drug Delivery via Hydrogel Contact Lenses

1.16.1 Hydrogels with Phosphate Groups

Hydrogels that contain phosphate groups in side chains were studied for their usefulness in drug-loaded soft contact lenses (143). Naphazoline (2-(1-naphthyl methyl)-2-imidazoline nitrate), a model drug having a cationic group, was incorporated into a soft contact lens because of its phosphate groups and was released over a period of about 14 *h*. For the soft contact lense, the naphazoline content was equivalent to the phosphate group content. Naphazoline is shown in Figure 1.60.

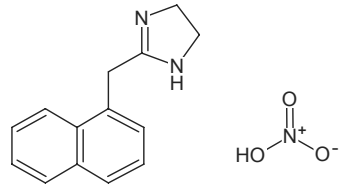


Figure 1.60 Naphazoline.

Drug-loaded soft contact lenses can be designed to contain the needed amount of a drug through the choice of the ionic group for the ligand. Furthermore, the soft contact lens having amide groups and phosphate groups had high transparency and an unchanged shape.

As monomers for the contact lenses, 2-methacryloxyethyl phosphate, cf. Figure 1.61, MA, and EGDMA were used (143). Here, EGDMA acts as crosslinking agent. As initiator, *AIBN* was used

for the preparation of the anionic hydrogels. The drugs were introduced into the hydrogel by immersion in a 0.5% naphazoline aqueous solution at 25°C for 2 *d* to allow naphazoline adsorption. Free naphazoline was removed from the hydrogel by consecutive washing with an aqueous solution at 25°C for 24 *h*.

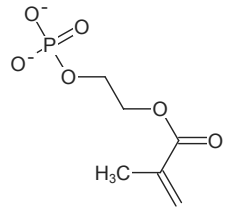


Figure 1.61 2-Methacryloxyethyl phosphate.

The relationship between the MA and 2-methacryloxyethyl phosphate ligand concentration and the naphazoline content of the hydrogel is shown in Figure 1.62.

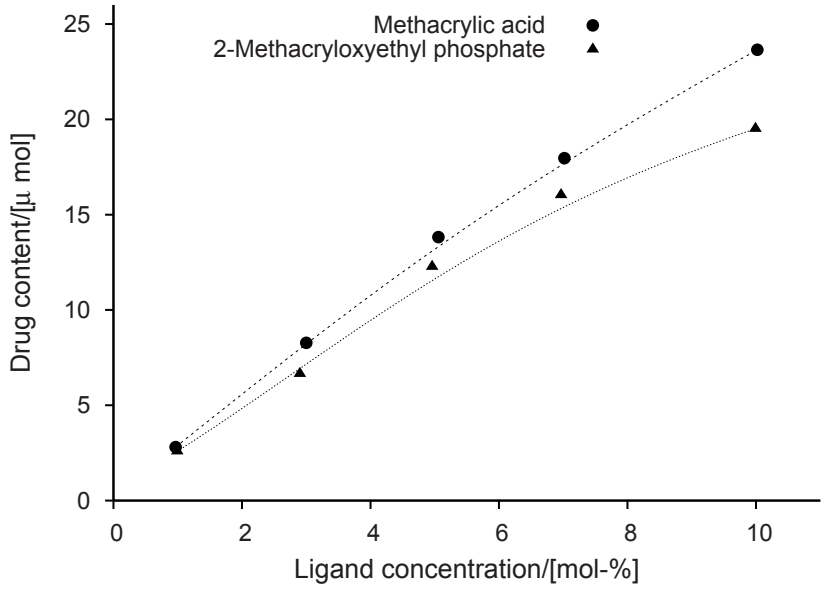


Figure 1.62 Ligand concentrations versus naphazoline content.

For MA hydrogels, naphazoline in the hydrogels was released for

over 5 *h*, but for 2-methacryloxyethyl phosphate hydrogels, naphazoline was continuously released for 14 *h*.

It is suggested that amide groups and phosphate groups must be introduced into the polymer in equimolar amounts to give the necessary polymer-drug interaction. Therefore, hydrogels having a drug delivery system were synthesized by the inclusion of a phosphate group and an amide group. These hydrogels are also applicable to soft contact lens materials (143).

1.16.2 Ophthalmic Drug Delivery

Polymeric hydrogels for contact lens-based ophthalmic drug delivery systems, their advantages and drawbacks, have been critically analyzed in reviews (144, 145).

Only about 5% of drugs administrated by eye drops are bioavailable, and currently eye drops account for more than 90% of all ophthalmic formulations. The bioavailability of ophthalmic drugs can be improved by a soft contact lens-based ophthalmic drug delivery system. Several polymeric hydrogels have been investigated for soft contact lens-based ophthalmic drug delivery systems (144):

1. Polymeric hydrogels for conventional contact lens to absorb and release ophthalmic drugs,
2. Polymeric hydrogels for piggyback contact lens combining with a drug plate or drug solution,
3. Surface-modified polymeric hydrogels to immobilize drugs on the surface of contact lenses,
4. Polymeric hydrogels for inclusion of drugs in a colloidal structure dispersed in the lens,
5. Ion ligand-containing polymeric hydrogels, and
6. Molecularly imprinted polymeric hydrogels which provide the contact lens with a high affinity and selectivity for a given drug.

Conventional soft contact lenses have the ability to absorb a number of drugs when the lenses are presoaked in the drug solution, subsequently releasing them into the post-lens lacrimal fluid. As an alternative, one can also insert conventional soft contact lenses

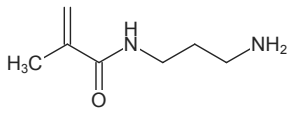
into eyes then apply eye drops. By this means, drugs can be absorbed and released by the soft contact lens, minimizing clearance and sorption through the conjunctiva (146–148).

HEMA polymers, which are widely used for preparing soft contact lenses, have been investigated for delivery of several ophthalmic drugs (149, 150).

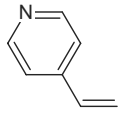
To enhance the potential of the PHEMA hydrogels as an effective biomaterial for a contact lens-based ophthalmic drug delivery system, 4-vinylpyridine and *N*-(3-aminopropyl)methacrylamide were incorporated into the network (151).

Also, copolymer hydrogels of DMA and 2-(*N*-ethylperfluorooctanesulfonamido)ethyl acrylate were investigated for their potential application in contact lens-based drug delivery systems (152).

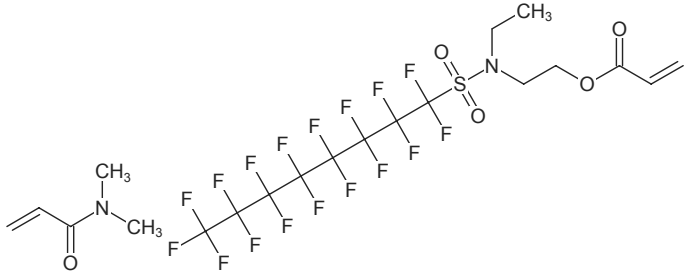
The abovementioned compounds are shown in Figure 1.63.



N-(3-Aminopropyl)methacrylamide



4-Vinylpyridine



N,*N*-Dimethyl acrylamide

2-(*N*-Ethylperfluorooctanesulfonamido) ethyl acrylate

Figure 1.63 Monomers for an ophthalmic drug delivery system.

2-(*N*-Ethylperfluorooctanesulfonamido)ethyl acrylate can be incorporated into the networks to modify the glass transition temperature and water sorption and desorption kinetics of the hydrogels by

changing the structure, location, or concentration of the hydrophobic group.

1.17 Simulation Methods

1.17.1 Ocular Topography Parameters

To evaluate the effect of varying lens and ocular topography parameters on soft contact lens fit, a computer spreadsheet model was used (153). The spreadsheet-based computer model used a ellipto-conical corneal model coupled with population data on the corneoscleral topography obtained in a clinical study. The model calculated the lens edge strain (circumferential elongation) as a predictor of the tightness of the lens. The following parameters were systematically varied (153):

1. Corneal curvature,
2. Corneal diameter,
3. Corneal shape factor,
4. Corneoscleral junction angle,
5. Lens base curve, and
6. Diameter.

The ellipto-conical corneal model showed a closer concordance with the actual measurements of the corneal sagittal height than a simple elliptical model (limits of agreement, ±0.20 vs. ±0.25 *mm*; p = 0.0015). For an eye with average ocular parameters wearing a typical soft contact lens design (lens base curve, 8.60; diameter, 14.2 *mm*), the model calculated an edge strain of 2.7%.

For the same soft contact lens, the tightest fit (8.5% strain) was found with the eye showing the combination of smallest, flattest, most aspheric cornea. Conversely, the loosest fit (−2.6%) was found with the eye showing the combination of largest, steepest, least aspheric cornea. A change in the lens base curve of 0.4 *mm* typically resulted in changes in edge strain of less than 2.5%, whereas a change in diameter of 0.5 *mm* resulted in a change of less than 2%. Using the typical soft contact lens design and average corneal model, wide variations in corneoscleral junction angle did not critically affect lens fit. More extreme combinations of soft contact lens and ocular

parameters resulted in an edge strain likely to result in a tight (>6%) or loose fit (<0%) (153).

1.17.2 Rigid Gas-Permeable Lenses

Multi-view learning has been one of the focuses in medical image analysis in the recent years. The combination of various image properties for medical decision-making has had a high impact on the medical field (154).

The Pentacam-4 refractive map is one of the sources for detecting rigid gas-permeable lens properties for irregular astigmatism patients. A radial-sectoral segmentation approach has been presented to analyze the Pentacam-4 refractive maps individually.

Canonical correlation analysis and a neural network with two hidden layers is applied as a means of multi-view learning and base curve identification. The combination of the segmentation method with canonical correlation analysis combinatory feature vector, results in a 0.970 coefficient of determination in rigid gas-permeable base curve identification.

This result considerably improves the current findings and confirms optometrist findings based on the importance of the image maps. The proposed method has a great impact on reducing patient chair time and optometrist and patient satisfaction (154).

1.17.3 Computerized Videokeratography

Computerized videokeratography has become the standard method for measuring the corneal curvature after refractive surgery. However, only a few resources exist on the use of computerized videokeratography data for postoperative contact lens fitting, and no recommendations exist on the selection of the best topographic algorithm relevant to gas-permeable lens fitting.

The optimal use of topographic data was investigated to fit spherical gas-permeable contact lenses on patients who have undergone laser-assisted *in-situ* keratomileusis (LASIK) (155).

LASIK is performed by lifting the front surface of an eye by forming a thin hinged flap under which the shape of the cornea is changed

by using an excimer laser or other surgical device (156). A microkeratome is usually used to cut the flap, but a femtosecond laser can also be used to make the flap.

A retrospective analysis of computerized videokeratography maps from eight post-LASIK eyes fitted with spherical gas-permeable lenses was performed in the Contact Lens Service of the Department of Ophthalmology at Case Western Reserve University and University Hospitals of Cleveland (155).

Axial and tangential maps from the Dicon CT 200 (version 3.50) or Humphrey Atlas (version A8) topographer were analyzed (155). Averaged dioptric curvatures from different locations (inferior, superior, and temporal) at various distances (2.0 *mm*, 2.5 *mm*, 3.0 *mm*, 3.5 *mm*, and 4.0 *mm*) from the vertex normal of each eye were compared with the base curves of the prescribed gas-permeable contact lenses.

One-way analysis of variance, Pearson correlation analysis, and paired t-tests showed that the best topographic predictors of a successful gas-permeable base curve were the average curvatures at the 4.0 *mm* distance on the axial maps ($r = 0.8078$, $P=0.05$) and at the 2.0 *mm* distance on the tangential maps ($r = 0.9738$, $P = 0.0002$).

The mean dioptric powers of the gas-permeable base curve, axial map 4.0 *mm* curvature, and tangential map 2.0 *mm* curvature were 41.50 *D* (diopters), 42.65 *D*, and 42.67 *D*, respectively.

So, to simplify and guide gas-permeable fitting after LASIK, the average dioptric curvature 4.0 *mm* from the vertex normal on axial maps or 2.0 *mm* from the vertex normal on tangential maps are the best predictors of accurate gas-permeable base curve selection (155).

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