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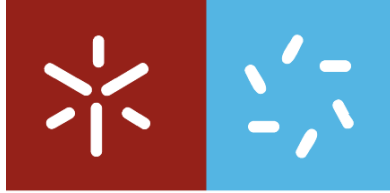
Ana Rita Ferreira da Silva

Ionic Permeability of Soft Contact Lenses

Permeabilidade Iónica das Lentes de

Contacto Moles

Outubro 2013



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Dissertação de Mestrado

Mestrado em Optometria Avançada

Trabalho efetuado sob a orientação de:

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To my home!

Acknowledgment

This dissertation is the final outcome of another of my academic journeys. A personal achievement, fruit of many labour hours and a constant challenge, since many concepts I hadn't previously studied were approached. This dissertation would not have been possible without the support of many people. Hence, in this page I would like name all of them.

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RESUMO

A permeabilidade iónica das lentes de contacto ao sal é considerada pelos fabricantes um parâmetro de controlo de qualidade do material. Este parâmetro diz respeito à capacidade dos iões de Na^+ Cl^- passarem através da matriz da lente de contacto e, acredita-se que o movimento da lente de contacto sobre a superfície ocular seja afetado quando este assume valores inferiores a $2-4 \times 10^{-7}$. Contudo existe pouca informação bibliográfica disponível referente a este assunto.

Recorrendo à técnica de Ionoflux, em que a lente estudada é colocada entre dois compartimentos contendo água ultrapura e solução de 1M de NaCl, medimos a permeabilidade iónica de uma lente de hidrogel convencional e de três de silicone hidrogel. A razão pelo qual estas lentes foram escolhidas deve-se ao facto de terem diferentes conteúdos em água e desenho similar quando são do mesmo fabricante. Foram avaliadas as seguintes condições experimentais: permeabilidade iónica das lentes de contacto a iões Na^+ Cl^- com agitação na câmara dadora, sem agitação na câmara dadora depois de estas terem sido previamente banhadas numa solução NaCl 1M ou em água ultra pura. Foi também avaliado qual o efeito da potência das lentes (-1.00,-1.50 e -4.75) e o efeito de 1 mês de uso no valor da permeabilidade iónica das lentes Comfilcon A.

Este trabalho permitiu constatar que existem diferenças na ordem de menos de 5% entre as condições experimentais com e sem agitação. Também se verificaram diferenças significantes no valor da permeabilidade iónica obtida quando as lentes foram previamente banhadas em água pura e em solução de 1M de NaCl. Resultados inovadores foram obtidos quando foi avaliado o efeito de uso durante um mês no valor de permeabilidade iónica: diminuição de cerca de 25 a 38% da permeabilidade iónica. Entre as lentes de -1.00 e -4.75 verificou-se um incremento de cerca de 26% na permeabilidade iónica.

Palavras-chave: difusão, hidrogel, permeabilidade iónica, silicone hidrogel

ABSTRACT

The ionic permeability of contact lenses salt, is regarded by manufacturers as a quality control parameter of the material. This parameter refers to the ability of the Na⁺ + Cl⁻ ions have to pass through the matrix of the contact lens and it is believed that the movement of the contact lens over the ocular surface is affected when this assumes values lower than 2.4×10^{-7} . However, there is little biographical information available concerning this subject.

Using the Ionoflux Technique, wherein the lens studied was placed between two compartments, containing ultrapure water and 1M NaCl solution, we measure the ion permeability of a lens of conventional hydrogel and three silicon hydrogel. The reason that these lenses were chosen due to the fact that they have different water contents and similar design when they are of the same manufacturer. We evaluated the following experimental conditions: ionic permeability of contact lenses to Na⁺ and Cl⁻ ions with stirring in the donor chamber, without stirring in the donor chamber, after they have previously been soaked in 1M NaCl solution or ultrapure water. It was also evaluated the effect of power lens (-1.00, -1.50 and -4.75) and the effect of 1 month using in the value of the ion permeability of lenses Comfilcon A.

With this work it was established that there are differences in the order of less than 5% between the experimental conditions with and without stirring. Also no significant differences were found in the ionic permeability value obtained when lenses were first soaked in pure water and in a 1M NaCl solution. Completely innovative results were obtained when we evaluated the effect of using for a month in the ionic permeability value. With use there was a decrease of about 25 to 38% of the ionic permeability. Between -1.00 and -4.75 D lenses there was an increase of about 26% in ionic permeability.

Keywords: diffusion, hydrogel, ionic permeability, silicone hydrogel

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ABBREVIATIONS AND ACRONYMS

AA	Acrylic Acid
BLs	Boundary Layers
C	Carbon
Ca⁺²	Calcium ions
Cl⁻	Chlorine ion
CLs	Contact Lenses
<i>D</i>	Diffusion coefficients
DEAA	N,N-diethylacrylamide
DEAEM	2-(diethylamino) ethyl methacrylate
Dk	Permeability to oxygen
DMAAM	<i>N,N</i> -dimethylacrylamide
DMS	Dexamethasone
DMSA	Dexamethasone 21 acetate
DSC	Catalyzation of disuccinimidyl carbonate
DSC	Differential Scanning Calorimetry
EGDMA	Ethylene glycol dimethacrylate
EWC	Equilibrium Water Content
FDA	Food and Drug Administration
FI	Fluorine
FOSA	2-(<i>N</i> -ethylperfluorooctanesulfonamido) ethyl acrylate
GMA	Glyceryl methacrylate
H	Hydrogen
HA	Hyaluronic Acid
HEAA	N-hydroxyethyl acrylamide
HEMA	Hydroxyethylmethacrylate
IOP	Intraocular pressure
ITC	Isothermal titration calorimetry
<i>k</i>	Partition coefficient

LbL platform	Layer-by-Layer platform
MA	Methacrylic acid
MAPTAC	Methacrylamide propyl trimethyl ammonium chloride
MEC	Minimum Effective Concentration
MMA	Methylmethacrylate
MOEP	2-methacryloxyethyl acid phosphate
MSC	Maximum safe concentration
N	Nitrogen
NaCl	Sodium Chloride
NMR	Nuclear Magnetic Resonance
NRF	Release Norfloxacin
NVP	N-vinyl pyrrolidone
O	Oxygen
PBAEs	Poly(β -amino esters)
PDMS	Polydimethylsiloxane
PMMA	Polymethylmethacrylate
Poltf	Posterior lens tear film
PolyCD	Poly (carboxymethyl- β -cyclodextrin)
PVA	Poly-vinyl alcohol
RPG	Rigid Permeable Gas
Rpm	Revolutions per minute
Si	Silicon
Si-Hy	Silicone Hydrogel
TGA	Thermogravimetric analysis
TRIS	Methacryloxypropyl tris(trimethylsiloxy)silane
UV	Ultraviolet
Zn⁺²	Zinc ions

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1. LITERATURE REVIEW

1.1 Soft contact lenses

A soft contact lens is a thin piece of rounded plastic placed directly onto the cornea of the eye. These can be used for vision correction or as a cosmetic or therapeutic (e.g. drug delivery and ocular tissue protective) device.

Currently, hydrogel materials are divided into two groups: conventional hydrogel material (low oxygen permeability) and silicone hydrogel material (high oxygen permeability).

An hydrogel polymer should have the following properties to be suitable as a contact lens material: optical transparency, a refractive index similar to the cornea (≈ 1.3376), oxygen-permeability, sufficient hydraulic and ionic permeability, dimensional stability, adequate mechanical properties and biocompatibility with the ocular environment¹. A biocompatible contact lens will not substantially damage the surrounding ocular tissue and ocular fluid during the time period of contact and will interact as less as possible with surrounding fluids.

The first commercial soft contact lenses were developed through Polymethylmethacrylate (PMMA)¹ lathing, but these had no oxygen permeability. In order to improve oxygen permeability, polymers containing silicone groups were developed. Siloxane –containing polymers have high oxygen permeability.

However, polysiloxanes are typically highly lipophilic. The contact lens containing polysiloxanes adhere to the eye and do not have the necessary movement. In addition, polysiloxanes lipophilicity promotes adhesion to the lens of lipids and proteins in the tear fluid, causing a haze which interferes with vision.

1.1.1 Main monomers of soft contact lens

Polymers are made from high-molecular-weight chains and consist of repeating units called monomers. Their long chain length, their composition (e.g. carbon(C), oxygen (O), hydrogen (H), nitrogen (N), silicon (Si) and fluorine (F)), their geometric arrangement and the stability of the established bonds achieve unique polymers with distinctive properties which in turn dictate a particular function and utility of the material. Materials made from one monomer are called homopolymers and materials made from more than one type of monomer are termed copolymers.

The soft contact lens is formed by polymerization, preferably copolymerization, of at least one oxypem polymerizable material and at least one ionopem polymerizable material.

1.1.1.1 Oxypem polymerizable materials

Oxypem polymerizable materials are material that can be polymerized to form a polymer displaying a relatively high oxygen diffusion rate.

These include siloxane-containing macromers and monomers, fluorine-containing macromers and monomers, and carbon-carbon triple bond-containing macromers and monomers. These can also contain hydrophilic groups. The preferred oxypem polymer contains dialkyl siloxane groups especially dimethyl siloxanes. The siloxane-containing macromer may also include hydrophilic groups².

1.1.1.2 Ionopem polymerizable materials

Ionopem polymerizable materials can be polymerized to form a polymer displaying a relatively high ion diffusion rate. These include acrylates and methacrylates, such as 2-hydroxyethyl methacrylate, acrylamide, methacrylamide, and dimethylacrylamide; poly (alkylene glycols), such as poly (ethylene glycol); N-vinyl pyrrolidone such as N-vinyl-2-pyrrolidone; and the like and mixtures thereof².

The main monomers used to manufacture soft contact lens³ are:

- Methylmethacrylate (MMA) is used in some hydrogel soft lenses to improve mechanical length, in some copolymers used in RPG lenses and in rigid PMMA lenses. Monomer with a good optical quality, impermeability to oxygen and that imparts rigidity. Figure 1
- Hydroxyethylmethacrylate (HEMA) is also known as 2-hydroxy-ethyl methacrylate. These have the same polymer backbone that MMA, but with the hydrophobic methyl (CH₃) ester side radical in place of hydrophilic hydroxyethyl radical (-CH₂CH₂OH). Wichterle and Lim developed HEMA polymer (PHEMA) that has 36% of EWC and ≈9 barrer of oxygen permeability⁴. HEMA also constitute several copolymers used in other hydrogel soft contact lens. Figure 1
- Methacrylic acid (MA) is highly hydrophilic and ionizable (COO⁻ and H⁺). This molecule is also related chemically to MMA and HEMA but with a carboxyl group (organic acid -COOH). These monomer is used in RPG Lens to improve the wettability and in FDA group IV, ionic material. Figure 1
- Glyceryl methacrylate (GMA) is highly hydrophilic and was originally copolymerized with MMA in the ultrathin CSI hydrogel lenses. These is also a methacrylate derivate, with two nonionizable hydrophilic groups (OH) versus one in HEMA. Actually these is copolymerized with HEMA to reduce the soft contact lens dehydration.

- Ethylene glycol dimethacrylate (EGDMA) also called ethylene dimethacrylate (EDMA) is a cross-linking agent that adds stability and stiffness to the polymer. Depending EGDMA amount present in the polymer, the hydration and gas permeability of hydrogels can be reduced.
- N-vinyl pyrrolidone (NVP) also known as vinyl pyrrolidone (VP) is a very hydrophilic nonionic cyclic lactam (-NCOCH₂-). These is copolymerized with HEMA or MMA to manufacture high EWC materials of FDA group II. NVP is also used in Si-Hi materials. It have been reported that the presence of vinyl pyrrolidone can be induce the lipid deposit. Figure 1
- Methacryloxypropyl tris(trimethylsiloxy)silane (TRIS) was an important constituent in the early RPG lens materials. Modifications in molecular structure of TRIS have been made to improve their compatibility with hydrophilic monomers in the Si-Hy lenses. TRIS contain the element silicon in the form of siloxane radicals (-Si-O-Si(CH₃)₃) that after polymerization have a carbon to carbon polymer backbone with the siloxane moieties on the side .TRIS and similar compounds are not members of the silicone family (such as polydimethylsiloxane used in elastometric CLs), where the siloxane radicals are the links forming the backbone of the polymer. Figure 1
- Siloxane: The widely silicone polymer used to manufacture silicone rubber is polydimethylsiloxane(PDMS). Silicone rubber is a cross-linked network of polysiloxanes with high oxygen permeability (about 600 barrer) but is unwettable by tears and needs to be surface-treated. Figure 1
- Fluoromethacrylates were used to increase the free volume fraction of TRIS copolymers in RPG, thus was possible to increase the RPG oxygen permeability.

Fluorinated compound as well as silicone, and TRIS are very hydrophobic. When these are linked to hydrophilic monomers in Si-Hy, the surface maintain hydrophobic and is necessary to treated to make the lens hydrophilic and compatible with the ocular surface.

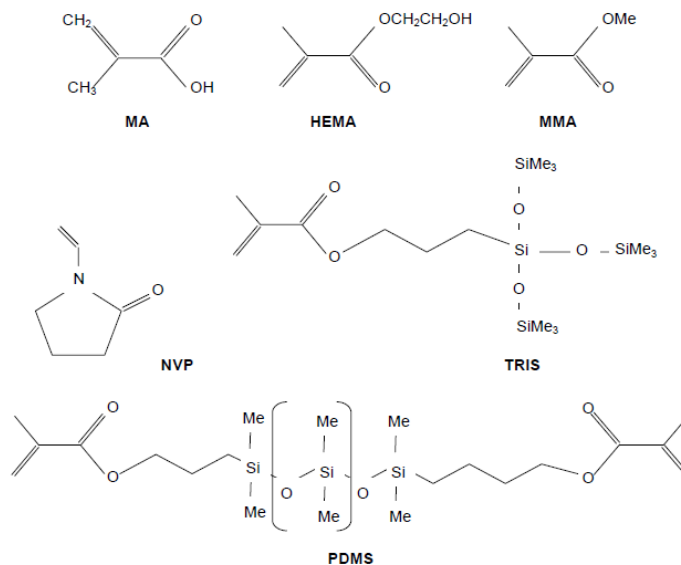


Figure 1 Illustration the monomers chemical structure of monomers used to manufacture soft contact lens (**MA, HEMA, MMA, NVP, TRIS and PDMS**)

1.1.2 *Soft contact lens properties*

A soft or hydrophilic contact lens is a water-swollen polymeric materials that can absorb a high amount of water molecules but not be dissolve in water. The water in soft contact lens brings some benefits but also some disadvantages. Soft contact lenses have a flexible nature due to water molecules which enhance the patient comfort. Water also provides a mechanism for oxygen delivery to the cornea due to its ability to dissolve and transmit oxygen. On the other hand, water can also decrease lens mechanical properties, which often requires the addition of ethylene glycol or other crosslinking agents to increase stability. The water can organic or inorganic deposit formation and serve as a ground for microbial growth which require an effective care system.

1.1.2.1 Equilibrium water content

Equilibrium water content is the ability of the material to bind water. The Food and Drug Administration classify soft contact lens according to the material properties of water content and electrostatic charge.

Table 1 FDA Soft Lens Classifications

Category (FDA)	Water content	Electrostatic Charge
Group 1	Low water (□ 50% H ₂ O)	Nonionic
Group 2	High water (□ 50% H ₂ O)	Nonionic
Group 3	Low water (□ 50% H ₂ O)	Ionic
Group 4	High water (□ 50% H ₂ O)	Ionic

1.1.2.2 Electrostatic charge

Soft contact lens polymers can be ionic or nonionic depending on the monomers used. An ionic hydrogel is defined as containing more than 0.20% of ionic constituents. Electrostatic charge is directly related to the level of protein (mainly lysozyme) adhesion. Several studies demonstrated that the level of protein adhesion is higher in ionic materials.⁵

1.1.2.3 Wettability

Wettability of contact lens relates to its ability to attract and interact with the precorneal tear film. Wettability depends on the surface energy of the contact lens and a low surface tension of the tear film. A wettable contact lens has a surface with high surface energy, which is a hydrophilic surface, which in combination with relatively low surface tension of the tear film promotes the interaction between the fluid and the material. To improve wettability of contact lenses are applied wetting agents to the surface which lower surface tension and allow water to spread across the lens surface. The main problem with this method is that wetting agents eventually wear off and the CL surface will become less wetted as the day goes on. Si-Hi contact lenses have hydrophobic silicone, siloxysilane (TRIS) and perfluoro moieties that affect the wettability of the lenses. Multiple strategies have been developed to overcome these problems such as creating lens surface with chemical properties similar to natural human tissue and

modifications of the polymer surface to limit interaction with surrounding materials instead of to imitate biological tissues.

1.1.2.4 Viscosity and friction

Viscosity and friction is closely correlated with surface energy and wettability and the movement of contact lens depend strongly on this parameter. Friction depends of contact lens hydration and surface properties.

1.1.2.5 Permeability to oxygen

Permeability to oxygen is a key performance characteristic for contact lenses. It is characterized by its Dk value. Dk is the product of the diffusivity (D) and the oxygen partition coefficient (k). A lens Dk value is an intrinsic property of the material to transport oxygen through its bulk and is independent of thickness. It is expressed in terms of barrer. A more clinically applicable measure is the oxygen transmissibility, or Dk/t , which refers to the ability of a specific lens to deliver oxygen to the cornea considering the thickness of the lens “membrane”. This value is expressed in terms of barrer/mm. To maintain ocular health under closed eye conditions, lens oxygen permeability should exceed 100 barrer while for daily (open eye) conditions, values in the order to 24 to 35 are sufficient .⁶

1.1.2.6 Ion permeability

The researchers have been defended that lens movement on the eye is compromised by the value of salt permeability through contact lens. Then, it was suggested that the salt (NaCl) permeability of an aqueous-saturated soft contact lens should exceed $2-4 \times 10^7$ cm²/s at eye temperature (35°C). When the salt permeability value is lower than reference value the lens movement on the eye is compromised. The salt permeability also permits exchange of water, electrolytes, and nutrients between the pre-lens and post-lens tear films.

Yasuda et al.⁷, in 1968, measured aqueous NaCl permeability (P), diffusion coefficients (D), and equilibrium partition coefficients (k) for crosslinked hydrogels. They verified that the salt diffusivity and partition coefficient increased as the membrane water content (w) increased. In agreement with free-volume theory, the NaCl increased monotonically with membrane water content once the partition coefficient varied linearly with water volume fraction for high-water-

content materials. Yoon and Jhon⁸ investigated Hydroxyethyl methacrylate (HEMA)-based membranes with different crosslink densities and confirmed the results obtained by Yasuda et al.

Hamilton et al. and Murphy et al. measured the permeability of aqueous strong electrolytes (including NaCl) through poly(hydroxyethyl methacrylate) (PHEMA) and pHEMA/methyl methacrylate copolymer membranes. The results demonstrated that salt permeability increase with the increase of hydrogel water content. They established that the influence of ion size, ion and polymer water structure also contribute to salt permeability in hydrogels.^{9,10}

Nicolson et al.¹¹ argue that water is compressed out of a contact lens during a blink and replenished during an interblink period. The squeezed-out water maintains a thick enough post-lens tear film which avoids the contact lens adhesion on ocular surface. Therefore, a threshold water hydraulic permeability is necessary to maintain lens movement. These authors, also suggested that the salt permeability indirectly reflects water transport rate through a soft contact lens, which is also a relevant parameter when it comes to understand the dynamics of solutes and gas molecules across the lens material.

Tighe¹², with a simple calculation demonstrated that to maintain an adequate PoLTF boundary layer thickness is necessary a critical hydraulic permeability.

Monticelli et al. disagree with the need of a squeeze-out nor a squeeze-through mechanism to maintain the PoLTF because hydraulic permeability of soft contact lens are tiny.

Domschke et al. and later Nicolson and Vogt argue an alternate explanation to critical salt permeability of soft contact lens. These authors suggested that continuous water paths disconnect below a critical water content in a hydrogel. A percolation model distinguishes lens material that bind on the cornea to those that will move over the ocular surface as required.¹¹

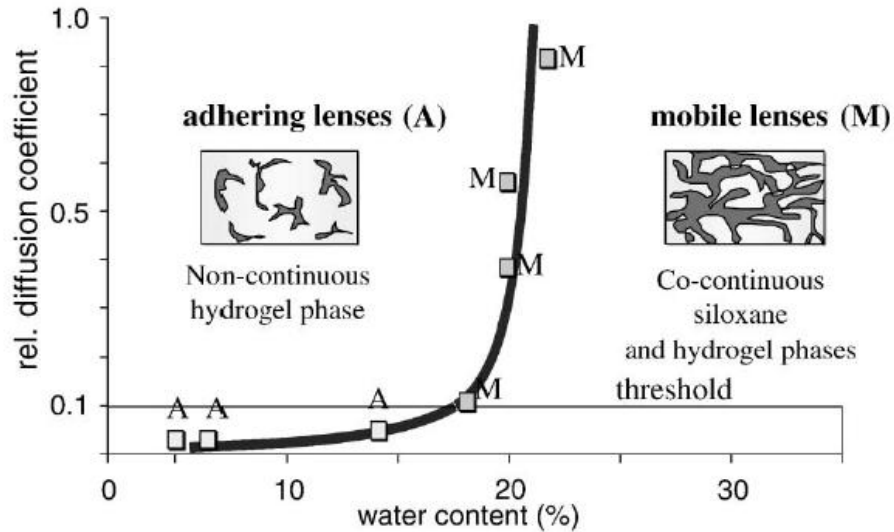


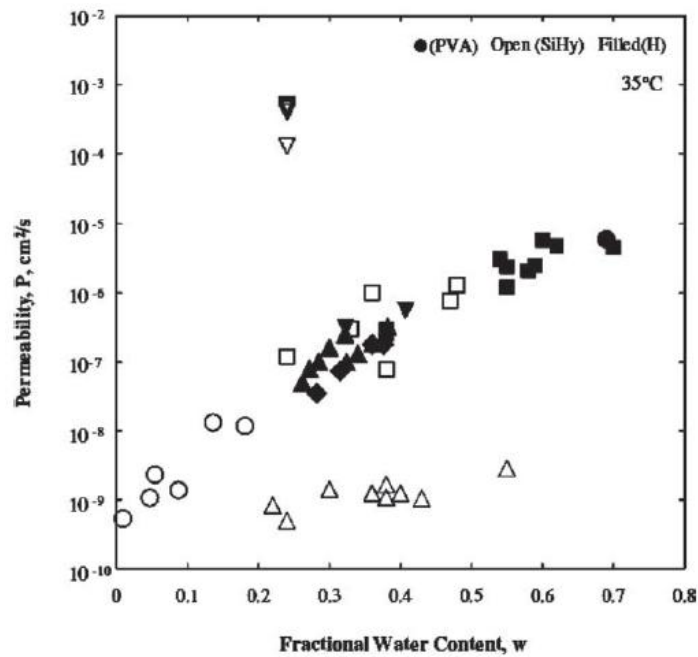
Figure 2 Percolation curve and diagrammatic representation of the phase morphologies derived from different siloxane hydrogel contact lenses manifesting either adherence or movement when placed on the eye. ¹¹

Recent measurements of salt permeability of low water content silicone hydrogel material demonstrated a continuous decline with decreasing water content down to 10^{-9} cm²/s at 0.2 wt% water which was well below the cited threshold necessary for on-eye movement.⁵⁷

Currently, there are two methods to measure the ion permeability, Ionoton and Ionoflux that will be explained in more detail in the next section. In recent work, Guan et al. measured the aqueous permeability, partition coefficient, and diffusion coefficient for commercial soft contact lens under physiological conditions. They used the Ionoton method in a miniature Stokes cell and demonstrated that the results obtained was similar to the values obtained with the Ionoflux method. The permeability increased exponentially with water content above a certain level. The partition is the ratio of concentrations of a compound in a mixture of two immiscible phases at equilibrium. This increased approximately linearly and the diffusivities decreased exponentially with increase in water content according to free-volume theory. They did not observe differences between the P , k , or D behavior for aqueous NaCl diffusion between HEMA-based and siloxane-based soft contact lenses.⁶

Table 2 a I (group I: nonionic, low w), II (group II: nonionic, high w), III (group III: ionic, low w), and IV (group IV: ionic, high w) give the FDA categories. H = HEMA; Si-Hy =siloxane; PVA = polyvinyl alcohol. Reproduced from Guan et al.⁶

Trade name (FDA category) ^a	<i>w</i> (wt %)	<i>P</i> (10 ⁸ cm ² /s)	<i>D</i> (10 ⁶ cm ² /s)	τ
Focus Night & Day (I/SiHy)	24	12	0.80	5.11
O2 Optix (I/SiHy)	33	30	1.25	4.09
PureVision (III/SiHy)	36	100	3.85	2.33
Acuvue Oasys (I/SiHy)	38	7.8	0.25	9.11
Biomedics 38 (I/H)	38	25	0.71	5.41
SofLens 38 (I/H)	38	29	1.12	4.33
Acuvue Advance (I/SiHy)	47	76	2.05	3.19
Biofinity (I/SiHy)	48	130	3.94	2.30
Clarity H ₂ O (II/H)	54	310	9.69	1.47
Biomedics 55 (IV/H)	55	120	7.06	1.72
Focus Monthly Visitint (IV/H)	55	240	8.89	1.53
Acuvue 2 (IV/H)	58	210	6.56	1.78
SofLens Daily Disposable (II/H)	59	251	7.84	1.63
Proclear One Day (II/H)	60	580	10.18	1.43
Proclear Sphere (II/H)	62	470	10.22	1.43
Focus Dailies (II/PVA)	69	600	8.45	1.57
SofLens One Day (II/H)	70	450	6.43	1.80



Graphic 1 Permeability (P) of aqueous NaCl in the SCL materials as a function of the equilibrium water content at 35°C: (●) PVA-based lens. The remaining filled symbols correspond to HEMA-based materials (H), whereas open symbols correspond to silicone-based materials (Si-Hy). (■□) Commercial lenses from this study. All other symbols represent hydrogel membranes: (△) from Willis et al.¹³, (▽) from Weikart et al.¹⁴, (○) from Kim et al.¹⁵, (▼) from Yasuda et al.⁷, (▲) from Yoon and Jhon⁸, and (◆) from Hamilton et al.¹⁶ and Murphy et al.¹⁷. The results of Yoon and Jhon⁸, Willis et al.¹³, and Weikart et al.¹⁴ were measured at room temperature. Reproduced from Guan et al.⁶

1.1.2.6.1 Technique for measuring the ionic permeability

1.1.2.6.1.1 Ionoflux Technique

This technique is a preferred method for determining the ion permeability of a lens that allows to determine the probability of adequate on-eye movement according to the Patent EP0819258B1. Ionoflux Technique use a conductimeter, an electrode with a temperature sensor, a donor chamber containing a salt solution, a receiving chamber containing milli-Q water (ultrapure water), a stir bar and a thermostat. The donor chamber is specially designed for sealing and securing contact lens. This has a glass tube which is threaded at the end and the glass tube.

The donor chamber has a sealing function of the contact lens and so that the donor solution does not pass around the lens (i.e., ions may only pass through the lens). It is constituted by a glass tube threaded at the end which is immersed in the receiving solution. The glass tube presents a centrally located aperture of about 9 mm in diameter. A lid, which is threaded to mate with the glass tube, holds a lens-retaining member which includes a centrally located hole of about 8 mm in diameter. The lens-retaining piece contains a male portion adapted to mate with and seal the edges of inner (concave) surface of lens and female portion adapted to mate with seal the edges of the outer (convex) surface of a lens.

In the lens-retaining piece the lens to be measured is placed between the male and the female portions which contains flexible sealing rings. When the lens is in the lens-retaining piece, the same device is placed in the threaded lid and this screwed onto the glass tube to define the donor chamber. Then, the donor chamber is filled with 16 mL of 0.1 M NaCl solution. The receiving chamber is filled with 60 mL of milli-Q water (ultrapure water). The leads of the conductivity meter are immersed in the milli-Q water of the receiving chamber and a stir bar is added to the receiving chamber. This chamber is positioned in a thermostat and the temperature is held at about 35°C. Finally, the donor chamber is immersed in the receiving chamber.

The conductivity measurements are taken every 20 minutes for about three hours, starting 10 minutes after immersion of the donor chamber into the receiving chamber.²

1.1.2.6.2 Ionoton measurement technique

The Ionoton technique is the method used for determining the relative ion permeability of a lens and is based on measurement of the diffusion of chloride sodium through a lens. This method involves the use of a pH meter, a VSC-1, a DCB-100B, and a 6 cm sodium ion-specific electrode and is not limited to the aforementioned instruments or materials. The first step consist in mount the contact lens onto an aperture of the DCB-100B (Crown-Bio) cell chamber, the donor chamber. Then, the connecting cell chamber (receptor chamber) is placed against the cell chamber containing the contact lens and tightly clamped on the clamp holder supplied with the VSC-1 Drive Console. A phosphate-buffered saline is placed into the receptor side of the cell chamber and stir bars added to each cell chamber. The 6 cm electrode is located into the Phosphate Buffered Saline (PBS) receptor side. The pH meter is placed in the mV function to establish the 0 mV point after the electrode has equilibrated in the PBS saline. To the donor chamber is added PBS saturated with sodium chloride. ²

1.1.2.7 Water permeability

Researchers believe that water permeability is an important feature for an extended-wear which includes oxypem polymers. The ability of water to pass thought siloxane-containing polymeric lens permits the lens move on the eye. The lens movement occurs via forces exerted by water being squeezed out of the lens. The water permeability of the lens is also believed important in replenishing lens water content once pressure is removed. The permeability of ions is believed to be directly proportional to the permeability water. Thus, ion permeability is a predictor of on eye movement.

1.1.2.7.1 The properties of water in soft contact lens

The physical properties of contact lenses are defined by interaction between hydrophilic/hydrophobic polymers groups and water molecules. The water molecules can be trapped in a small space within the polymer or bound to the polymer molecules. The water properties of contact lenses influence the ion and gas permeability¹¹,mechanical properties¹⁸,surface properties ¹²,fitting characteristics ¹¹,biocompatibility ¹² and clinical performance of these lenses.

Thus a better understanding of mobility status and binding of water molecules in hydrogels polymers is important to optimize the material properties contact lens.

Hydrogel contact lens material have tendency to dehydrate when placed on the eye. It was demonstrated that for higher equilibrium water content the material dehydration is more severe^{19,20}. *In vivo*, the dehydration of contact lenses is related to the state of binding and average mobility of the water molecules in hydrogel materials^{21,22} and it is mainly caused by an evaporative-dehydration process^{23,24}. Decreasing hydration may cause discomfort and dryness symptoms²⁵, reduce oxygen transmissibility²⁶, change the lens fit and corrective power of the lens²⁴. When water transport rate from the post-lens tear film through the lens and into the outer environment is high it may induce corneal desiccation^{27,28}, reduced contact lens movement^{29,30}, and in extreme case, lens adherence to the corneal surface^{24,31}.

State of water

There are two models that explain the state of water molecules within the materials of soft contact lenses: the discrete model and the continuum model. These models are not in agreement with the theory that the binding of water molecules to hydrophilic sites on the polymer chain is a necessary pre-requisite for observing tightly bound or nonfreezable water, which are described below.

- Continuum model
These school of thought the irregular behavior of water in calorimetric experiments occur due of the development of nonequilibrium conditions and not because exists different classes of water.³²
- Discrete model
This model assumes that there are thermodynamically different types of water in hydrogel materials and that the number of different water types detected in polymer depends on the techniques used.

Bound water refers to water molecules that becomes mobile at relatively low temperatures. These water molecules are thought to be strongly associated with the polymer matrix by polar interactions and hydrogen bonding. This type of water has also been called nonfreezing water when investigated using calorimetric method. These model assumes that the non-freezing water is bonded to hydrophilic sites and surrounded by other hydration shells of freezing water molecules³³.

Loosely bound water define water that reach mobility at -43°C to -13°C . This water form is more vaguely defined and cover all classes of water that maintain in liquid state below the normal freezing temperature. The melting temperature of water is influenced by the amount of water present and the state of bonding with polymer matrix.

Loosely bound water in poly(hydroxyethyl methacrylate) (pHEMA), has been viewed as interfacial water experiencing that establish hydroxyl or hydrophobic interactions with segments of the host polymer. ³³

Free or freezing water is usually present in hydrogels with higher EWC, has hydrogen-bonding characteristic of pure water and achieve mobility at the normal melting point of free water 0°C (273K). ³³

Bound water include tightly bound water and loosely bound water.

The relationship between water content and tightly bound, loosely bound and free water in hydrogel material is easily explained. For hydrogels of the same polymeric system, the amount of tightly bound water is the same for low water content hydrogel, high water content hydrogel such as those with $y\%$, $z\%$ or $w\%$ of water. A hydrogel with water content $z\%$ would have the same amount of tightly and loosely bound water as a hydrogel with a much higher water content, such as that with $w\%$ of water. In other words, for lenses with low water content all water exist in a tightly bound form. At medium level of water content, loosely bound water exists in addition to tightly bound water. On the other hand, in contact lens with higher levels of water content free water is also present. ³³

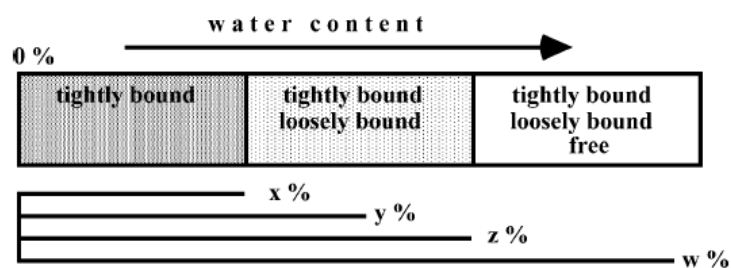


Figure 3 The relationship between water content and tightly-bound ,loosely bound and free water for hydrogels.³³

The distribution of bound to free water is affected by different degrees of binding between water and functional groups of different polarity in the polymer matrix. When compared on the basis of number of water molecules per functional group, water molecules bind more strongly with ionic functional groups/residues and strong acids than other non-ionic polar groups.

Limited information existing in the literature refers that a functional group with stronger water binding capacity does not necessarily induce into a higher bound to free water ratio. An example is HEMA that is formed by polymers with functional groups of average water binding capacity and have higher ratios of bound to free water compared with those polymers containing functional groups of higher water-binding capability, such as pyrrolidone group.

Cross-linking are agents that hold a system together. By increasing the density of cross-linking agents a decrease of water content of the final mixture is induced ³⁴. As the amount of free water decreases the absolute amount of bound water increases which decreases mobility of water molecules. ^{34,35}

The ratio of freezing to nonfreezing water within the gel and EWC strongly influenced the properties of hydrogel material.

There exists a great confusion on definition of non-freezable and freezable bound water due of the limitations of measurement by some analytical techniques. The determination and quantification of free water, bound water, freezable water and nonfreezable water have been determined through the use of differential scanning calorimetry (DSC), Thermogravimetric analysis (TGA) and nuclear magnetic resonance (NMR) spectroscopy. To determine the state of water have also been used infra-red spectroscopy and chromatography.

Maldonado and N.Efron^{1,32} demonstrated in their investigation that do not exist significant differences in the total of non-freezing water between different lens materials or between materials of the same type made by different manufacturers. In contact lens with high EWC, it is not the amount of nonfreezing water that increases but the amount of freezing water.

Roorda et al. ^{22,36} disagree with the discrete model. They demonstrated in their experiments how total melting enthalpy and the actual shape of the melting curve are extremely sensitive to the experimental conditions which make complicate to interpret of data.

Mirejovsky et al.²¹ in their work demonstrated that hydrogel lens materials with a larger proportion of free-freezing water can induce a corneal epithelial desiccation more readily than materials with the same total water content, but containing a higher proportion of nonfreezing water.

They observed that lens containing a higher amount of nonfreezing water are associated to lower levels of corneal staining than a control lens of similar EWC and lens thickness profile containing less nonfreezing water.

Proton NMR is another experimental approach to evaluate dehydration process of contact lenses. Proton nuclear magnetic resonance (NMR) has the potential to characterize this water binding and mobility in a directly quantifiable manner, and has been commonly used in studies of the water-polymer interaction.^{9,10} Maldonado and Efron³² correlated Proton NMR relaxations in hydrogel lenses³⁷ with *in vivo* lens dehydration data previously published by Larsen et al.^{37,38} The results demonstrated that material with the highest water molecules mobility have the greatest amount of dehydration. Lenses having more freezing water or higher free-to-bound water ratios can show more dehydration than lenses having relatively smaller proportions of freezing water because free water demonstrate the most mobility in NMR investigations.³²

1.2 Solute transport through hydrogel membranes

Two distinct frameworks are commonly used to describe solute transport through hydrogel membranes: the *solution-diffusion model* and the *pore-flow model*.

The pore-flow model

This model suggested that the membrane polymer is a porous through which the solute flows hydraulically.

The solution-diffusion model

The permeation of a solute through a polymeric membrane can be described by a process called solution-diffusion model. Primarily a solute dissolve in the membrane material and then diffuses through the membrane through a concentration gradient. The partition coefficient or solubility of the solute in the membrane is responsible to maintain the thermodynamic equilibrium. On the other hand, the diffusion of solute contributes to kinetic part in the permeation process through the membrane. In hydrogel membrane system this transport mechanism is slightly different because the water molecules may occupy a significant portion in the membrane. The diffusion through a hydrogel membrane can be defined by two modes: porous and non-porous.

The non-porous is define by polymer with chain flexible and molecular level movement of polymer chain that restrict the diffusion or movement of solutes (size is below 10 Amstrong).

Yasuda et al.^{7,39} proposed that in non-porous membranes the solutes diffused through the free volume of the polymer and water within the hydrogel.

Porous mode could be defined as polymer chain networks that stand a rigid structure. The diffusion of solutes or surrounding fluid is affected by hindrance or friction. Relatively the pore size, these must be larger than the solute in order to permit the permeation solutes.

Wijmans and Baker⁴⁰ suggest that in a solution-diffusion membrane the free-volume elements are a consequence of statistical concentration fluctuations in membrane and this elements appear and disappear in about the same time scale as that for the motion of the penetrating solute. The pores are relatively stable and not fluctuate in position and size on the time scale of penetrant transport.

Formasiero et al.⁴¹ suggest that water transport in hydrogel contact lens occur according to the porous-medium model.

One logical and promising field of application of solute and fluid transport through contact lenses is in the field of Drug Delivery to the ocular surface.

1.2.1 Drug Delivery through soft contact lens

Eye drops and eye ointments represent 90% of drug forms used in ocular disorder. For an effective therapy is important to maintain the optimal drug concentration at the required site of action. Nowadays all ophthalmic formulations used are very inefficient and in some cases leads to serious side effects.

When we apply eye drops in ocular surface, the drugs mixes with tear film and remain approximately 2 min there. Only 1-5% of the administered drug is effectively used and absorbed into to the cornea and the remaining drug enters the bloodstream by conjunctival and nasal absorption. The poor bioavailability of eye drops happens due to pre-corneal loss factor such as tear dynamics, non-productive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the corneal epithelial membrane ⁴².As a consequence the clinician recommends frequent instillation of tear with high concentration of the drug which can cause serious side effects. On the other hand, the ointments have a high residence time than eye drops, but they can irritate eye tissue and induce blurred vision⁴³. Novel strategies have been developed to improve the eye drops residence time and bioactivities. Researchers are capable of increase the corneal permeability, however they failed to fully satisfy the needs of eye diseases, especially in the case of diseases with long-time therapy. To increase bioavailability, other researchers developed eye drop formulations such *in situ* forming gels based on pH,

temperature, and ionic triggering, colloidal particles and collagen shields.⁴⁴ However, only increased the residence time a few hours and minimally increased bioavailability.⁴⁴

The goal has been to achieve the drug delivery system that not only prolongs the ocular contact time of drugs but also simultaneously reduce its elimination from the eye. Systems such as ocuserts, collagen shields, nanoparticles and microspheres, penetration enhancers, colloidal delivery systems, and implantable systems, have been explored.

Patel et al.²¹ prepared ocular inserts of gatifloxacin sesquihydrate and moxifloxacin hydrochloride that had a good *in vitro-in vivo* correlation and show to be stable for up to 2 years. Bhagav et al.⁴⁵ developed ocular inserts that revealed sustained release of brimonidine tartrate with no ocular irritation and improved intraocular pressure (IOP) lowering ability compared with normal eye drops.

Colloidal drug delivery systems have a fast uptake with a long residence time and for this reason have been explored for the ocular delivery of drugs. The tobramycin-loaded solid lipid nanoparticles (SLNs) when compared with a conventional solution demonstrated to have a longer retention on the corneal surface and conjunctival sac. *In vivo* experiments, showed that nanoparticles afforded drug release over a period of 6 h compared with the short residence time of normal eye drops. Collagen shields are not fully transparent and are not fitted individually to each patient. Nanoparticles poly(alkyl cyanoacrylate) composed and colloidal drug delivery systems damage the corneal epithelium due the disruption of the cell membrane. Implantable systems are not easy for patient due to needed surgery.⁴²

1.2.1.1 Polymeric hydrogels for conventional contact lens to absorb and release ophthalmic drug

Several polymeric hydrogels have been investigated in order to manufacture a conventional soft contact lens-based ophthalmic drug delivery system. Poly-hydroxyethylmethacrylate (PHEMA) has been the most widely used material to deliver ophthalmic drugs. However, the conventional contact lenses have some limitations such as fast release rate of drugs and low loaded drug amount.

The marketed contact lenses can be soaked for hours in a drug solution and then applied into the eye to release drug due their ability to absorb a number of drugs. This procedure is called of pre-soaked contact lens. When the contact lens is placed on the cornea, and then the eye drops applied, the drug is released over a prolong period of time, which is known as post-

soaked contact lens procedure. Otherwise, we can place the ophthalmic solution in the concavity of contact lens and then put the lens onto the eye. It increase residence time of drug in ocular surface⁴².

In order to enhance the potential of hydrogel as an effective biomaterial for contact lens-based ophthalmic drug delivery, 4-vinylpyridine (VP) and N-(3-aminopropyl) methacrylamide (APMA) was incorporated in pHEMA hydrogels. The incorporated monomers did not change the viscoelastic properties or the state of water in the contact lens, but increase the interaction between hydrogel and drugs resulting in greater difficulty of the drug's spread in the hydrogel (Andrade - Vivero et al.).

The drug release profile of PHEMA-APMA could be controlled by ions in the media and the remaining by hydrophobic interactions. The high polymeric density of the pHEMA hydrogels contributed to sustaining release process for at least 24 h for ibuprofen and almost 1 week for diclofenac. This release rate was also independent of the salt content and pH in the physiological range of values, which enables the design of hydrogel-based delivery systems with predictable and tunable release rates.^{43,46}

Mullarneya et al.⁴⁷ used hydrophobically modified hydrogels to release pheniramine maleate. The copolymer hydrogels of *N,N*-dimethylacrylamide (DMAAM) and 2-(*N*-ethylperfluorooctanesulfonamido) ethyl acrylate (FOSA) were prepared by free-radical polymerization. The power law exponent ($n \approx 0.5$) and the swelling interface number ($Sw \gg 1$) suggested that the drug release mechanism from these developed hydrogels was Fickian and not swelling controlled.⁴²

It was demonstrated that the ability of conventional soft contact lens to store an ophthalmic drug strongly depends of the water content and thickness of the lens, the molecular weight of the drug, the concentration of the drug loading solution, the solubility of the drug in the gel matrix, and the time that lens remains in it. They cannot be used for a long-term drug delivery because they only are able to deliver most drugs for a period of few hours after the pre-soaking in the drug solutions.⁴⁶

In order to increase the oxygen permeability, silicone polymers replace the conventional contact lenses monomers. Kim et al. ⁴⁸ synthesized silicone macromer (bis-alpha,omega-(methacryloxypropyl) polydimethylsiloxane), hydrophobic monomer containing silicon (3 - methacryloxypropyltris (trimethylsiloxy) silane, TRIS) and hydrophilic monomer (N,N-dimethylacrylamide, DMA) to develop a silicone hydrogel contact lens able to transport

ophthalmic drugs such as timolol, dexamethasone and dexamethasone 21-acetate. The results proved that the sustained drug release process of silicone hydrogels varied from 20 days up or more than three months depending on the compositions of hydrophobic and hydrophilic components of silicone hydrogels. The mechanical properties, ion permeability, equilibrium water content, transparency and surface contact angles were suitable for contact lens application. Hydrophilic/hydrophobic copolymer hydrogel would become opaque if hydrophilic/hydrophobic ratio was improper because of phase separation.⁴³

Dracopoulos et al.⁴⁹ analyzed the interactions between benzalkonium chloride (BAK) and silicone-containing (lotrafilcon A and galyfilcon A) and PHEMA-containing (etafilcon A and vifilcon A) hydrogels contact lenses. These four soft contact lens types were soaked for 24h in different concentrations of BAK (1%, 0.1%, 0.01% and 0.001%) in 20 ml glass vials. The results demonstrated the increase levels of the back vertex distance variability of the cultured bovine lens, indicating that unknown chemical agents might be leached from contact lens polymers.⁴²

Copolymer hydrogels of HEMA and acrylic acid (AA) were also evaluated for a contact lens based ophthalmic drug delivery system.⁴² Soft contact lenses based on commercially available silicon-containing hydrogels and poly-vinyl alcohol (PVA) hydrogels were also investigated for delivery of ophthalmic drugs.^{50,51}

Many strategies are developed to modify the Conventional and Hydrogel contact lenses, in order to increase the amount of load drug and to control their release at the expected intervals. Below it is explained these strategies.

1.2.1.2 Molecular Imprinting

In *Molecular Imprinting* the contact lens are synthesized in presence of the drug molecules which behave as template for the monomers arrangement. The spatial arrangements monomers occurs based in their affinity⁵². With this manufacture technique the contact lens in their structure have specific receptors, with the most adequate size and chemical groups, able to connect with the drugs with the highest affinity.

Imprinting process include five steps. First, the crosslinking monomer, functional monomer and initiator in solution are self-assembled into the pre-polymerization complex via covalent or non-covalent chemistry. Second, UV light or heat starts the complex to form crosslinked network. Third, the original template is removed through wash step and the crosslinked polymer network

is formed with cavities that can recognize the spatial features and bonding preferences of the target molecules which permit that contact lens have a high affinity and selectivity for a given drug. Fourth, new template is rebinding into the crosslinked polymer. Fifth, the new template diffuses into solution via stimulation. The polymerization is usually performed in an organic solvent, such a porogen, to give a macro-porous structure that allows the access of target molecule to the imprinted sites but this can be avoided taking advantage of the liquid state of monomers in preparation of molecular imprinted polymer hydrogels. Figure 4

Hiratani and Alvarez-Lorenzo developed imprinted contact lenses from HEMA or N,N-diethylacrylamide (DEAA), low cross-linked proportions, and a small proportion of functional monomer of methacrylic acid (MAA). This imprinted contact lens was able to interact with timolol maleate via ionic and hydrogen bonds and acquired more timolol than non-imprinted systems. HEMA-based and DEAA-based could sustain timolol drug release in lacrimal fluid for more than 12h and then recharged with drug overnight for use next day. When available *in vivo* experiments, the imprinted contact lens was able to retain timolol for more time in precorneal area than conventional contact lens and eye drops.⁴³ More recently, Hiratani and Alvarez-Lorenzo designed pHEMA using acrylic acid (AA) as spatial order functional monomers to load and release norfloxacin (NRF). Isothermal titration calorimetry (ITC) studies demonstrated that the maximum binding interaction between NRF and acrylic acid (AA) occurred at a ratio of 1:1, and that process saturates at a molar ratio of 1:4. After immersion in 0.025, 0.050 and 0.10mM in NRF drug solutions, they observed that imprinted hydrogels loaded greater amounts of drug than non imprinted contact lens but the time of drug release in this lens using one functional monomer was limited less than 1 day *in vitro* and *in vivo* experiments.^{42,43}

Venkatesh et al. synthesized imprinted HEMA-co-polyethylene glycol (200) dimethacrylate – (PEG200DMA) based contact lenses with multiple functional monomers of AA, acrylamide (AM) and N-vinyl 2-pyrrolidinone (NVP) for delivery drug such as H1-anti-histamines. The results demonstrated that this imprinted based contact lens can load important amounts of H1-antihistamines and release a therapeutic dosage of a drug *in vitro* in a controlled fashion for 5 days with an even further extension in the presence of protein.^{42,43}

Ali and Byrne developed imprinted poly(vinylalcohol)-(PVA) based contact lenses containing multiple functional monomers of AM, NVP, and 2-(diethylamino) ethyl methacrylate (DEAEM) for the therapeutic delivery of hyaluronic acid (HA) at the eye surface. The goal was to improve the wettability of contact lens and treat symptoms of dry eye.⁴³

Ribeiro et al. combined zinc methacrylate, 1- or 4 vinyl imidazole (1VI or 4 VI), and N-hydroxyethyl acrylamide (HEAA) to reproduce in the hydrogels the cone-shaped cavity of the Ca^{+2} (which contains a Zn^{+2} ion coordinated to three histidine residues). As a result, the biomimetic can load more drug and better control the drug release than conventionally synthesized pHEMA hydrogels^{42,43}.

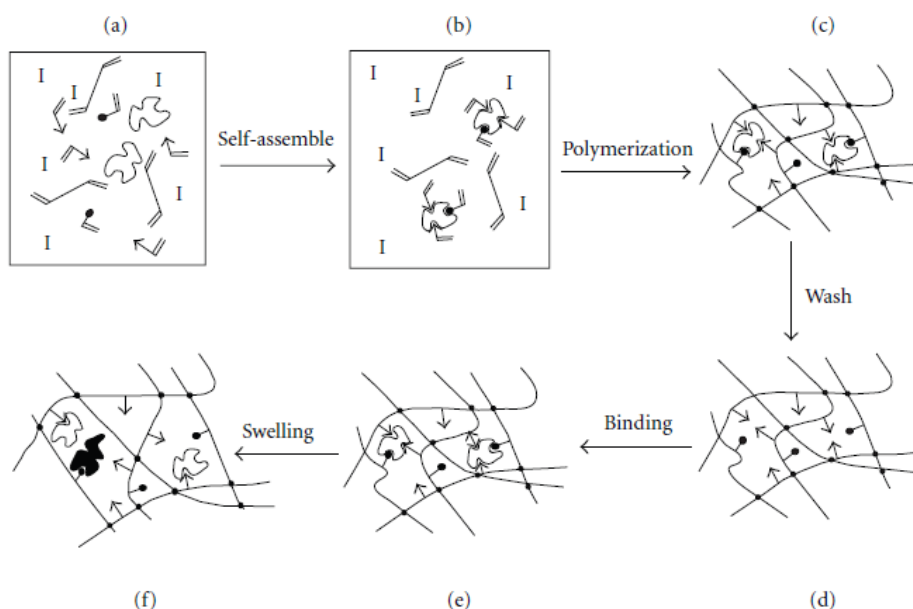


Figure 4 Imprinting process. (a) Solution mixture of template, functional monomer(s) (triangles and circles), crosslinking monomer, solvent, and initiator (I). (b) The prepolymerization complex is formed via covalent or noncovalent chemistry. (c) The formation of the network. (d) Wash step where original template is removed. (e) Rebinding of template. (f) In less crosslinked systems, movement of the macromolecular chains will produce areas of differing affinity and specificity (filled molecule is isomer of template).Reproduced from Byrne et al.⁵³

1.2.1.3 Particle-laden or colloid-laden Soft contact lens

“Particle laden soft contact lens” is a method that incorporate colloidal particles such as micro-/nanoparticles, micro-/nanoemulsions, nanosuspensions and liposomes in matrix of contact lens for drug delivery⁴³ (Figure 5). It is reported that these colloidal system is able to prolong sustained release time of drug and enhance their bioavailability in ocular surface without affect the vision of the patient because it is very small. These processes require two steps: preparation of colloidal particles drops followed by their entrapment in the hydrogel matrix^{42,43,52}

Gulsen and Chauhan encapsulated the ophthalmic drug formulations in micro emulsion drops and dispersed these drug-laden particles in the pHEMA hydrogels. They demonstrated that these colloid-laden hydrogel is transparent, releases drugs for a period over 8 days and is possible to adjust the drug delivery rates by controlling the particle and the drug loading⁴³ . In

other hand, it was proposed the creation of colloid-laden hydrogel *in situ* in one step. The surfactants were added during the manufacturing process of surfactant laden hydrogels which interact with polymer chains and form micelles creating hydrophobic cores, where the hydrophobic drugs will preferentially enter into. The presence of surfactant micelles will be inhibiting the drug transport.

Li et al. trapped ethyl butyrate in water micro emulsions which was stabilized by pluronic F127 surfactant in HEMA gels. The results demonstrated that this microemulsion -laden could have higher drug loading such as Timolol base.⁴²

Kappor and Chauhan developed Brij® surfactant-laden pHEMA hydrogels able to release cyclosporine A (CyA) at a control rate for 20 days^{43,52}.The results also demonstrated that these hydrogel have suitable mechanical and optical properties for contact lens applications even after exposure to all the relevant processing conditions ⁴². These hydrogels are not adequate for extended release of two other hydrophobic ophthalmic drugs, such as dexamethasone (DMS) and dexamethasone 21 acetate (DMSA), due to the insufficient partitioning inside the surfactant aggregates ⁴³.

Colloid laden hydrogel contact lens have some drawbacks, like their instability during preservation and transportation, due to the diffusion into the hydrogel matrix of the loaded drugs ⁴³ and the decaying release rate of particle-laden hydrogel in ophthalmic drug delivery ⁴³.

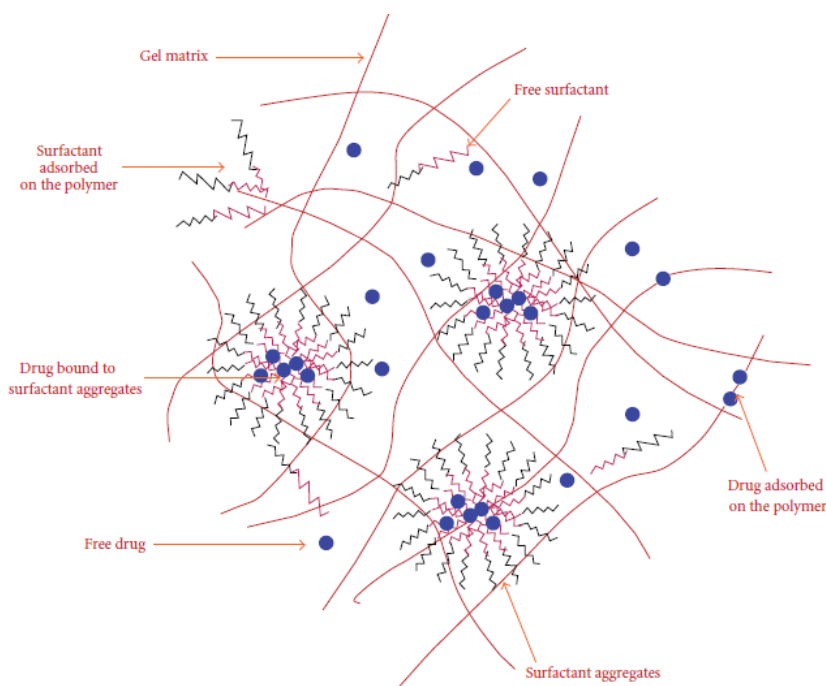


Figure 5 A schematic of the microstructure of the surfactant-laden gels. Reproduced from Kappor et al.⁵⁴

1.2.1.4 Surface-modified Hydrogels

The main goal of modifying hydrogel's surface is to immobilize ophthalmic drugs onto the surface of commercial disposable soft contact lens and making them deliverable to treat ocular disorders.

Danion et al. encapsulated drugs into liposomes and then bound these vesicles onto both the anterior and posterior surfaces of commercial contact lenses. The immobilization process of liposomes on the surface modified soft contact lens consists in three steps. In first step, polyethylenimine was covalently bounded onto the hydroxyl groups available on the surface of a contact lens (Hioxifilcon B) via amidation under the catalyzation of disuccinimidyl carbonate (DSC). NHS-PEG-biotin molecules were following bounded onto the surface amino groups by carbodiimide chemistry.⁴⁶ In the second step, Neutraavidin was immobilized in the PEG-biotin layer via biotin-avidin affinity. Liposomes containing PEG-biotinylated lipids were then docked onto the surface-immobilized Neutraavidin. In the third step, multilayers of liposome were also produced by exposing contact lenses coated with Neutraavidin to liposome aggregates produced by the addition of free biotin in solution.

The results demonstrated that the surface-immobilized, drug-filled liposome multilayers provided a promising avenue for site-specific delivery. However, no actual drug was investigated in this research^{43,46}.

More recently, layer-by-layer platforms have been applied for drug delivery but these do not allow the small molecule drug delivery with highly controlled release kinetics, and their release time is short. To modify this condition some efforts have been made such as incorporating the cyclodextrin into LbL platform⁴³. Smith et al. developed layer-by-layer platforms to deliver small-molecule therapeutics from virtually surface, regardless the surface geometry or chemistry. Poly(carboxymethyl- β -cyclodextrin) (polyCD) was complexed with a small molecule as the anionic supramolecular complex. Poly(β -amino esters) (PBAEs) as the degradable polycations and the anionic supramolecular complex were alternately immobilized on the surface of the films via LbL technique. In the LbL film, the ophthalmic drug of Diclofenac or Flurbiprofen could sustain release for 15 days in zero-order release kinetics.⁴³

The decrease of oxygen permeability caused by multilayer scheme of the liposomes and the risk of liposomes detaching from contact lens surface although this risk is low are the disadvantage of surface-modified hydrogels⁴⁶.

1.2.1.5 Ion Ligands

Ion ligands are molecules or ions that binds to a central metal atom to form a coordinated complex⁴². Ion ligand-containing polymer hydrogels have been synthesized for a contact-based ophthalmic drug delivery system. The ionized ophthalmic drugs is connected to the matrix of contact lens and released into tear film by ion exchange. ^{42,46}

Sato et al⁵⁵. investigated hydrogels containing anionic functional groups for cationic drugs delivery and hydrogels containing cationic functional groups for anionic drugs delivery.

In order to investigate hydrogels containing cationic functional groups, Rei et al⁵⁶. copolymerized methacrylamide propyl trimethyl ammonium chloride (MAPTAC) and HEMA and they observed their capability to store anionic drug. The complex obtained was capable to store anionic drugs, such as azulene through ion-exchange reaction. Before and after drug release, the size of hydrogel changed. However, it was discovered that to prevent the size change, anionic monomers, such as methacrylic acid (MAA) and 2-methacryloxyethyl acid phosphate (MOEP) can be added. ^{42,5}

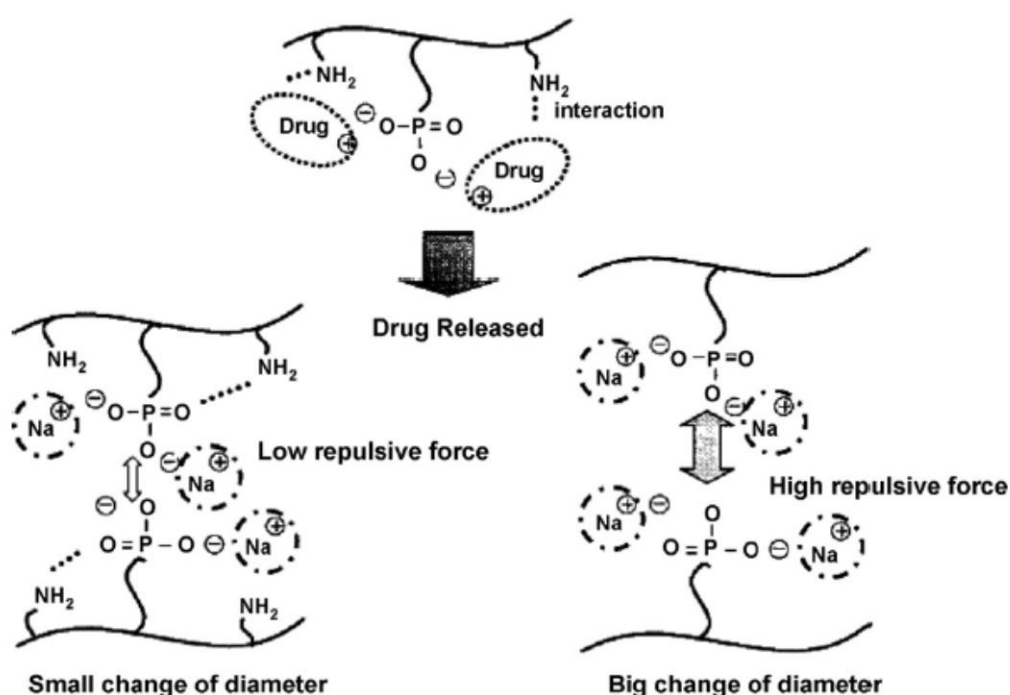


Figure 6 Size change during drug release of ion ligand-containing polymeric hydrogels for soft contact lens-based ophthalmic drug delivery systems. Reproduced from Xinming et al. ⁴⁶

Sato et al.⁵⁵ incorporated naphazoline, a model drug containing a cationic group, into soft contact lens via its phosphate groups. It was released over a period of 14h. The naphazoline content of the contact lens was equivalent to its phosphate group content⁴². It has been suggested that therapeutic soft contact lens can be designed to contain the required amount of drug by choosing the ionic group. Thus, the inclusion of amide groups and phosphate groups into the polymer in equi-molar amounts it was suggested to give the necessary polymer-drug interaction. Soft contact lens containing amide groups and phosphate groups showed high transparency and an unchanged shape.^{42,46}

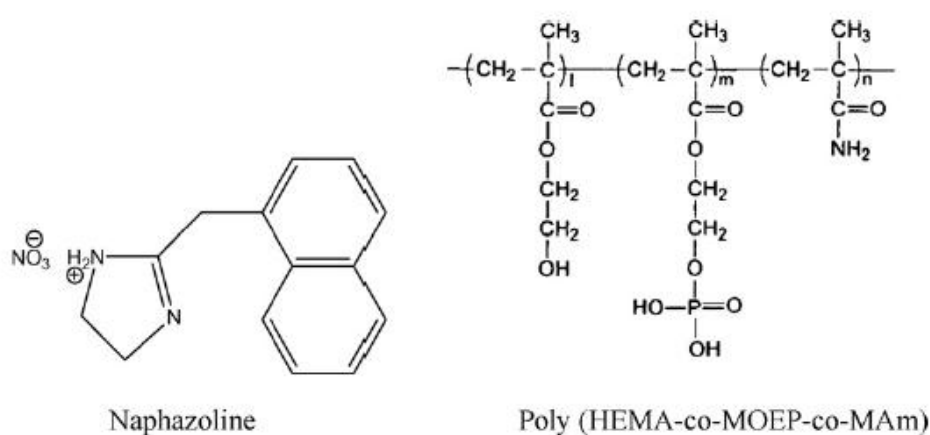


Figure 7 Chemical structures of the model drug and poly(HEMA-co-MOEP-co-MAM) hydrogels. For ion ligand-containing polymeric hydrogels, the main drawbacks include the size change of the contact lens that may occur before and after drug release as a result of drug concentration change, and the incorporated drug concentration cannot exceed the ion concentration in the tear fluid, because the release of drugs relies on ion exchange. Reproduced from Ximming et al.⁴⁶

1.2.1.6 An Ideal Soft contact lens-based ophthalmic drug delivery

The number of people wearing contact lenses is increasing. Although contact lenses are designed to correct ametropia or for aesthetic motives, a novel approach to deliver ophthalmic drugs through contact lenses have been investigated.

Despite all the researchers' efforts, they cannot developed an ideal soft contact lens-based ophthalmic drug delivery, as we can see by the approaches presented above.

An ideal soft contact lens-based ophthalmic drug delivery should have an improved maximum drug loading propriety for extended time delivery; controllable zero-order release profiles; shape retaining and transparency stability during the drug release; stability during preservation and transportation; no burst release drug profiles; drug concentration in the tear

fluid between maximum safe concentration (MSC) and minimum effective concentration (MEC); acceptable oxygen and carbon dioxide permeability and contact lens thickness.

2. OBJECTIVES AND HYPOTHESIS OF WORK

2.1 Problem Formulation

Ionic permeability is an intrinsic parameter of the contact lenses made of hydrophilic polymers. Researchers believe that ionic permeability was responsible to maintain the movement of contact lenses on the ocular surface but this fact remains yet to be proven. Although previous studies have addressed this measurements there is no knowledge about the changes induced by lens wear, how this property changes with the power of the lens or how some experimental setups might affect the reliability of the measurements. We used the IonoFlux Technique (the preferred technique) to obtain the ionic permeability of hydrogel (pHEMA-based) and silicone hydrogel (Si-Hy) contact lenses.

2.2 Purpose of the Study

This study intends to provide new information about ionic permeability of Si-Hy contact lenses.

The goals of this study were:

- Determine ionic permeability of some soft contact lens with stirring in donor chamber
- Determine ionic permeability of some soft contact lens without stirring in donor chamber
- Determine ionic permeability of some soft contact lens previously equilibrated with milli-Q without stirring in donor chamber
- Determine ionic permeability of some soft contact lens previously equilibrated with 1M without stirring in donor chamber
- Determine ionic permeability of new Comfilcon A contact lens
- Determine ionic permeability of used Comfilcon A contact lens
- Analyze the data to see if there is variation in permeability values when this is measured in different experimental conditions.

2.3 Project Hypothesis

Based on bibliographic reviews we propose the following hypothesis:

H1) Without stirring of the donor chamber affects the measurements of ionic permeability decreasing it compared to the stirring condition.

H2) An increase in ionic permeability and/or delayed time for steady-state condition will be observed with the lenses are initially equilibrated in 1M solution instead of ultrapure water

H3) The thickness profile of the contact lens, which varies with the optical power of the lenses will not affect the ionic permeability obtained

H4) Lenses worn during one month will present a decay in the ionic permeability compared with new lenses of the same material, power and thickness profile

3. MATERIAL AND METHODS

3.1 Type of study

The present work consists in an experimental study. The aim of this work was to measure the ionic permeability of different contact lenses when these were subjected to different experimental conditions using EC-Meter GLP 31, had different dioptric power and thickness profile or had been subjected to daily wear over a period of 1 month in a different clinical trial not related with this thesis.

All experimental measurements were performed in Clinical and Experimental Optometry Research Lab (CEORLab) at Physics Department of the University of Minho.

3.2 Description of the Samples

In order to be able to compare different silicone hydrogel contact lenses and 1 conventional hydrogel the following lenses were used: Acuvue Oasys (Senofilcon A) and Acuvue Advance (Galyfilcon A) both of Johnson&Johnson manufacture; Biofinity (Comfilcon A) and Proclear (Omafilcon A) both of Coopervision manufacture. These lenses were chosen because they have a different EWC and similar design when they are of the same manufacturer. Proclear is a conventional material, not a Si-Hy material. The table below displays the main characteristics of these lenses.

Table 3 Manufacturer data of the different contact lens

Trade name	Manufacturer	Material (USAN)	EWC (%)	Dk (barrer)	Dk/t (-3.00 diopters)	Power (diopters)	Base Curve (mm)	Diameter (mm)
Acuvue Oasys	Johnson&Johnson	Senofilcon A	38	103	147	-3	8.4	14
Acuvue Advance	Johnson&Johnson	Galyfilcon A	47	60	86	-3	8.3	14
Biofinity	Coopervision	Comfilcon A	48	128	160	-3	8.6	14
Proclear	Coopervision	Omafilcon A	62	27	42	-3	8.6	14.2

In total twelve lenses with -3.00D were evaluated, each of a different material (Omafilcon A, Galyfilcon, Senofilcon, Comfilcon A) and, furthermore, six lenses of each of the following powers:-1.00 D, -1.50D, -4.75D Comfilcon A. Another sample of the same six powers listed above was measured after one month of use.

3.3 Methods

3.3.1 Thickness contact lenses

In this work five measurements were made to obtain the harmonic central thickness across the central 8 mm of the contact lenses using Redher ET-3. Before the measurement of ionic permeability, the thickness of contact lenses were measured.

3.3.1.1 Operating principle of Redher ET-3 (Rehder Developments,CA)

The model ET-3 is an instrument used by contact lenses manufacturers and researchers to measure the thickness of soft contact lenses and other soft materials. In this work, the instruments were manually operated. The instrument has a sensor that can be gently and mechanically raised and lowered over the sphere (where the contact lens is placed) to measure the soft contact lens thickness. It is possible to measure the soft contact lens thickness on different positions rotating the knob attached to the lens holder. This instrument has an accuracy of ± 2 microns ($\pm 1 \mu\text{m}$, plus, $\pm 1 \mu\text{m}$ digital rounding).

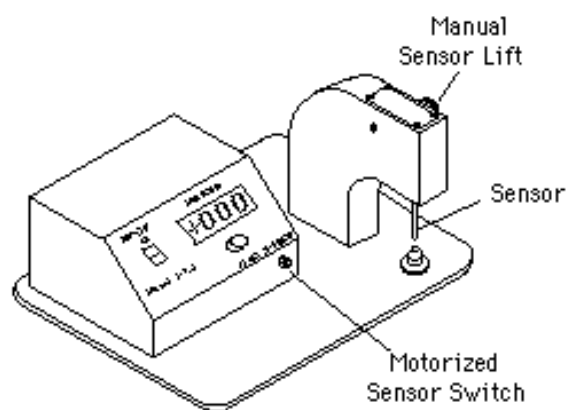


Figure 8 Illustration of Electronic thickness gauge model ET-3

3.3.2 Calibration of conductivity electrodes

The electrode's conductivity is calibrated beforehand. The calibration curve was obtained at different concentrations of salt and milli-Q water ($18.2 \mu\text{S}/\text{cm}$). The solutions used in the calibration had the following concentrations of NaCl, 10^{-1} , 10^{-2} , 10^{-3} , 5×10^{-4} , 10^{-4} and 10^{-5} M. The conductivity of each solution was measured with the electrode and its values are plotted for each concentration.

3.3.3 Ion permeability measurements

The ion permeability of a silicone hydrogel contact lens can be determined from the rate of ion penetration through the lens, from one surface of the lens to another according to the experimental device shown in the Figure 9. In this device of the lens is positioned between two solutions contained in chambers with known and different ionic concentrations salts. In compartment A (the donor chamber), there is a solution of NaCl 1M and in the compartment B (receiver chamber), milli-Q water. In compartment B, is positioned an ion selective Na⁺ electrode (Model EC meter GLP31) for measuring the conductivity in a time function due to the amount of ions reaching the reservoir after passing through the contact lens.

The sensor is attached with a temperature sensor to control the temperature over time inside Compartment B. The compartment B (receiver chamber) has a volume of 100 cm³. A stirring magnetic bar to make constant agitation (800 rpm) and a thermostat to ensure that the temperature is constant during the measurements were also placed inside Compartment B. In one of the experiments, a smaller agitator is placed on the donor chamber to evaluate the influence of this process on the final result. The chamber A (donor chamber) has a volume of 10 cm³ and it is designed to perfectly seal a lens so that the donor solution doesn't go around the lens (and ions can only pass through exposed contact lens). The camera consists in a teflon tube which contain a hole of 7 mm diameter (Figure 9).

The retainer includes a male portion adapted (concave) to coincide with the lens, and a female portion adapted to mate and seal the edges of the outer surface (convex) lens. Finally the lens to be measured is placed between the male and female portions of the cell and the Teflon tube is screwed so that the lens is completely sealed in the donor chamber. Once the lens is placed, it is filled with a volume of 10 cm³ of saline solution and immersed in 100 cm³ of milli-Q water of the receiving chamber. Then it is added a magnetic stir bar to homogenize the solution under the lens and further decrease the resistance of water layers. The conductivity meter and magnetic stir bar was placed in the receiving chamber that is thermostatically controlled by thermostat so that the experience is carried out at 35°C.

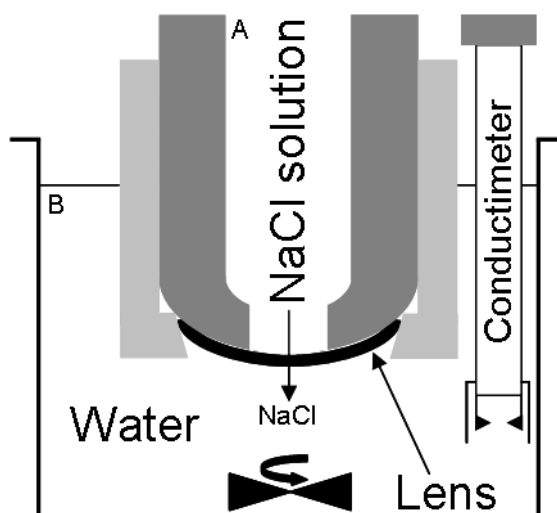


Figure 9 Schematic representation of the experimental set-up used for the determination of the methanol permeability across the membranes. The potentiometric method is specifically represented.

In a first state (Experiment #1) of the experimental work different experimental conditions were simulated and the measures were compared in order to evaluate which ones might affect the results more significantly. The different procedures are explained below.

In a second experiment (Experiment #2), worn contact lenses made of one of the materials (Comfilcon A) were measured and then compared to new samples from the same batch in order to evaluate the effect of lens wear on ionic permeability. Additionally, these lenses had different optical powers (-1.00, 1.50 and -4.75) allowing us to evaluate the effect of refractive power and its thickness profiles in ionic permeability measures.

Experiment #1

A) The lens removed from the manufacturer package is placed on the cell of the experimental set-up without stirring on solution 1M in donor chamber (A) situated above of receiving chamber (B). In receiving chamber (B) milli-Q water together with the conductivity sensor is situated. In receiving chamber the stirring is always working at 800 rpm.

B) The lens removed from the vial is situated on the cell of the experimental set-up with stirring in both chambers at the same rpm.

C) The lens is previously equilibrated with distilled water during one week before of each measurement with several changes of recipient to remove all the solutes from present in the original packaging solution. Then the lens is placed in the cell without stirring on solution 1M in donor chamber (A). In receiving chamber the stirring is always working at 800 rpm.

D) The lens previously is equilibrated with a solution of NaCl (aq) 1M during one week before of each measurement. Then the lens is placed in the cell without stirring on solution 1M in donor chamber (A), while in receiving chamber the stirring is always working at 800 rpm.

Experiment #2

E)The lens with -1.00,-1.50 and -4.75 D was removed from the vial is situated on the cell of the experimental set-up without stirring on solution 1M in donor chamber (A) situated above of receiving chamber (B). In receiving chamber (B) distilled water together with the conductivity sensor is situated. In receiving chamber the stirring is always working at 800 rpm.

F)Lenses used during 1 month and with power of -1.00,-1.50,-4.75 D previously is equilibrated with a solution of NaCl(ac) 1M during one week before of each measurement. Then the lens is placed in the cell without stirring on solution 1M in donor chamber (A), while in receiving chamber the stirring is always working at 800 rpm.

3.3.3.1 EC-Metro GLP 31

The GLP 31 conductivity meter permits to measure the electric conductivity and the salinity of solutions and can be calibrated chosen 1, 2 or 3 standards between 4 possible standards. In this work, the instrument was calibrated with 147 $\mu\text{S}/\text{cm}$ (microSiemens/centimeter) standard. The GPL 31 was connected to a pc using ComLabo software allowing acquisition data in real time. The instruments permits to obtain the measurements by stability, continuous or time, with coefficient of temperature and temperature reference being programmable. Once that this has a Data Logger the data of calibration, history of conductivity meter and the last 400 measurements are saved.

3.3.4. Method of analysis: Pseudo-steady state permeation

Though ionic diffusion in polymeric membranes is not a well understood phenomenon, this process presumably involves dissociation of the ions from the salt, subsequent transfer of the anion and cation to the aqueous medium, and finally, diffusion of the ions in the confined water within the polymer matrix. Therefore, ionic mobility will depend on water flux which is a critical parameter together with the water uptake by the lens.

The salt permeability was calculated as follows. The diffusion process of NaCl (aq) across a membrane, in the stationary state, is described by the Fick's first law:

$$J = -D_m \frac{\partial C^m}{\partial x} = D_m \frac{\Delta C^m}{L} \quad \text{Equation 1}$$

where ΔC^m represents the variation of salt concentration between the right and left side of the membrane, with a average thickness L , and can be expressed as $C_L - C_R$. D_m is the salt diffusion coefficient into the membrane. This coefficient is not a measurable quantity because the concentration profile into the membrane is not known. However, from a strict point of view, the salt concentrations at both sides of the membrane, C_L^m and C_R^m , cannot be considered the same as the concentrations in bulk solution, C_L and C_R respectively; since this transfer process is governed by the salt solubility in such a membrane and by the mass transport limitation within the boundary layers (BLs), such is shown in figure 10.

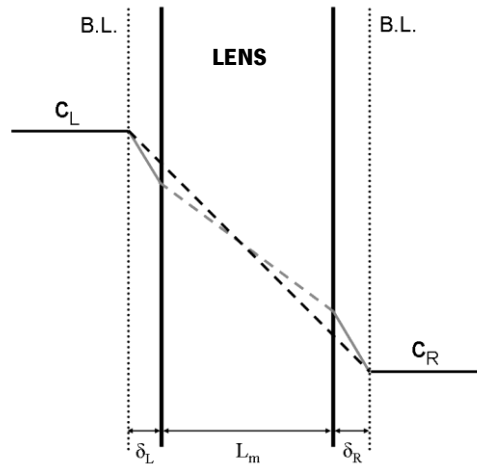


Figure 10 Scheme of the permeation phenomenon across a membrane. The gray profile represents the real process occurring, while the black discontinuous line represents the apparent permeability of the membrane by neglecting the boundary layer (B.L.) effects. The gray discontinuous line inside the membrane shows the true (intrinsic) permeability profile.

Thus, we can define the membrane partition coefficient k_m (or salt solubility as in the polymer) between the solution and membrane phases. k_m is usually taken to be the same value on both the feed and permeate sides of the membrane, as

$$k_m = \frac{C_R^m}{C_R} = \frac{C_L^m}{C_L} \quad \text{Equation 2}$$

The units of k_m are (g salt/cm³ swollen hydrogel)/(g salt/cm³ solution), and therefore, the variation in the salt concentration across the membrane will be given by,

$$\Delta C^m = C_R^m - C_L^m = k_m (C_R - C_L) = k_m \cdot \Delta C \quad \text{Equation 3}$$

The flux of salt J can also be expressed as the amount of NaCl in moles n crossing the membrane (of thickness L) per unit of time t and area A . We can rewrite the Fick's law as:

$$J = \frac{dn}{Adt} = Dk_m \frac{\Delta C}{L} \quad \text{Equation 4}$$

where,

$$n = C_R \cdot V_R \rightarrow dn = V_R \cdot dC_R \quad \text{Equation 5}$$

Thus:

$$\frac{V_R dC_R}{Adt} = Dk_m \frac{\Delta C}{L} \quad \text{Equation 6}$$

Integrating equation 6, the following expression is obtained⁷ :

$$\ln \left(1 - \frac{2c_R(t)}{c_{L,0}} \right) = -\frac{2 \cdot A \cdot P}{V_R \cdot L} (t - t_0) \quad \text{Equation 7}$$

in which $c_R(t)$ is the concentration of sodium ions at time t in the receiving chamber, $c_{L,0}$ is the initial concentration of sodium ions in donor chamber, A is the area of the lens exposed to the salt flux, L represent the average lens thickness of area exposed, V_R is the volume of the receiving cell compartment (magnitudes that are known), and P is the apparent permeability coefficient of the sodium ion ($P = Dk_m$, where k_m is the lens partition coefficient) and t_0 is the time lag.

The partition coefficient, k_m , of the solute in the hydrogel phase and in the solution is defined as $k_m = \frac{c_{NaCl}^m}{c_{NaCl}^{sol}}$, where c_{NaCl}^m is the equilibrated solute concentration in the hydrogel and

c_{NaCl}^{sol} represent the equilibrated solute concentration in the solution.

If we take into account that the difference in concentration between both sides of the lens, $\Delta c = c_R - c_{L,0}$, is practically constant due to the fact that $c_R \ll c_{L,0}$.

From eq. (7), the salt concentration in the receiver compartment will be,

$$c_R(t) = \frac{c_{L,0}}{2} \left[1 - \exp \left(\frac{-2 \cdot A \cdot P}{V_R \cdot L} \right) (t - t_0) \right] \quad \text{Equation 8}$$

and the salt flux will be

$$J(t) = \frac{c_{L,0} \cdot A \cdot P}{V_R \cdot L} \left[\exp\left(\frac{-2 \cdot A \cdot P}{V_R \cdot L}(t - t_0)\right) \right] \quad \text{Equation 9}$$

In case of $c_R \ll c_{L,0}$, as it happens in our experiments, we can obtain,

$$c_R = \frac{A \cdot P \cdot c_{L,0}}{V_R \cdot L} (t - t_0) \quad \text{Equation 10}$$

Being $c_{A,0}$ the initial concentration of salt in the chamber where the distilled water has been introduced and the salt conductivity is measuring, and t_0 represent the time lag. Thus, from the slope of eq.(7) or eq.(10) we can obtain the apparent salt permeability of the hydrogel, from the plot of $c_R(t)$ vs. time. Calculating the slope in these plot $m = \frac{dc_R(t)}{dt}$ together with the values of V_R and the area, A , and the thickness, L , of the membrane, is easily to calculate the apparent salt permeability

$$P = \frac{m \cdot V_R \cdot L}{A \cdot c_{L,0}} \quad \text{Equation 11}$$

Thus, plotting the concentration of Na⁺ ions in chamber R versus time, allows us to obtain the apparent Na⁺ permeability of the lens from the slope of eq.(10). When the lens has high solute sorption capacity, there will be a time lag before the pseudo-steady state is reached in the permeation experiment. From the curve of concentration vs. time, the time lag t_0 can be estimated from the intercept of pseudo-state line with the x-axis representing time.⁵⁷ The diffusion coefficient can be then calculated as

$$D = \frac{L^2}{6t_0} \quad \text{Equation 12}$$

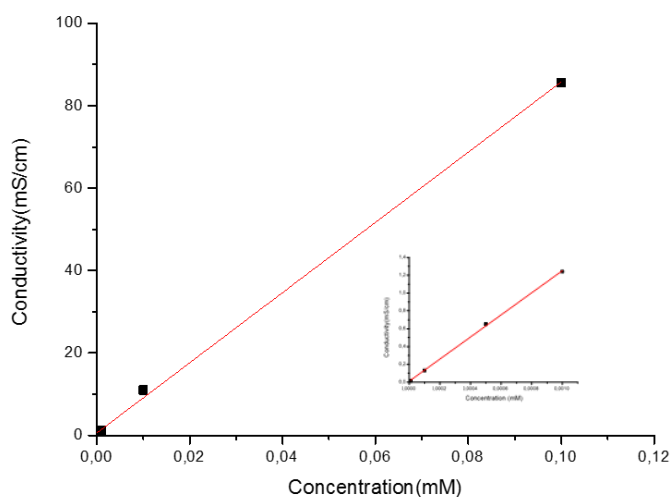
Finally the tortuosity, τ , of each hydrogel can be estimated from the relation⁵⁸

$$D_0 = D \cdot \tau^2 \quad \text{Equation 13}$$

Where D_0 is the molecular self-diffusion coefficient of aqueous sodium chloride (2.089×10^{-5} cm²/s at 35°C)⁵⁹

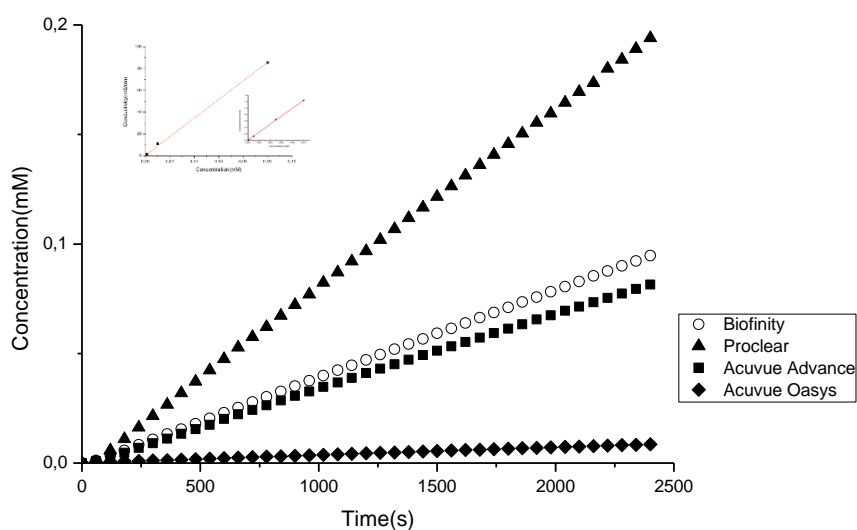
4. RESULTS AND DISCUSSION

The conductivity measured for each NaCl solutions prepared for calibration curve has been plotted vs. concentration of salt. The calibration curve obtained for almost four orders of magnitude of salt concentrations is shown in graphic 2. The inset represent a zoom which correspond to low concentrations (less than 0.01M concentration of NaCl).



Graphic 2. Calibration curve for the conductivity of NaCl (aq) solutions versus NaCl concentration. The inset graphic represents conductivity versus 1×10^{-5} , 1×10^{-4} , 5×10^{-4} , 1×10^{-3} NaCl concentrations. The large graphic represents conductivity versus 1×10^{-2} , 1×10^{-1} , 5×10^{-1} , 1×10^0 , 1×10^1 e 1×10^2 NaCl concentrations.

The conductivity shift has a linear correlation with NaCl concentration with a slope of 1222 ± 39 mS (miliSiemens). From this calibration curve and under the same conditions and experimental set-up shown in graphic 2, the behaviour of the Na^+ concentration as a function of time was obtained and it is showed in graphic 3 for conventional hydrogel (Proclear) and Si-Hy lenses (Biofinity, Acuvue Advance and Acuvue Oasys), respectively.



Graphic 3 Sodium ionic concentration versus time for each of one of the Si-Hy and conventional hydrogel contact lenses used in this study. In the inset we show the calibration curve correlating conductivity with salt concentration of NaCl (aq).

Taking into account the correlation curve we have calculated the apparent permeability coefficient from the equation 7. In all the cases the correlation coefficient of the linear fit to the experimental data is $r^2=0.9998$. The results obtained are given in Table 4.

Following the procedure described in section 3.3.4 and from graphic 3, the time lag (t_0), can be obtained from the intersection of pseudo-state line with the t-axis. One time the time lag have been estimated the diffusion coefficient has been calculated from equation 12.

Furthermore, the tortuosity can be also calculated from the self-diffusion coefficient of sodium ion in water (i.e. $2.089 \times 10^{-5} \text{ cm}^2/\text{s}$ at 35°C).

Finally, the partition coefficient, (k_m), was determined from apparent permeability coefficient and diffusion coefficient as $k_m=P/D$.

The values obtained for the Na+ apparent permeability coefficient, diffusion coefficient, partition coefficient and tortuosity determined from the conductivity measurements in aqueous solution to each of the lenses studied at different conditions (stirring in the donor chamber, pretreatment. with a NaCl 1 M solution or milli-Q water) were represent in table 4.

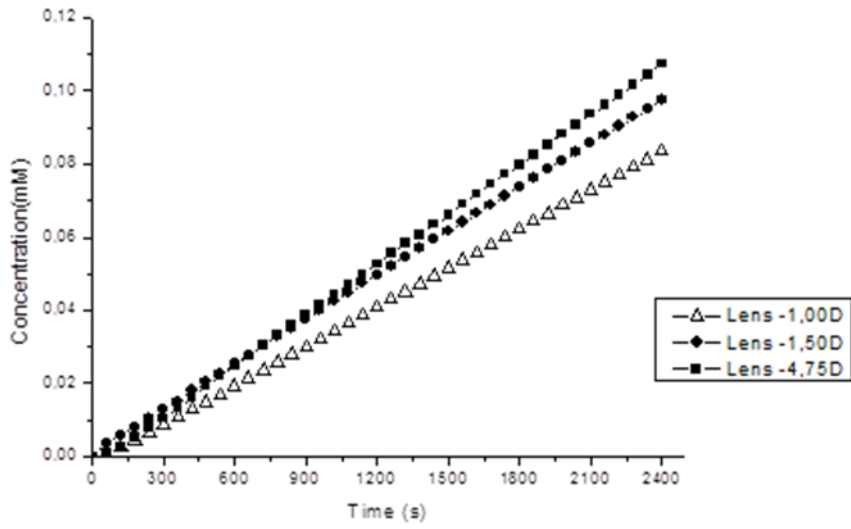
All the obtained results corresponds to the average of three measurements and the error represent its corresponding standard deviation.

Table 4 Values obtained for the Na⁺ apparent coefficient permeability (P), diffusion coefficient (D), partition coefficient (k_m) and tortuosity (τ) determined from the conductivity measurements in aqueous solution to each of the lenses studied at different conditions

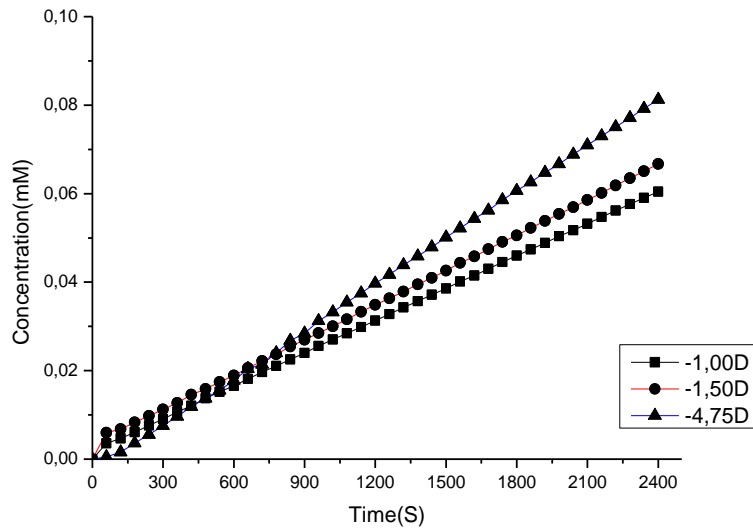
Trade name	Material (USAN)	L (10 ⁻³ mm)	P (10 ³ cm ² /s)	D (107cm ² /s)	k _m (10 ⁻¹)	τ
Without Stirring						
Biofinity	Comfilcon A	9.8±0.05	9.44±0.07	5.44±0.03	1.73±0.01	6.2
Proclear	Omafilcon A	9.7±0.6	23.4±2.1	3.9±0.7	6.1±1.7	7.4
Advance	Galyfilcon A	8.82±0.09	9.17±0.13	5.21±0.05	1.76±0.01	6.3
Oasys	Senofilcon A	8.4±0.3	0.82±0.07	-	-	-
With Stirring						
Biofinity	Comfilcon A	9.20±0.06	10.9±0.5	2.4±1.1	4.5±2.3	9.3
Proclear	Omafilcon A	9.6±0.2	24.57±0.08	5.0±1.7	4.9±1.7	6.5
Advance	Galyfilcon A	9.14±0.16	9.6±0.7	30.0±2.0	0.32±0.01	2.6
Oasys	Senofilcon A	8.5±0.3	0.82±0.02	-	-	-
Milli-Q						
Biofinity	Comfilcon A	9.22±0.08	2.39±0.02	1.56±0.02	1,53±0.01	11.6
Proclear	Omafilcon A	-	-	-	-	-
Advance	Galyfilcon A	8.8±0.3	6.9±0.2	2.6±0.7	2.6±0.8	8.9
Oasys	Senofilcon A	8.7±0.2	0.68±0.05	1.90±0.04	0.36±0.01	10.5
1M						
Biofinity	Comfilcon A	9.13±0.14	12.0±1.8	8.9±0.4	1.4±0.3	4.8
Proclear	Omafilcon A	-	-	-	-	-
Advance	Galyfilcon A	9.1±0.2	9.4±0.5	12.0±0.3	0.79±0.01	4.2
Oasys	Senofilcon A	-	-	-	-	-

Similarly as it was described above, the permeability coefficient of three new and used Biofinity lenses (-1, -1.5, -4.75) was determined with the aim of studying the behavior of ionic permeability of contact lenses for different optical powers and after being worn for 1 month.

In graphics 4 and 5 we plot the concentrations obtained for the new and used Biofinity contact lenses, respectively. From the slope one time the stationary state is reached we have calculate the ionic apparent permeability. In table 5 we report the found values. These values represent the average of the three measurements and the error represents the standard deviation.



Graphic 4 Variation of the concentration in the receiving chamber versus time for new Biofinity lenses.



Graphic 5 Variation of the concentration in the receiving chamber versus time for used Biofinity lenses.

Table 5 Ionic Permeability (P) and Thickness (L) of new and Biofinty contact lens (-1.00,-1.50,-4.75 D)

Power	P (10⁸cm²/s)	L (10²mm)
New Biofinty		
-1.00	10,0±1,6	1,19±0,01
-1.50	11,50±0,12	1,12±0,02
-4.75	12,6±1,0	0,99±0,01
Used Biofinty		
-1.00	7,4±0,2	1,14±0,05
-1.50	7,1±0,2	1,04±0,02
-4.75	8,8±0,5	1,04±0,08

The knowledge of transport of molecules absorbed in contact lenses as ionic molecules and water, will provide a better understanding of whether a contact lens is physiologically compatible with the cornea. Though ionic diffusion in polymeric membranes is not a well understood phenomenon, this process presumably involves dissociation of the ions from the salt, subsequent transfer of the anion and cation to the aqueous medium, and finally, diffusion of the ions in the confined water within the polymer matrix. Therefore, ionic mobility will depend on water flux which is a critical parameter together with the water uptake by the lens. It is worth noting that both evaporation present during contact lens wear and electro-osmotic drag processes have the potential to severely diminish the contact lens hydration, causing a significant increase of the ionic resistance.

The table 4 present values obtained for the NaCl permeability for the 4 commercial lenses investigated following different protocol in the experimental procedure:

A) The lens removed from the vial is situated on the cell of the experimental set-up without stirring on solution 1M in donor chamber (L) situated above of receiving chamber (R). In receiving chamber (R) distilled water together with the conductivity sensor is situated. In receiving chamber the stirring is always working at 800 rpm.

B) The lens removed from the vial is situated on the cell of the experimental set-up with stirring in both chambers at the same rpm.

C) The lens previously is equilibrated with distilled water during one week before of each measurement. Then the lens is placed in the cell without stirring on solution 1M in donor chamber (L). In receiving chamber the stirring is always working at 800 rpm.

D) The lens previously is equilibrated with a solution of NaCl (aq) 1M during one week before of each measurement. Then the lens is placed in the cell without stirring on solution 1M in donor chamber (L), while in receiving chamber the stirring is always working at 800 rpm, reported in the table 4 shows that both the values of the diffusion coefficient and the apparent permeability follow the trends:

$$P_{\text{without stirring - milli-Q}} < P_{\text{without stirring-Vial}} < P_{\text{without stirring-1M}} < P_{\text{with stirring-Vial}}$$

$$D_{\text{without stirring - milli-Q}} < D_{\text{without stirring-Vial}} < D_{\text{without stirring-1M}} < D_{\text{with stirring-Vial}}$$

This behavior could be explained by the following way:

Aqueous NaCl transport in the permeation cell is due not only to diffusion across the lens but also to convective diffusion across the boundary layers adjacent to the lens in contact with the two chambers (donor and receiving chambers). Accordingly with salt mass balance on each chamber together with Fick's law for the diffusion in the lens, we can obtain for the system represented in figure 10: ⁶

$$\ln \frac{\Delta c(0)}{\Delta c(t)} = \frac{\beta \cdot t}{R} \quad \text{Equation 14}$$

Where t is time, C_L and C_R are the transient salt concentrations in the high concentration donor chamber and receiving chamber, respectively β represent the cell constant for a lens of area A, exposed to the flux between the chambers of liquid volumes V_L and V_R by

$$\beta = A \left(\frac{1}{V_L} + \frac{1}{V_R} \right) \quad \text{Equation 15}$$

And R is the total resistance to the mass transfer through the lens from donor chamber to receiving chamber:

$$R = \frac{\delta_L}{k_L} + \frac{L_m}{P} + \frac{\delta_R}{k_R} \quad \text{Equation 16}$$

Where k_l and k_r are the mass-transfer coefficients and δ_l and δ_r its thicknesses, respectively, P the apparent permeability of a lens of thickness L_m .

When only there is stirring in the lower chamber (Receiving chamber) the resistance due to the upper water layer is higher than when there is stirring in the lower and upper chamber. Therefore decrease the lens transmissibility so that for the same thickness lenses. The apparent permeability to sodium ions will be smaller when there is no stirring in the upper chamber, such as in all cases for the lenses studied.

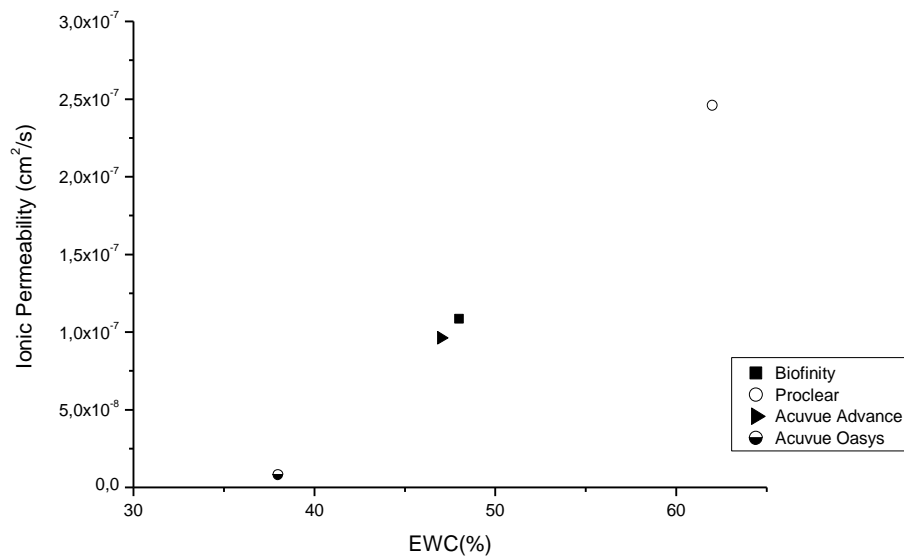
Thus, for example comparing the permeability results found for the Biofinity lens without stirring and stirring we can observe that in the first case $P = (9.40 \pm 0.07) \times 10^{-8} \text{ cm}^2/\text{s}$ while the value of the same lens with stirring is higher, $P = (10.90 \pm 0.05) \times 10^{-8} \text{ cm}^2/\text{s}$. The same can be said about the other lenses tested (see the results given in Table 4).

If we compare the same lenses with stirring and without stirring but in the case that pretreatment of the lens has been equilibrated with water or solution of NaCl 1M for a period of one week, we observed that the apparent permeability values were $(2.40 \pm 0.18) \times 10^{-8} \text{ cm}^2/\text{s}$ and $(1.20 \pm 0.18) \times 10^{-7} \text{ cm}^2/\text{s}$, respectively, to $(1.09 \pm 0.05) \times 10^{-8} \text{ cm}^2/\text{s}$ for Biofinity lens. I.e. the effect of the water layer resistance is diminished and furthermore the diffusion process is faster than lens equilibrated with the same solution that we place in the donor chamber.

Finally, when we compare the effect of equilibration the lens with ultrapure water and solution of NaCl 1M (which is the same solution on the donor chamber) we can observed that the permeability values and apparent diffusion coefficient increases when the lens is equilibrated with 1M solution. It is logical since the balance between the lens and the donor chamber exists from the initial time and the difference in chemical potential of the salt in the membrane and in the receiving chamber is bigger than in the case when this are equilibrated with water. When the chemical potential gradient is higher, the flux produced by drag force will be increased resulting in a higher diffusivity, as we can see from the values obtained and reported in table 4.

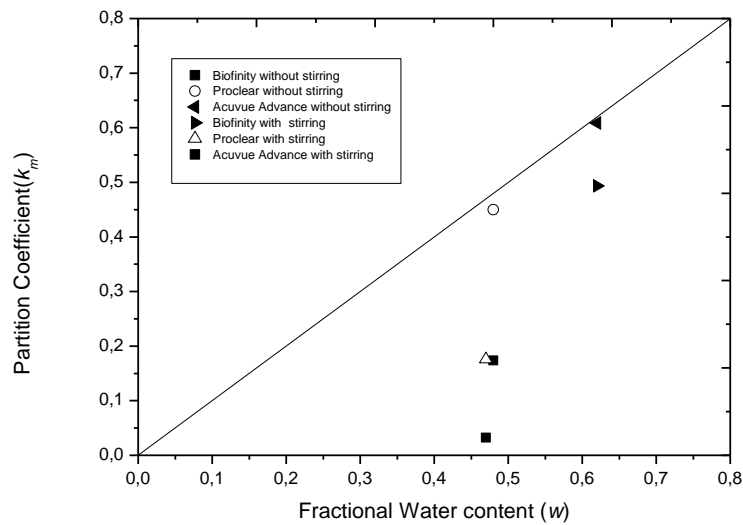
Furthermore, the effect of pre-treatment given to the lens is reflected by the values obtained for the diffusion coefficient. When the lens was equilibrated with milli-Q for a week and then it is located in the cell without stirring in the donor chamber, it was observed that the diffusion of NaCl through contact lens milli-Q (chamber R) suffered a delay time larger than in other cases. If the lens is taken directly from the vial and arranged in the cell, this delay time will be slightly smaller because this lens already has a 0.9% NaCl (aq) and finally when the lens is

balanced with the same solution disposed in the donor chamber, the diffusion process occurs instantaneously and delay time is shorter and therefore the diffusion coefficient is greater.



Graphic 6 Ionic Permeability (cm²/s) of soft contact lens as a function EWC (%)

At graphic 6 we can see that for the studied lenses there is an exponential increase in ionic permeability to water content. From this result we can confirm that the transport of salt occurs in the gel phase of the contact lens.



Graphic 7 Equilibrium partition coefficients (k_m) of 1M aqueous NaCl in SCL materials as a function of the equilibrium water content at 35°C.

At graphic 7 the line represent the partition coefficient equals the saturated-water volume in the lens when neither salt ions nor water interact with the polymer matrix. We replace the water volume fraction by w since the mass densities of water and the polymer components are close. According with the finding in other work, the measured partition coefficients fall below the ideal partition line. ⁶

The variation of the diffusion coefficient of Na^+ and Cl^- is linked to water flow through the lens. When the diffusion of water through the lens is high, the diffusion of ions will also be high and therefore, a better physiological behaviour of the lens should be expected because ion diffusion has been shown to be critical for the metabolism of the cornea but also to warrant the movement of the lens on the eye and improve the comfort.

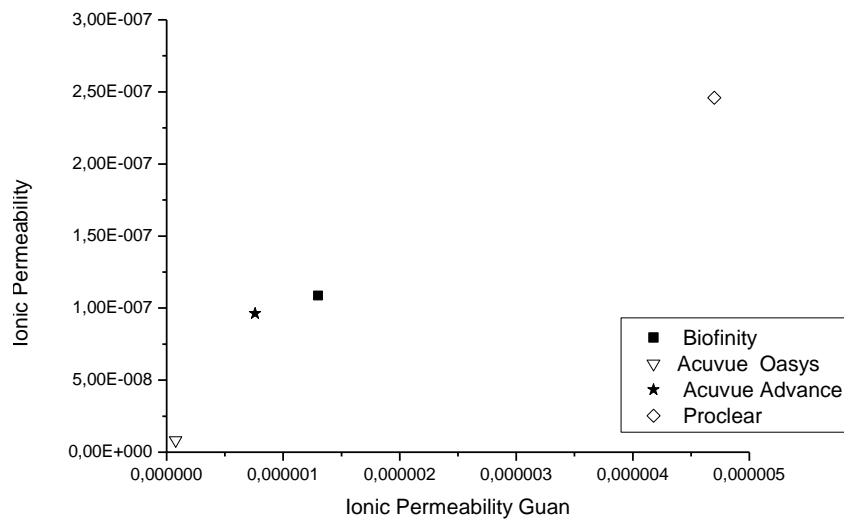
Presumably, freezing water is more mobile than non-freezing water and may be responsible for facilitating of salt transport. Ionic permeability vary two or three times depending of the water content and its weaker interaction with the hydrophilic sites in the polymer backbone. In our study we can observe from graphic 6 that Proclear lens with high water content has higher ionic permeability than Si-Hy contact lenses. That means that ionic permeability increases as the amount of freezing water increases. Similar results have been obtained by Kazukiyo Nagai et al.⁶⁰

Studies related with the characterization of sodium chloride and water transport in crosslinked poly(ethylene oxide) hydrogels⁶¹, have conclude that exist a perfect correlation between water content and hydraulic and diffusive water permeability in hydrogels, indicating that water permeability is strongly correlated with water uptake. Therefore, the increasing ionic permeability observed in graphic 6 is in agreement with the amount of water uptake of the hydrogel.

Similar results have been obtained by Formasiero et al.⁴¹. These researchers, have reported values of water diffusion through Soft contact lens materials such as conventional hydrogel (2-hydroxyethyl methacrylate (HEMA)), (SofLens™ One Day, hilafilcon A) and Si-Hy contact lens (PureVision™ Bafilcon A). The values obtained have been measured with an evaporation-cell technique. The results obtained for the diffusion coefficient (Fickian diffusion coefficient) of water are $0.9 \times 10^{-6} \text{ cm}^2/\text{s}$ and $1.6 \times 10^{-6} \text{ cm}^2/\text{s}$ for SofLens™ with 32% and 42%, of average water content in the lens at steady state, respectively. While for silicone hydrogel lens (Si-Hy), such as PureVision™ (Balafilcon A), this coefficient is between 0.4 and $0.8 \times 10^{-6} \text{ cm}^2/\text{s}$ for a water contents of the lens equal to 20%. Similar results have been reported by Yasuda et al.^{7,39} in conventional hydrogels HEMA.

Guan et al⁶. studied the ionic permeability in soft contact lens of -0.75D, using the classical diaphragm-cell method. This method consists in two compartments containing aqueous solutions of different sal concentrations (0.1 e 1M), separated by a single SCL. Before the measurements of lenses permeability, they were previously pretreated with milli-Q water for 48h with water renewed at least twice a day.

From the values plotted in graphic 1 and taking into account the results obtained in case of stirring in the donor chamber (Table 4) we trace the graphic 8. It was demonstrated that there are a linear tendency with correlation value 0.94 between these two different studies, beside the different obtained results and methods applied.



Graphic 8. Representation of ionic permeability values of Guan et al versus the ionic permeability values obtained in our study.

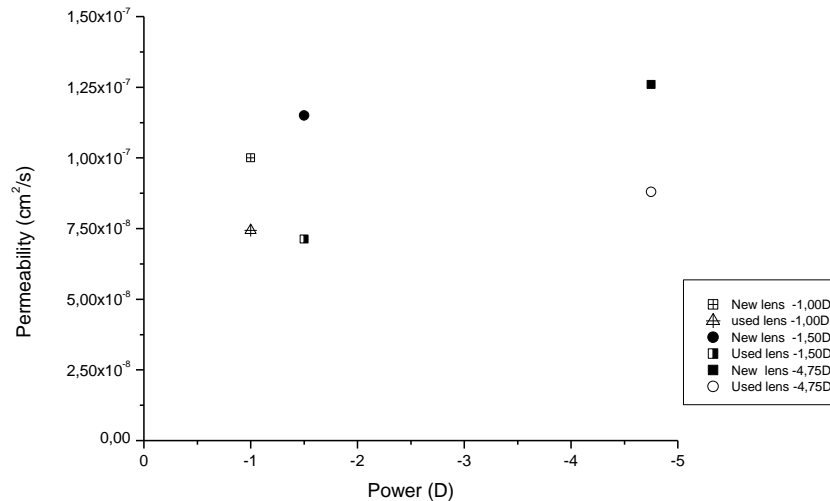
The values of tortuosity of the silicone lenses, hydrogel Biofinity and Acuvue Advance provided from experimental procedure without agitation, with Pure and 1M conditions have very close values, which agrees with what is expected since they have the same water content. If we had values of tortuosity from silicone hydrogel lenses with different water contents we should verified a decrease of tortuosity with the increasing water content⁵, although the porosity of the polymer networks into the hydrogel can also have a significant influence on the increasing of decreasing of the tortuosity parameter.

Study of the new and worn Biofinity lenses with different powers

According with Domscheke et al.⁶² the ion permeability of materials used as contact lenses is a critical parameter for the lenses because it permit predict the motion of the lens when it is situated onto the cornea. The effect of lens optical power and used lens in the ionic permeability has never been studied before.

The value of apparent permeability to all powers, both new and used is represented in graphic 9. A brief observation of these values allows us to infer that the new lenses shows greater coefficient permeability than the used lenses. In all cases, new and used is greater than the value

indicated by Nicolson et al.⁶³ $P_{ion} = 10^{-9}$ cm²/s and this critical value required to ensure that the lens can move on the eye.



Graphic 9 Variation of ionic permeability for new and used Biofinity contact Lens vs their power

Taking in account the values obtained for the ionic permeability and considering that this coefficient is a characteristic parameter intrinsic of each lens, we can conclude that the permeability of the new Biofinity lens to sodium ions is equal to $(11.4 \pm 1.1) \times 10^{-8}$ cm²/s while the used lens is equal to $(7.8 \pm 0.7) \times 10^{-8}$ cm²/s which means that the ionic permeability of the used lenses decreases 31% when it is compared to new lenses will.

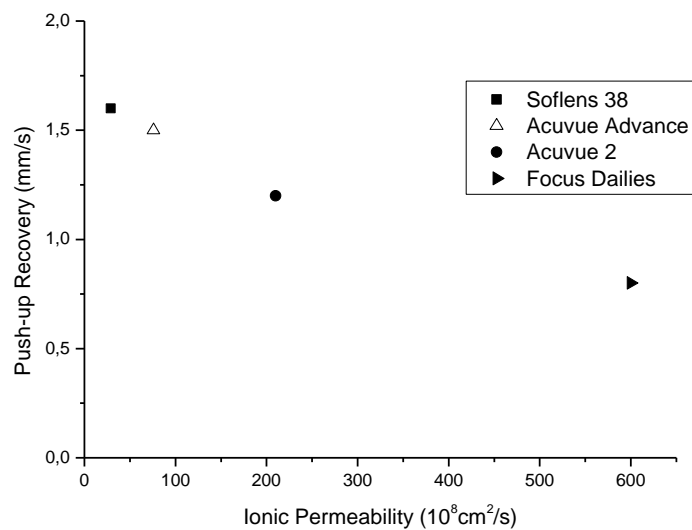
We can connect the decrease of ionic permeability in used contact lens with dehydration lens and deposits on their surfaces. The evaporation present during contact lens wear and electro-osmotic drag processes have the potential to severely diminish the contact lens hydration. If decrease the contact lens hydration the ionic permeability also will be decreased because the NaCl transport occurs in the water phase of the gel.

If one compares the apparent ionic permeability between lenses with -1.00 and -1.50 D, we can observe that there are an increment in the -1.50 D lenses of 15%.

In the case of -1.00 and -4.75 D lenses there is an increase of 26%. These values were not the expected because this parameter should be an intrinsic parameter characteristic of the material.

Wolffsohn et al.⁶⁴, demonstrated that together with centration and limbal incursions, horizontal lag, movement on blink in up-gaze and push-up recovery speed should be recorded to adequately describe soft contact lens fit.

Using the ionic permeability values obtained by Guan et al.⁶ for Soft Lens 38, Acuvue Advance, Acuvue 2, Focus Dailies and the push up recovery values, for example, obtained by Wolffsohn et al.⁶⁴ we plot the graphic 10. We can observe that with the increase of the ionic permeability values, the push up recovery values decreases. If we have evaluated the push up recovery for new and used Biofinity lenses we will observe that the push up recovery value in used lenses it will be higher than new lenses because the used lens permeability is shorter than new lenses.



Graphic 10. Permeability value obtained by Guan et al. versus push up recovery values obtained by Wolffsohn et al.⁶⁴

5. CONCLUSIONS

Using the Ionoflux method the Permeability to Na^+ and Cl^- ions has been measured for one conventional and three Si-Hy contact Lens, in different experimental conditions such as: pretreatment with a solution of NaCl 1M, milli-Q water and with/without stirring on the donor chamber.

From this study we can conclude that stirring on the donor chamber does not have a significant effect on the measurement obtained. Differences between stirring and non-stirring were in the order of less than 5%. Similar results were obtained when the lens first were equilibrated with a solution of NaCl 1M or with ultrapure water. However, some lenses could not be measured in either condition.

The ionic permeability of new and used myopic contact lens of different optical powers - 1.00D, -1.50D and -4.75D were also measured. From these measurements we can observe that Lens already used affects the ionic permeability in about 25 to 38%.

Finally, lenses with different thicknesses have different ionic permeability, with a significant reduction for moderately myopic lenses around -5.00 as measured in this study.

6. FUTURE WORK

This study demonstrated that there is more to understand about ionic permeability of soft contact lenses. In future studies, we suggest that would be important the simultaneous evaluation of ionic conductivity and on-eye lens performance; measure ionic permeability in high myopic lens (above -6.00D) and positive lens (thicker at the lens center might be worse this parameter); evaluate if the ionic permeability decrease is accompanied by changes in the dynamic behavior of the contact lenses on the eye.

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